

# **The Science, Economics, and Politics of Malaria Vaccine Policy**

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A submission to  
UK Department for International Development<sup>2</sup>  
and  
The Malaria Vaccine Technology Roadmap<sup>3</sup>  
and a response to the  
Tremonti Report to G8 Finance Ministers<sup>4</sup>

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<sup>1</sup> © Andrew Farlow 2006. Further papers on vaccines, neglected diseases, and pharmaceutical R&D at: [www.economics.ox.ac.uk/members/andrew.farlow](http://www.economics.ox.ac.uk/members/andrew.farlow). In particular, previous papers contain many more angles on ‘Advance Purchase Commitments/Contracts’, APCs, than are contained in the current report. Feedback and corrections greatly appreciated: [andrew.farlow@economics.ox.ac.uk](mailto:andrew.farlow@economics.ox.ac.uk). A list of thanks is to be added when those involved agree to be listed or to remain as anonymous referees, given the sensitivity of some of the feedback the author has received.

<sup>2</sup> UK Department for International Development consultation process on Advance ‘Market’ Commitments.

<sup>3</sup> [www.malariavaccineroadmap.net](http://www.malariavaccineroadmap.net). The draft “Malaria Vaccine Technology Roadmap” (henceforth MVTR) is available on [www.malariavaccineroadmap.net/pdfs/roadmap\\_071905.pdf](http://www.malariavaccineroadmap.net/pdfs/roadmap_071905.pdf). The “Roadmap Summary Results” (henceforth RMSR) is at [www.malariavaccineroadmap.net/pdfs/roadmap\\_results.pdf](http://www.malariavaccineroadmap.net/pdfs/roadmap_results.pdf). The “Malaria Vaccine Vision Meeting Summary Results” (henceforth VMSR) is here: [www.malariavaccineroadmap.net/pdfs/summary.pdf](http://www.malariavaccineroadmap.net/pdfs/summary.pdf).

<sup>4</sup> “Advance Market Commitments for vaccines: A new tool in the fight against disease and poverty.” Report to the G8 Finance Ministers by Giulio Tremonti, Minister of the Economy and Finance, Italy, London, December 2, 2005, [www.dfid.gov.uk/consultations/amc-report-tremonti.pdf](http://www.dfid.gov.uk/consultations/amc-report-tremonti.pdf). Background papers to the ‘Tremonti Report’ at: [www.dfid.gov.uk/consultations/background-papers-tremonti.pdf](http://www.dfid.gov.uk/consultations/background-papers-tremonti.pdf).

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## **Executive Summary**

Malaria vaccine policy has been an unusually busy field just recently, with a range of new proposals under consideration by policymakers and global leaders. This report seeks to explore the complexity of the underlying malaria science to try to work out some of the potential consequences for the economics and the finance of some of these proposals. In particular, the report is especially interested in evaluating the proposal of two malaria vaccine goals – one earlier lower efficacy vaccine and one later higher efficacy vaccine based on product-and region-specific characteristics, as suggested in the recently-initiated “Malaria Vaccine Technology Roadmap” – in combination with an elaborate subsidy/R&D funding scheme called an ‘Advance Purchase Commitment/Contract’ (APC), as currently promoted by G8 finance ministers, the UK Finance Minister, Gordon Brown, and US Senators Kerry and Lugar. The APC subsidy scheme is supposed to incentivize new privately financed investment into malaria vaccine R&D, and is not a procurement fund just to cover production costs of a vaccine that already exists.

Under the APC proposal, firms first sink their privately-funded R&D costs, to be repaid much later through a committee vested with the job of spreading a fixed pool of public subsidy over all developers at the end (with most getting nothing if it is being used as an R&D device). Each potential malaria vaccine developer is tied in to the scheme via legally-binding contracts from the beginning. The overall size of the subsidy pool and the terms for its disbursement are set by policymakers at the start and managed by the committee at the end. We are told that this can be done so as to generate the required investment returns to investors such that they will invest in the development of a string of malaria vaccines of ever increasing ‘quality’. These subsidy schemes have been very carefully crafted in the language of the market, as Advance ‘Market’ Commitments (AMCs), though they have precious few market-based credentials to them, and are really just large statist funding schemes. Wherever possible this report avoids the nomenclature AMC and uses the nomenclature APC, for ‘Advance Purchase Commitment/Contract’, instead. Indeed, even the nomenclature APC is highly imperfect: The extent to which anything is ‘committed’ is increasingly unclear in the APC literature, and the ability of ‘contracts’ to create a credible commitment becomes increasingly difficult to believe the more one analyzes what such contracts would have to do. We proceed mindful of the dangers of creating, via the use of terminology, a false sense of security in the veracity of the underlying ideas.

The report finds that the *combination* of the two goals and the APC subsidy scheme would, in practice, put any new commercial pressure onto the lower efficacy first-goal malaria vaccine and current vaccine candidates. Indeed, in realistic applications, given strong self-fulfilling tendencies, such schemes would simply collapse down to provide the subsidy to cover the high production costs of the first low-efficacy vaccine generated, and struggle, and almost certainly fail, to generate multiple generations of malaria vaccines. By gambling on too few potential vaccine leads in an area of very risky science, this would increase the chances of not getting any vaccine. The argument that an overemphasis on goal-one vaccines – or even just one goal-one vaccine – is part of a long-term strategy to get ‘better’ vaccines later is explored, but is found to be not without extra costs and risks.

The report finds that recent analysis has tended to isolate parts of vaccine R&D from analysis of an overall package of measures to tackle malaria, including prevention and treatment, and from other parts of the vaccine R&D process. In consequence, malaria vaccine proposals generate tensions with, and burdens on, other parts of an overall package of malaria control measures. Unbalanced R&D subsidies would over-emphasize the creation and use of lower efficacy vaccines, thus harming incentives to create higher efficacy vaccines (and even vaccines at all) and to research and develop other parts of the greater global solution. The paper argues that malaria vaccine goals should not be set separately from an overall malaria control strategy, and that treating the two together will benefit the targeting of vaccines too.

The report finds that for all the recent talk that ‘purchasers decide’ by *their purchase decisions* the efficacy of any ultimate vaccines created via an APC, they do not. Their choices are highly subsidized, such that they face no relevant price signals *at the time of purchase* to guide choice over vaccine efficacy and the value of potential vaccines, even as they face worries about an ever-depleting subsidy pool, and rent-seeking and corruption pressures placed on them (terms like ‘rent-seeking’ are explained as they are encountered in the report, but are also gathered in a small glossary at the end). Whether purchasers get a 30%, 50%, 70% or any other efficacy, or a one-, three-, five-year or any other duration vaccine is principally driven, before they get to make their purchases, by the goal-setting process and the decisions of the committee running the APC scheme.

Similarly, because of the sunk nature of the subsidies, purchasers’ decisions are distorted away from other control measures costing more to them ‘at the margin’ at the time of purchase, even if these other control measures would have been higher-value choices, and had it been better to have instead targeted resources at higher-efficacy, longer-duration, vaccines rather than lower-efficacy, shorter-duration, vaccines. It is crucial, therefore, that the ultimate users of vaccines have a say at every point in the decision-making process affecting the likely efficacy and duration of vaccines being targeted, and that the overall control strategy and range of options is fully articulated, and integrated into the budget constraint that they face. This suggests *real* markets and all ‘malaria control products’ treated equally, whether vector control, impregnated bednets, drugs, *or* vaccines. If this requires long-term commitment of global funding to bolster national malaria control programs so as to be able to purchase these products, then the attention of policymakers and global leaders should be on this and not on a malaria APC.

The report investigates the likely impact of the science and the twin-goals on the production costs of malaria vaccines in both the short-run and the long-run. It finds a complicated and elaborate set of interactions between the twin-goals, with each goal creating risks to the other. Combined with the complicated scientific problem – for example the need to tackle polymorphism and antigenic variation – this feeds extra costs and risks onto firms. These issues have not been fully explored yet, and will tend to drive up average costs. The report argues that these production cost issues will repeatedly feed back to harm R&D incentives at any prefixed level of subsidy, and also to make APC-based incentive schemes difficult to relate to firms’ R&D efforts, making these schemes

more risky to firms than currently suggested by their promoters. The report concludes that APC subsidy schemes run the risk of having to be topped-up even as developers face a great deal of uncertainty about the level of overall funding available, with risk imposed on their investment decisions.

The report finds that the proposals made by APC advocates for assuring long-term access and low-price malaria vaccines, will instead increase risks to firms and create potential for long-term breakdowns and delays in access to vaccines (contrary to what is claimed). This is especially so for the proposal of never-before-used legally-binding low-price long-term supply contracts signed *before* R&D is even performed. The report argues that these sorts of ‘legally binding’ promises could never be relied upon to generate long-term access, and would harm many of the firms involved, or wishing to be involved, in R&D. It finds that many of the ways suggested to get around this problem – such as waivers of the contract conditions or flexible pricing rules – are simply ad hoc, creating a whole new range of risks to firms, as well as perverse incentives.

Instead, the report argues that much more attention needs to be placed on a range of ways to expand production capacity and competition, and to increase the number of players involved in vaccine discovery and production, with much more attention to delivery issues. This is just one of very many instances throughout the report where we find that a range of issues many years out have not been fully thought through such that they will feed back to harm R&D incentives. The report wonders whether targeting a higher efficacy vaccine from the start, with only an ‘option’ on a lower efficacy vaccine, would not actually save on these costs and ultimately speed up and stabilize access should a vaccine ever be created.

Given the dysfunctional nature of ‘the market’ and the risks this imposes on developers, the report tentatively argues for more (but not complete) separation between payments from purchasers and repayments of R&D investments, to try to mitigate some of these risks, with greater access to technology and competition at the later stages of the process. This is good for those doing R&D too, to the extent that they can benefit from the lower costs via greater returns to their R&D. This runs counter to recent proposals that seem intent on facing developers with ‘market’ risk if they wish to get repaid, even if the market is highly dysfunctional and would impose heavy downside risks on the value of firms’ investments. Rather than a mechanism based on a sole supplier, a structure starts to emerge of more open and democratic collaboration and a system of financial risk-sharing contracts, possibly PPP (Public-Private Partnerships) based, until development of a vaccine (or vaccines), phasing into more competition in manufacture (with competition used to extract information, to drive prices lower, and to cover costs).

The report reviews the ‘cost-effectiveness’ evidence generated by supporters of a malaria vaccine APC, and finds that it has been designed to favor the APC idea and lower-quality malaria vaccines, in a way that would not be justified by a fuller consideration of the overall financial constraint and the consequent tradeoffs between vaccines and non-vaccine options, and tradeoffs between different efficacies and ‘qualities’ of vaccines. The evidence is biased by: ignoring the true underlying costs of developing vaccines;

ignoring components of development that are not paid for by the APC subsidy scheme; ignoring delay; ignoring any risk created by the workings of the APC subsidy scheme itself; presuming a vaccine that will last for ever with minimal consideration of the need for follow-on generations of vaccines, even in the case of low-efficacy short-duration early vaccines; presuming low manufacturing costs in both the short- and the long-run (even as the two-goal structure, the APC subsidy scheme, and the nature of the underlying scientific problem make this difficult); ignoring the impact of a vaccine on other parts of a complete package of measures to control malaria; and by assuming masses of failure and imperfect policy application elsewhere but perfect application of the two-goal and APC subsidy scheme proposal itself. The biggest distortion of all is the way that the extremely high value of dealing with malaria, and therefore the high value of malaria vaccines themselves, has been routinely converted into the high value of any favored vaccine R&D funding proposal however unknown its workings, and however unclear it is that it is actually likely to work. The cost-effectiveness methodology allows even for proposals that are likely to fail to nevertheless be judged as highly cost-effective.

The report shows how this cost-effectiveness literature has been wrongly used to set the size of malaria, HIV, and TB vaccine APCs. The notion has been that by making the revenues from R&D investments on 'a' malaria, HIV, or TB vaccine similar to the revenues realized from investments in typical existing commercial pharmaceutical products, investors will be attracted. However this ignores the basic economic principle that it is revenues minus the costs of generating those revenues – i.e. overall investment returns – that matter to investors, and not revenues alone. These costs include out-of-pocket R&D cost and appropriate costs of finance. Realizing that we have no handle at all on these costs for malaria, HIV, and TB vaccines, those advocating for a malaria vaccine APC have simply chosen to ignore them. An APC is first and foremost a financial instrument that needs to appeal to investors based on investment returns. Yet, appealing to politicians seems to have been a more important priority than appealing to the harshest of all judges of such instruments – namely financial markets themselves.

The report explores a range of 'risk' issues already faced by firms working on malaria vaccine R&D, and the further risks that they would face under forthcoming proposals. It explains why it is good to face private developers with some risk and not to fully insure them, but observes that there is only an optimal amount of risk that developers should face, before it becomes self-defeating. The report argues that a big danger with a 'precommitted' subsidy-based R&D repayment scheme in an area of complicated science is that it faces firms with a range of extra risks all of which have to be priced in to required investor returns. These include in particular: heavy risks of 'time-inconsistency' resulting in too little incentive to do R&D in the first place; risks of having to 'rent-seek' the subsidy scheme and to engage in corrupt practices; and reputational risks reminiscent of AIDS drug price debacles of the past. The report argues that many of the risks created by APC subsidy schemes would not be hedgeable by privately-funded developers, since these risks are not idiosyncratic.

The report finds that biotechs would be especially open to risk under such schemes, because larger players would be able to delay their response and treat the APC as much

more of a financial ‘option’; if it does not work, it is the biotechs who take most of the loss. The report worries that high rates of risk created in these attempts to solve the vaccine R&D problem will just feed back to harm the efforts. It argues that the current priority should be for more direct funding to biotechs, PPPs, and into research to resolve key fundamental scientific issues, but that this funding also needs to be more transparent and more fully and openly debated. It also finds that low-efficacy short-lived malaria vaccines (contrary, it would seem, to what some commentators say), do raise a range of liability issues that still have not been adequately resolved, and that feed back to harm R&D incentives and to face sponsors with risk too.

In a review of ‘innovative financing mechanisms’, the report finds the notion of ‘stimulating the market’ to be very narrowly and inadequately defined. Given that, relative to their health impact, a huge range of potentially very valuable markets are being ‘underexploited’ (Alzheimer’s, diabetes, cancer, etc.) and given evidence of the very poor response of privately-financed developers to potential HIV vaccine markets, the report worries that there are dangers of simply misidentifying the problem as “too little purchasing power”. The consequence is that too little attention is paid to tackling the scientific and institutional limitations, and too much attention is paid to apparently simpler fixes based on ‘size’ of purchasing power, that cause little or no private firm response, or heavily favor just a few and maybe even just one firm, and yet use up a lot of political and systems capacity in new-institution building, monitoring, and policing activities.

The word ‘market’ is heavily used in the wording of recent proposals, but this paper finds market thinking being repeatedly thwarted, replaced by rules administered by a committee after large private costs have been sunk, and actions driven by contracts that would be extremely difficult to set up in advance and to make credible and efficient, with an over-reliance on sole suppliers, and with competition ignored at important stages of the development and production process. Tackling scientific, economic and finance problems has given way to, supposedly, simpler legalistic fixes, that then, on closer examination, turn out to be far from simple in practice.

The report explores the tradeoff between, on the one hand, price-based bidding of purchasers to try to control the corruption and rent-seeking generated by APC subsidy schemes, versus, on the other hand, the need to extract R&D costs that may be undermined by this bidding process. The rent-seeking and corruption pressures arise mainly because of the build-up of sunk costs and the difficulty of setting terms in advance in APC subsidy schemes (as compared to the very different sort of subsidy schemes being proposed for procurement of ACT drugs as also discussed in the report). Most of the payment to a ‘winning’ firm (presuming that there are multiple parallel developers and that an APC is first and foremost an R&D instrument) is a ‘windfall’ and not simply to cover manufacturing costs, and will therefore be many times the winning firm’s actual R&D outlays. This is the fuel for rent-seeking and corruption. The report argues that policymakers should not under-use the positive properties of competition and price-bidding at later stages of the development process to tackle these problems.

The report explores the nature of ‘collaboration’ to tackle such a complicated scientific problem, and finds it generally overlooked and inadequately treated by policymakers and politicians, more interested in masking the collaboration problem with bigger promised payments. Given the importance of information-sharing in the solving of such a highly complex scientific problem, the report finds that it might even be counterproductive to adopt a system that places no commercial value on a goal-2 malaria vaccine even as it creates some pressure on a goal-1 malaria vaccine, but in a way that puts most commercial players off even goal-1 vaccines.

The report worries about a range of under-explored issues, including the presence of various ‘option value’ and ‘option cost’ components to vaccine R&D projects, and ‘crowding out’. Malaria vaccine R&D has an ‘option value’ component because it provides a good environment in which to test platform technologies, that is technologies (such as adjuvants and delivery technologies) usable across malaria and non-malaria applications and submarkets, and because there is also potentially a degree of market segmentation, including across income level and type of users (in the case of malaria, transient visitors to endemic areas, such as tourists or military personnel). There are also some potentially high ‘option cost’ components to early R&D on account of potential changes in technology. All these option elements make it difficult to know how to set APC terms, including the size of an APC, and to judge progress towards those terms. High option costs probably also underlie some of the resistance of firms and investors to get involved in research, the more so the earlier the stage of research and the more uncertain the science, but we simply have too little analysis to know how big the problem is.

Any scheme based on subsidy payments also has to concern itself with ‘crowding out’, that is, how it can exclusively target those who genuinely need subsidies to purchase the products, and how it can target those firms who need to be incentivized by the subsidies, so as to maintain the pull-power of the subsidies and to stop subsidies from being ‘crowded out’. This involves decisions about which countries to treat as ‘eligible’ and ‘non-eligible’, with the latter left to face (tiered) monopoly prices instead. It also needs monitoring and mechanisms for denying many-multiples of subsidy payments to each firm in proportion to other financial help received.

In an extraordinarily complicated R&D process involving many different sources of funding, privately-funded developers would naturally worry, given the very long horizons, that this ‘crowding out’ would not be handled well, and that the economic-rent-seeking behavior of other players would bias the outcome. The paper argues that poorly-handled ‘crowding out’ would especially harm those nearer to scratch in their R&D efforts, and smaller and emerging firms, and would also reinforce the bad choices of projects by sponsors.

The paper argues against over-reliance on firm-level verbal evidence regarding new funding proposals, given the dangers, as repeatedly found in the public choice literature, of getting a highly misleading result. It argues for questions to be much more directly

linked to an obligation (and cost) on firms to do something. It suggests better use of data, including the use of event studies, to explore market responses to large new initiatives.

The paper takes a detailed look at the recent trial results of the candidate malaria vaccine RTS,S/AS02A. It finds an interesting set of results with respect to duration, source of efficacy, generalizability of result, and so forth. However, it finds that the science is still extremely high risk, and yet that the results have been very heavily, and uncritically, promoted by politicians and in parts of the press. The main concern here is that funding decisions in response to this do not so distort the malaria vaccine and treatment playing field as to harm efforts (and, indeed, private financial incentives) elsewhere. Past vaccine failures – both for malaria and otherwise – suggest extreme caution in over-hyping one particular vaccine candidate over all others.

The report takes a detailed look at the recently announced Kerry-Lugar “Vaccines for the New Millennium Bill 2005”. It finds that the legislation proposes to set up a mechanism to repay investors that is very risky and lacking in credibility to developers, even though it is crucial to get developers to respond. In particular, it is very unclear whether investors will get a fair and adequate return to their investments. To credibly sustain a precommitment – over very long stretches of time – requires either a costly action (for example, when a firm invests in excess capacity to deter rivals) or a costly punishment for renegeing (for example, when interest rates rise rapidly if a country shows any sign of defaulting on its debt, including by allowing inflation). With neither of these available for vaccine precommitments, the wording of the legislation is everything, and, in this case, it is found to be seriously deficient.

On closer inspection, the Bill is also found to limit itself to malaria, HIV, TB, and pneumococcal (*streptococcus pneumoniae*) disease, missing out huge areas of infectious and other diseases. Since the Bill will have no impact on malaria, HIV or TB vaccine R&D, one concern is that, even if the Bill gets through, it would only in reality be used to try to achieve a result on pneumococcal disease – itself a useful outcome if it is achievable – even if this could have been achieved with less delay by other means, while misleadingly suggesting that a solution has been found for the other three vaccine problems. If the Bill fails, it would even harm the pneumococcal disease outcome.

The Kerry-Lugar Bill also sets up potential tensions between European (and other) malaria vaccine efforts and the US Treasury, because it would require all developers to be signed in to contracts, the purse strings of which would run through the US Treasury and the President of the United States of America. The Bill also places conditions on the countries deemed ‘eligible’ and ‘non-eligible’ for APC subsidies, and this would create later tensions between the US and Russia, China, India and middle-low income countries with regard to HIV vaccines, and possibly even malaria vaccines, since the scheme is set up to deny subsidies to them, leaving them to face monopoly prices instead. The fear is that this sets sponsors and firms up for vaccine price debacles, reminiscent of those over HIV drugs in the past, but this time dragging in G8 governments too. Indeed, at various points the report questions the logic of pitching funding instruments so heavily at G8 nations, given that most of them are running balance of payments deficits. It suggests that

there is some logic in incorporating into funding mechanisms those countries and regions running balance of payments surpluses, several of which would benefit greatly from the development of vaccines for killer diseases. Unfortunately, this route has been ignored because it conflicts with the desire to set up APCs, even though such heavy interest in APCs is itself partly generated by the pitch to deficit countries.

The report reviews a number of perverse incentives generated by the wording of the Kerry-Lugar Bill. It also finds that the wording goes out of its way to avoid action to bolster malaria control programs now, and on funding, especially of vaccine PPPs and of basic science, which might actually have a genuine impact on malaria, HIV, and TB and other vaccines in five to ten years time.

The report describes in detail the policymaking process of the past two years or so. It describes how this process has recently become driven by short-term political needs, and a highly simplistic notion of malaria vaccine science and of the problems of malaria control in general. It outlines the ways in which the goal of current endeavors has been gradually set lower, and the way a huge list of practical issues have been ignored in thinking about malaria vaccines in order to get a ‘policy success’ even if not a ‘successful policy’.

The report details how an early and perfectly legitimate interest in ‘novel financial instruments’ degenerated into being only about APCs. Subsequently, far from being an honest assessment of whether or not this particular instrument would work for vaccines such as malaria, interest in it was exploited to further other goals instead, some good (such as to promote action on late-stage vaccines even if APCs are not, strictly speaking, used) and some less so. We review how those vested with the job of evaluating APCs, failed on all counts to satisfy the brief they were set. Just for illustration we pick a selection of issues from a much longer list: Who will want to run a malaria APC? How will APCs be treated as financial liabilities? Why were health infrastructure, vaccine distribution issues, and other interventions ignored?

The report assesses the involvement of key players, such as Britain’s finance minister, in distorting this process, first by unbalancing the malaria playing field by making promises to influential players, and then by distorting the behavior of policy advocates. We see how this shows up in the wording of major policy pronouncements and in the overwhelming drive to push for an APC for malaria over other policy options. The key need to generate a financially sound policy for all investors and sponsors to respond to, has been displaced by the need to generate language that will be appealing to politicians, even if it means a policy that will fail when financial markets and investors do not respond. The report extensively reviews the Tremonti Report prepared for G8 Finance Ministers and finds the financial thinking within it regarding malaria, HIV, and TB APCs to be especially poor.

The paper analyses the constraints of the G8 process, and the failures that emanate from institutional defects – often very subtle – of the UK policymaking process in particular. In each case we see how this has tended in recent years to favor some outcomes over

others, and has even undermined progress on good policy. The report likens the thinking processes in the UK Treasury and DFID, with respect to this issue, to that of NASA on the eve of the 1986 Challenger disaster. In his closing address of the commission enquiring into the disaster, Richard Feynman famously performed an extremely simple experiment with a piece of rubber and a glass of iced water that demonstrated that the shuttle was doomed to perish. NASA officials took a huge gamble – ignoring the engineers who tried desperately to get the launch cancelled – and it failed. Similar institutional failings have impacted the launch of APCs for malaria, HIV, and TB.

The report argues that even the language used has become highly obfuscatious to try to get around actually having to prove any evidence of effectiveness, especially of malaria, HIV, and TB APCs. The report argues that the rush to prematurely lock in outcomes in highly command-and-control, statist, APC mechanisms is likely to intensify bad results, create later problems for both firms and sponsors, and risks damaging the reputations of policymakers and politicians. This rush isn't even necessary since there is good analysis on the horizon of issues that will help to better set policy, and the option value of waiting before locking in is very high. As bad subsidy schemes go, the particular subsidy scheme described here, in combination with the two operational goals, takes a lot of beating. So, what is the rush?

The report concludes that neither malaria vaccine nor drug scientists, nor biotechs, nor 'big pharma' (most, if not all, of whom regard APCs for malaria, HIV, and TB in particular as 'looming disasters'), nor PPPs would come out well from what is being proposed on the malaria APC front. This has been repeatedly reflected in feedback from correspondents across all of these diverse groups. The report concludes that even GSK stumbled into agreeing to something that they will only come to regret, given the 'dammed if they do, dammed if they don't' set of choices it will force upon them. The only people seemingly benefiting are policy-advocates and politicians. Only 'seemingly', since ultimately it will not even turn out to have benefited them either. Similarly, for all the high-sounding promises of funding, neglected diseases in general have lost out from the concentration on APCs. They continue to suffer from relative public (as opposed to foundation) funding neglect, and the push for APCs has conveniently concealed this, and, even, neutralized efforts to tackle it.

The paper finishes by outlining several potential Roadmap trajectories for the future. It proposes a different set of goals based on process and risk metrics to mitigate some of the inefficiencies and risks of the current goals. It summarizes 50 key recommendations in an attempt to rebalance the debate and to move the thought process forward. Frequently, the paper argues for more consideration of the ethical dimension underlying scientific decisions, and for a more open and democratic decision-making process.

In many ways this report has ended up as a defense of these more open democratic processes, such as those of the Malaria Vaccine Technology Roadmap, against largely politically-driven processes that force out certain economic and financial solutions to the malaria vaccine problem, with the science then forced to fit in with these. During the writing of the report, much discontent surfaced both within the malaria vaccine

community and across the malaria and global health community in general. There was a clear disjoint between the science and industry people and the Malaria Vaccine Technology Roadmap on the one hand, and the politicians and a relatively small group of policy advocates on the other hand, with current policy driven largely by the latter. This discontent suggests that there is a real opportunity for policy to move on, by allowing the voices of the former to be heard instead. The report concludes that it is now time for scientific reasoning to drive the creation of economic and financial instruments, with politicians made to fit, and for good financial thinking to take over from ultimately hollow big-gesture politics.

## 1. Introduction

This report is an economist's attempt to add value to the debate surrounding current proposals to drive the creation of a malaria vaccine or vaccines. To help keep things specific, it reviews the ideas contained in the "Malaria Vaccine Technology Roadmap" (MVTR)<sup>5</sup> and in the recent UK and Italian proposal for a purchase subsidy scheme for a malaria vaccine, an 'Advance Purchase Commitment/Contract'.<sup>6</sup> The Malaria Vaccine Technology Roadmap is a discussion document reflecting the views of a wide range of individuals (mostly, but not exclusively, scientists) interested in malaria vaccine development, and is along the lines of several previous documents produced over the years by WHO and other organizations. As yet, it carries no official mandate, and is an informal open forum for the sharing of ideas. The second proposal, of a malaria vaccine APC, is more concrete and seems to have more official backing – recently via the G8 process – but still has a long way to go before becoming a fixed formal mechanism. To help illustrate the views of the malaria community, this report liberally quotes the recorded remarks of those involved in the Technology Roadmap process ('stakeholder' views), and it also reports the private remarks of a wide range of scientific, industrial, and global health experts ('correspondents' with the author during the writing of this report).<sup>7</sup>

This report is a follow-up to the UK Malaria Vaccine Technology Roadmap Stakeholder meeting<sup>8</sup> – where the Roadmap was described as a "living document" and "created and owned by the entire malaria vaccine community"<sup>9</sup> – and a submission to the UK's Department for International Development consultation process for a vaccine advance subsidy scheme, popularized by advocates as an Advance 'Market' Commitment/Contract (AMC).<sup>10</sup> This report, however, tries to avoid the nomenclature 'AMC' wherever possible, given that what is being offered is not market-based at all – but, instead, a potentially highly complicated subsidy scheme. Rather than prejudge the truth of the AMC claim and continue to feed this myth, wherever possible the nomenclature APC, 'Advance Purchase Commitment', is used instead, even though this too can give too much of a sense of security.

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<sup>5</sup> The nomenclature from now on is MVTR (The draft Malaria Vaccine Technology Roadmap is available at [www.malariavaccineroadmap.net/pdfs/roadmap\\_071905.pdf](http://www.malariavaccineroadmap.net/pdfs/roadmap_071905.pdf)), RMSR (The Roadmap Summary results, [www.malariavaccineroadmap.net/pdfs/roadmap\\_results.pdf](http://www.malariavaccineroadmap.net/pdfs/roadmap_results.pdf)), and VMSR (The Vision Meeting Summary Results, [www.malariavaccineroadmap.net/pdfs/summary.pdf](http://www.malariavaccineroadmap.net/pdfs/summary.pdf)).

<sup>6</sup> See recently, "Advance Market Commitments for vaccines: A new tool in the fight against disease and poverty." Report to the G8 Finance Ministers, by Giulio Tremonti, Minister of the Economy and Finance, Italy, London, December 2, 2005, [www.dfid.gov.uk/consultations/amc-report-tremonti.pdf](http://www.dfid.gov.uk/consultations/amc-report-tremonti.pdf). Background papers to the Tremonti Report at: [www.dfid.gov.uk/consultations/background-papers-tremonti.pdf](http://www.dfid.gov.uk/consultations/background-papers-tremonti.pdf).

<sup>7</sup> The author has kept good records of all of this correspondence, and where a remark was not recorded and linked to the person making it, it was not included.

<sup>8</sup> [www.malariavaccineroadmap.net/pdfs/stake3\\_sum.pdf](http://www.malariavaccineroadmap.net/pdfs/stake3_sum.pdf), Oxford, 23 August 2005.

<sup>9</sup> MVTR pii.

<sup>10</sup> [www.dfid.gov.uk/news/files/amc-vaccines.asp](http://www.dfid.gov.uk/news/files/amc-vaccines.asp), and [www.dfid.gov.uk/consultations/amc-presentation-2.pdf](http://www.dfid.gov.uk/consultations/amc-presentation-2.pdf).

The Roadmap process is jointly sponsored by the Bill and Melinda Gates Foundation and the Wellcome Trust. A Roadmap Working Group, consisting of representatives of the sponsors, the World Health Organization, and the PATH Malaria Vaccine Initiative (MVI) has guided the overall roadmap development process. MVI has coordinated the process with the support of Energetics Incorporated.

These two initiatives are highlighted for no other reason than that they are recent, and attracting a great deal of attention, and not because they carry more weight than the extensive body of thinking that long precedes them. It will also become clear that in many ways this report is a defense of the former Roadmap process in the face of the pressures of a few highly vocal advocates pushing for the latter subsidy mechanism,<sup>11</sup> and driving the politicization of the whole policy process.

The author is extremely grateful that the Roadmap debate has been opened to all the malaria vaccine community (even economists) and beyond, and hopes that this paper can help a little bit in clarifying some, but by no means all, of the finance and economics of what is going on. The author was pleasantly surprised to find himself being described by members of the malaria community as ‘independent’ and encouraged to use that independence to critically evaluate the Roadmap and APC from a financial and economics, and even, at times, a malaria science perspective. One of the realizations that eventually dawns is that many of the ‘factions’ in the malaria community are driven by the policy process. One hoped for side-effect of this report is that it will encourage less factious policy by exposing some of the sources of this. Far from being a merely negative assessment of the problems of current policy, the hope is that this report is written with plenty of hope that something better is possible, and with enough positive insights waiting to be explored further that, with a bit more vision, something better can be achieved.

### **Incentives and resource constraints in the face of a difficult and dynamic scientific problem**

Economics is all about ‘incentives’ and the most efficient use of limited resources. Here, these tools of analysis interact with an extremely intricate and dynamic scientific problem. Achieving good incentives and efficient use of resources involves a lot of thinking about how this problem might evolve over time – indeed, over decades – and the expectations of all the different players as the process evolves. The author is not a malaria scientist – he tries to understand it – and he has been known to criticize policy thinkers and economists, for trivializing the difficulties of the underlying scientific problem when thinking about the underlying economic and financial solutions, and conversely for ignoring the ways in which inadequate economic and financial thinking feeds back to impact on the process of scientific discovery. Treading this path runs the risk of exposing the limitations of one’s own understanding of the science. But, with busy scientists having little time to understand the consequences to them of the economic

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<sup>11</sup> Tremonti subtitles his report “A new tool in the fight against disease and poverty,” as if he is describing just another tool in the box. By the time the reader has got to the end of this report, he/she will realize that when we use the phrase APC we are describing a highly interventionist, statist, mechanism. Anything less is immediately open to corruption and capture (but so is the interventionist mechanism).

structures being imposed upon them from above (with those imposing those structures having no inclination to explain all the consequences) it has to be done by someone. Thankfully, some of these scientists have very generously given of their time to help me better understand the hugely challenging and awe-inspiring scientific problems they face. I am extremely grateful to them, but take all responsibility for any remaining faults in my scientific understanding.

### **Part of a thought process**

In many ways this paper is a thought *experiment*, exploring how some pretty standard financial and economic thinking might suggest the possible consequences of the Roadmap and of other current policy processes such as that being pushed by the UK through DFID and the G7/G8 process, in the hope that it might help those who make decisions to know a bit more about what they are doing when they plump for one choice over another and ultimately, in the light of fuller evidence of its impacts, to take full responsibility for what they are doing. Similarly, it is hoped that those involved in more loose and open discussion forums such as the Malaria Vaccine Technology Roadmap can be helped to be more mindful of the dangers of locking in more formal and permanent measures in the less open part of the process.

A key concern is to evaluate whether investors will respond to any of these recent proposals. In particular, investors cannot be expected to respond to schemes stretching 20 to 30 years into the future, if all the implications of such schemes are not fully explained to them, or if they *expect* that such schemes will force them at some point to behave in ways that are contrary to their interests. If investors do not respond, proposals fail, and meanwhile opportunities to instigate approaches that might have worked have been lost. The ultimate judge of the value of policy is not a politician, but a far tougher judge – the collective will of financial markets.

### **There will be imperfections in the report**

Some of the recent proposals for dealing with vaccines have involved literally dozens of individuals.<sup>12</sup> There is only one of this author. There will be weaknesses. In particular, it is clear that there are many opposing and even contradictory economic and financial forces at work; deeper work would clarify which would most likely come to predominate. Perhaps it would not be unreasonable to suggest that the burden of proof on the findings of the body of work that has had hugely more resources given over to it should be a little higher, and that this report has a legitimate obligation, for all its undoubted faults, to question the veracity of some of the heavily-promoted claims made by that body of work?

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<sup>12</sup> The Center for Global Development lists over 100 (including this author) involved in some capacity in their recent report, “Making Markets for Vaccines: Ideas into Action.” April 2005, [www.cgdev.org/section/initiatives/active/vaccinedevelopment](http://www.cgdev.org/section/initiatives/active/vaccinedevelopment). Even a recent paper on the ‘cost-effectiveness’ of a malaria APC, has seven names: Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., Williams, H., “Advanced Purchase Commitments for a Malaria Vaccine: Estimating Costs and Effectiveness.” NBER Working Paper Series Working Paper 11288 [www.nber.org/papers/w11288](http://www.nber.org/papers/w11288), April 2005.

This paper cannot claim to clearly work through every point, but it is hoped that it can also act as a reference source for many of the issues that need to be tackled for a comprehensive solution to be found, and to move debate away from simplistic fixes. It may be painful, but given that the really huge financial decisions and potential mistakes are still off in the future, it is better to have the debate now than wait till it is too late. It is hoped that many of the identified issues will have resonance outside of malaria, particularly for HIV and TB vaccines, and that some of the principles of a solution will have application outside of malaria too.

### **Two product goals and a committee-run purchase-based subsidy scheme**

The Malaria Vaccine Technology Roadmap proposes two strategic goals:

#### **Goal 1:**

*“By 2015, develop and license a malaria vaccine that has protective efficacy of more than 50% against severe disease and death and lasts longer than one year.”*

#### **Goal 2:**

*“By 2025, develop and license a malaria vaccine that has protective efficacy of more than 80% against severe disease and death and lasts longer than four years.”*

### **A committee-run subsidy scheme paying out at the end of the whole development process**

Following the launch in April 2005 by the Center for Global Development in Washington, DC, of a paper titled “Making Markets for Vaccines”<sup>13</sup> there has been heavy promotion of a large, pre-committed, sunk,<sup>14</sup> size-fixed, pool of public funding, to be distributed *after* the goal or goals have been achieved, as large pre-designed subsidies attached to vaccines purchased by ‘eligible’ countries. As we will see later, according to the Tremonti Report and the wording of the Kerry-Lugar Bill, it is now not clear whether these public funds are at least partly deposited in advance or only all at the end of the process.

The claim<sup>15</sup> is that the overall size of the subsidy pool and the allocation of subsidies across ‘winning’ firms over time would be engineered to repay the collective privately-funded R&D costs (including finance costs) of *all* firms (both the ‘winners’ and all the ‘losers’), of all generations of vaccines, for ‘eligible’ countries (and only eligible countries), and there would be rules legally binding firms to supply at low price in the long term: “Vaccine purchases would be subsidized by sponsors until the price was

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<sup>13</sup> CGD, April 2005, *ibid*.

<sup>14</sup> ‘Sunk’ refers to something irretrievable. A sunk investment (as apposed to a fixed investment) is one that has no resale value in any alternative market; bygones are bygones. Fixed investments may be partly or all sunk. The notion is that once set up, the fund is irretrievably committed to the mechanism (though, we will later see that it is not clear that this would, or ever could, actually hold).

<sup>15</sup> It is not clear what the current idea is exactly. The Tremonti Report seems to base itself in various places on the notion that APCs are not pre-set R&D subsidy schemes to motivate multiple parallel developers at all, but procurement devices with the added inefficiency of having pre-set the prices 20 plus years in advance (or not, as the case may be).

reduced to an affordable level as required by the contract.”<sup>16</sup> Since production costs would, it is claimed, be very low (and known to be very low from the start) most of the payment for even the early vaccines would be this R&D subsidy, and not the production costs of the vaccines actually used.<sup>17</sup> According to the Tremonti Report, there would be a committee monitoring all activity, readjusting terms over time, and deciding the returns investors would get (adjusting, late in the process, for the underlying complexity of the science, R&D and production costs, and any other financial help firms had been given, etc.). ‘Winning’ firms would get ‘monopoly’ rights to sales in non-eligible countries that would be separated from the subsidy scheme.

### **Earlier papers**

A series of previous papers sought to explain what needed to be done to make APCs for complicated vaccines like malaria, HIV, and TB more ‘like a market’, and especially to avoid some of the problems of APCs being like a winner-take-all prize, and why this would be extremely difficult to achieve in practice.<sup>18 19</sup> The APC literature until only a year or two ago had emphasized the notion of ‘a’ vaccine – instead of a *dynamic series of vaccines* – resulting from an extremely simple scientific process, involving only private players, paid for only by the subsidy scheme at the end, and involving no interactions with issues like drug R&D and vector control. The author has repeatedly argued that, when used as an R&D funding route for malaria, HIV, or TB vaccines, APC schemes would contain a huge amount of self-fulfilling pressure in the direction of feeding the subsidy pool to the least challenging result, to one or very few players, to encouraging a low-quality high-cost outcome on average, and even to failure and a great deal of waste of political and systems capacity.

The earlier 2004 paper was discussed with a tiny handful of individuals at CGD and the World Bank in Washington in April 2004. The general consensus seemed to be that malaria, HIV, and TB were not suitable targets for APCs, and that this would not be

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<sup>16</sup> Barder, O., Kremer, M., and Levine, R., “Answering concerns about Making Markets for Vaccines.” Center for Global Development, May 2005, [www.cgdev.org/doc/vaccines/ResponsetoFarlow.pdf](http://www.cgdev.org/doc/vaccines/ResponsetoFarlow.pdf), p6.

<sup>17</sup> Jeffrey Sachs claims part-credit for getting the idea going: “In order to stimulate the needed research and clinical testing of new vaccine candidates, I have recommended together with Harvard economist Michael Kremer that donor agencies and the Global Fund to Fight AIDS, TB, and Malaria commit ahead of time to purchasing a successful vaccine on a large scale for distribution in Africa, thereby creating a financial incentive for vaccine research and development,” in *The End of Poverty*, Penguin Books, 2005, pp. 283-4. Sachs has also advocated the idea in the popular press several times, though he has not worked out any of the details of how the proposal might work in practice for diseases like HIV, malaria, or TB. Sachs, J., “Sachs on Development: Helping the Worlds Poorest,” *The Economist*, 1999, 352 (8132), pp. 17-20, and Sachs, J and Kremer, M., “A Cure for Indifference,” *Financial Times*, 5 May 1999.

<sup>18</sup> Farlow, A.W.K., “An Analysis of the Problems of R&D Finance for Vaccines and an Appraisal of Advance Purchase Commitments,” 2004, oxford University Department of Economics, [www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf).

<sup>19</sup> See also Farlow, A.W.K., “The Global HIV Vaccine Enterprise, Malaria Vaccines, and Purchase Commitments: What is the Fit?” Submission to Commission on Intellectual Property Rights, Innovation and Public Health, WHO, March 2005, [www.economics.ox.ac.uk/members/andrew.farlow/GlobalHIVVaccine.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/GlobalHIVVaccine.pdf), and Farlow, A.W.K., “Accelerating the Innovation of Vaccines: Can the Global HIV Vaccine Enterprise, Malaria Vaccine Initiatives, and Purchase Commitments Deliver?” *Innovation Strategy Today*, Vol. 1, No. 2, July 2005, [www.biodevelopments.org/innovation](http://www.biodevelopments.org/innovation).

pursued, in spite of the ‘overbearing pressure’ from some to emphasize an application to HIV, malaria, and TB vaccines. There was even a strong desire to steer away from these early-stage vaccines and to concentrate instead on the development of suitable ‘pull’ instruments for pneumococcal and rotavirus and other late-stage vaccines, and to encourage efforts on developing mechanisms for early-stage vaccines. All concurred that it was a valuable initiative to explore late-stage vaccines, whether or not APCs were, strictly speaking, needed for these (i.e. instead of ‘best practice’ procurement policy, a large procurement fund with competition, good long-term planning, decent and fair contracts, and a reasonable rate of return for firms). It was also agreed that it was imperative not to conflate the problems of late-stage vaccines with those of early-stage, extremely challenging, vaccines like those for HIV, malaria, and TB, given the dangers of trivializing the challenges of the latter, and harming efforts on the former.

**Rebranding an essentially statist scheme with the language of the ‘market’**

Within a year, and for some so far inexplicable reason, some of the ‘what needed to be done’ bit had stuck and suitable ‘market’ language had been appended (“Creating a market rather than a prize solves many of the challenges in designing incentives for R&D”<sup>20</sup>), but the ‘why this would be difficult to achieve in practice’ bit did not. The proposal was renamed (or rebranded?) an ‘Advance *Market* Commitment’ and ended up being heavily marketed as a solution for HIV, malaria, and TB vaccines. The nomenclature AMC, ‘advance market commitment/contract’, was, ironically perhaps, itself generated for ‘marketing’ purposes, and as a way to annul the awkward fact that APCs are devoid of most market-based principles. The reader might try re-reading the last tautological quote as “Solving the many challenges, by solving the challenges, solves many of the challenges,” to get some flavor for the logic driving the ‘market’ argument.

We have ended up with the heavy promotion of instruments that are really just extremely complicated pre-set ex post subsidy schemes run by a committee according to a set of rules, but with discretion because of the complicated nature of the science and the many unknowns. Since such schemes acquire most of their faults when they are badly executed pre-sunk pre-set subsidy schemes, it is slightly unfortunate that they are given the evocative nomenclature of the ‘market’. One side effect is that APCs have been interpreted by some as the only way to interpret ‘pull’ incentives for vaccines. This report finds that this is far from the case, and that there are many ways to employ genuine markets.<sup>21</sup>

The Malaria Vaccine Initiative, one of the driving forces behind the Malaria Vaccine Technology Roadmap, and source of the current leading malaria vaccine candidate, RTS,S/AS02A, has come out strongly in favor of these subsidy schemes. So have BIO Ventures for Global Health,<sup>22</sup> even though the recent Kerry-Lugar vaccine bill pretty

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<sup>20</sup> CGD, April 2005, *ibid.* Summary page of Chapter 4, p41. See also “Our proposal is for a market not a prize. There is no winner-take-all.” Summary page of Chapter 3, p29.

<sup>21</sup> In the case of new malaria drugs technology, see later in this report for uses of ‘pull’ market instruments with commitment elements, that do not employ APC logic or need any of the heroic assumptions of APCs.

<sup>22</sup> [www.bvgh.org](http://www.bvgh.org). Reading press releases of BIO Ventures for Global Health, it seems that they have never had an APC properly explained to them, but have largely interpreted them as large procurement funds or

much clarifies the non-use of APCs for most of the things that BIO Ventures for Global Health may expect them to be used for. The International Aids Vaccine Initiative<sup>23</sup> have also come out in favor of the APC scheme; though it is not quite clear in favor of what, given the range of interpretations of what such subsidy schemes actually are, given the lack of any clear articulation by IAVI itself of what an APC for HIV vaccines actually is even after 7 years of voicing support for such schemes, and given that IAVI draws its analysis of APCs off CGD. It is not clear that many of these organizations know exactly what it is they are supporting. Clearly, we will need large procurement funds to purchase new vaccines, but this is not the same as supporting an APC.

### **Previous debate about two goals**

One correspondent explained that at one previous Roadmap meeting there had been four hours of debate about the two-goal Roadmap structure, with some also arguing that it was a bad idea to set these goals. Indeed, in private correspondence, it has been explained that the 50% figure emerged as a general consensus of the sort of effect that might be considered useful by Ministries of Health in malaria endemic countries. Previous work had suggested that 30% efficacy would make a vaccine cost-effective, but it was considered, in view of the impact of other control measures, that this was probably too low and that something higher would be needed to interest the ultimate customers. Tremonti observes that “The product specifications demanded by developing countries are for child vaccines with efficacy in excess of 70% and limited to 3 or fewer doses. Adoption would be facilitated by a vaccine that can fit within the EPI [Expanded Program on Immunization, of The World Health Organization] which is perceived as the only distribution system.”<sup>24</sup>

As one correspondent put it, however, “if anything, the 50% was related to the efficacy of ITNs [insecticide-treated mosquito nets] which is also around 50%,” and was not to be taken as in any way definitive, there being no particular ‘scientific’ basis to 50%. Nor, it must be added, should there need to be; if terms are not being permanently fixed, and if there is still flexibility for them to rise as scientific possibilities are revealed, and as other control measures are improved, an inspirational goal may have some value. Problems only arise when attempts are made to lock in 50% as an *operational* goal and to even make this the ceiling on efficacy.

This debate is worth revisiting from an economics and finance perspective. The author recognizes the value in having goals for advocacy purposes and as a way to draw in further funding. It is almost certain that the two goals have been set on this basis. However, this paper is not interested in goals that are aspirational, but rather in the implications should the goals ever be made to have genuine *operational value* – something that is being increasingly urged. The danger, as another correspondent put it to the author, is that the goals have limited value scientifically, but because there is no operational connection between them and the rest of the Roadmap, “they start to become

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late-stage product instruments, or they have been badly advised as to what an APC for early-stage vaccines would look like.

<sup>23</sup> [www.iavi.org](http://www.iavi.org).

<sup>24</sup> Tremonti, G. Background Papers, 2005, *ibid.* p35.

dangerous.” Specifically, the Roadmap proposes no operational strategy with milestones that could lead to these goals. The only thing that might give them operational value is an APC.

Besides, if the goals are supposed to incentivize investors to sink private finance into multiple, parallel, and very costly investments, there is no point in having such goals if they are not credible, and investors must therefore *expect* the goals to be genuinely operational – and hence fixed. All funding decisions and incentive structures would therefore have to be geared towards satisfying the two goals. This paper will therefore explore the practical implications of this two-goal structure as it interacts with the APC subsidy scheme.

There was concern amongst some at the UK stakeholders meeting about the use to which the Malaria Vaccine Technology Roadmap might be put, in particular the worry that it might be used to justify funding in ways that would be detrimental to some vaccine researchers, and to others working on malaria in non-vaccine ways, with this funding imbalance legitimized because ‘the vaccine community had been consulted’. Though Roadmap stakeholders were assured that this was *not* the case, one can also see that, perhaps, a tiny minority of very vocal voices are pushing certain proposals more than others. This paper concludes that policymakers and scientists need to be mindful of the dangers, and to find ways to keep control *of the whole process* in the hands of *all* of the malaria community.<sup>25</sup> The overriding principle – just as with any other excursion into the unknown – should be to “guard against the worst, and plan for the best” (as one correspondent put it to the author). The big financial decisions are, thankfully, still some way off in the future. This is an opportune moment for a deep and vigorous discussion before locking in.

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<sup>25</sup> As of the Funders meeting of 17 November 2005, the Roadmap working group planned to commission a synthesis strategy that would focus activities more clearly, and hopefully this will help.

## 2. The Scientific Challenges of Malaria Vaccines

### 2.1. Emphasis on current leading candidates for the goal-1 vaccine

It is said, in the Malaria Vaccine Technology Roadmap, that even with acceleration it is “unlikely that newly discovered candidates will be able to achieve this [2015] goal.”<sup>26</sup> A number of observations are in order:

- a) This seems to suggest that the ‘first generation’ vaccine will most likely have to come from *existing* vaccine candidates. There are about 40 candidate malaria vaccines in clinical trials, with a further 45 or so in preclinical development, and about 20 at the bench research stage. They can be divided into four groups: pre-erythrocyte vaccines<sup>27</sup> that target the initial infection or liver stage of the disease; vaccines for the blood stage,<sup>28</sup> when symptoms appear; vaccines that seek to block parasite transmission;<sup>29</sup> and antidisease agents that reduce the effect of parasite toxicity and pathogenicity.<sup>30 31 32</sup>

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<sup>26</sup> MVTR p5.

<sup>27</sup> Pre-erythrocytic vaccine candidates targeting sporozoites would only prevent disease in a population completely if they were 100% effective. However, this does not mean that such vaccines could not achieve a major impact when used in endemic countries at lower than 100% efficacy as part of a package of measures.

<sup>28</sup> Vaccines using blood-stage antigens should mimic natural immunity, so although still infected, a human host might suffer very much less from the consequences of infection.

<sup>29</sup> Transmission-blocking vaccines would not protect the vaccinated individual against infection/disease but would prevent mosquitoes from spreading the disease. However, such vaccine technology would require extremely good coordination and complete coverage of areas of transmission. In the absence of complete coverage, such a vaccine would decrease the number of infections only in low-transmission areas. Furthermore, despite its efficacy in models, this approach might be limited by overall poor immunogenicity and lack of natural boosting.

<sup>30</sup> Anti-disease vaccines aim to alleviate morbidity by suppressing immunopathological reactions in the host. Antidisease vaccines are based on neutralizing specific parasite components that induce host pathology, leaving the parasite itself directly unaffected.

<sup>31</sup> Carter, R., Mendis, K.N., Miller, L.H., Molineaux, L., Saul, A., “Malaria transmission-blocking vaccines: how can their development be supported?” *Nat Med*, 2000, Vol. 6, pp. 241-244.

<sup>32</sup> Immunisation with entire (irradiated) sporozoites can produce protective immunity. However:

i) The experimental methods of conferring protection via multiple repeated exposures to bites of hundreds of irradiated mosquitoes are currently not practicable at large-scale (Hoffman, S.L., Goh, L.M., Luke, T.C., et al. “Protection of humans against malaria by immunization with radiation-attenuated *Plasmodium falciparum* sporozoites.” *J Infect Dis*, 2002, Vol. 185, pp. 1155-1164);

ii) Attempts to produce the same degree of protection have hitherto failed with parts/moieties of sporozoites (Brown, A.E., Singharaj, P., Webster, H.K., et al. “Safety, immunogenicity and limited efficacy study of a recombinant *Plasmodium falciparum* circumsporozoite vaccine in Thai soldiers.” *Vaccine*, 1994, Vol. 12, pp. 102-108; Kester, K.E., McKinney, D.A., Tornieporth, N., et al. “Efficacy of recombinant circumsporozoite protein vaccine regimens against experimental *Plasmodium falciparum* malaria.” *J Infect Dis*, 2001, Vol. 183, pp. 640-647; Hoffman, S.L., Carrucci, D.J., Rogers, W.O., “Using DNA based vaccine technology and the Malaria Genome Project to overcome obstacles to malaria vaccine development.” In Sherman, I.W., ed., *Malaria: parasite biology, pathogenesis and protection*. Washington DC: American Society for Microbiology, 1998, pp. 545-556);

- b) This implies a focus on candidates that have already been tested. This, some suggest, implies a heavy emphasis on RTS,S. There seems wide support for the notion that, though it may have demonstrated proof of concept (not all agree with what exactly has been proved), it is not at all clear that RTS,S will be the technology on which a successful malaria vaccine will be based, and the author has privately received plenty of lively commentary on RTS,S, much of it concerned with the ‘distortion’ of funding flows in the direction of RTS,S-based approaches. A whole chapter below gathers some of the evidence, for and against. A goal that focuses on those targets that have already been tested, may be too technologically limiting.
- c) Though their numbers have doubled in recent years, only a proportion of candidates are amenable to being turned into products, and this narrows the choice down even further. Recently this seems to have improved. MVI’s Scientific Director, Filip Dubovsky, is quoted as saying that two-thirds of MVI’s potential products are ‘productlike’, or based on technologies that, it is believed, might be scalable and economically feasible for making millions of doses, since selection has been based on a much more rigorous industrial approach.<sup>33</sup> Nevertheless, once practicalities such as ‘manufacturability’ and durability of response are considered, even the pool of current vaccine leads may risk being too small.
- d) This concentrates the search on subunit vaccines, requiring a package of supportive measures, including treatment and prevention – defined to include also R&D funding into better treatment and new methods of prevention – the provision and coordination of which we cannot be certain of achieving. This creates even more uncertainty to investors in vaccine R&D, whether firms, governments, or foundations. None of the cost-effectiveness evidence discussed in Chapter 6 below even considers this as an important issue in the case of lower efficacy vaccines.
- e) Though this pool of potential vaccines is much larger than even a few years ago, it is the result of a relative underspend on vaccine R&D in the past. Is it sensible to base a goal – involving maybe a century’s worth of anything previously spent on malaria vaccine R&D – on this limited investment of the past?

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iii) Guerin et al. observe that difficulties include substantial polymorphism in immunologically important regions of the proteins (epitopes) and also low immunogenicity (Guerin, P.J., Olliaro, P., Nosten, F., Druilhe, P., Laxminarayan, R., Binka, F., Kilama, W.L., Ford, N., White, N.J., “Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development.” *The Lancet Infectious Diseases*, 2002, Vol. 2, pp. 564-573).

<sup>33</sup> See comment of Filip Dubovsky, in Thayer, A.M., “Preventing Malaria.” *Chemical and Engineering News*, October 24, 2005, Vol. 83, No. 43, pp. 85-95.

<http://pubs.acs.org/cen/coverstory/83/8343malaria2.html>.

- f) Is it even obvious that a ‘first generation’ vaccine suitable for use in the target group is amongst those currently in trial? After all, “tremendous scientific challenges remain...”<sup>34</sup> and “the malaria parasite presents exceptionally difficult scientific challenges. Developing a safe and effective malaria vaccine remains elusive despite decades of effort.”<sup>35</sup>
- g) What are the ethical dimensions of such a heavy emphasis on lower-efficacy products? Arguably, if lives can be saved, we should go forward with even a low efficacy vaccine. The dilemma is how to balance R&D funding over time and over vaccines, and how also to balance this R&D with other funding – to save the most lives over time. In particular, a key issue is not to create incentives to overuse, or force the use, of low-efficacy vaccines when the expectation of this overuse harms better outcomes. On the one hand, some of those corresponding with this author observe that it is extremely difficult to judge these issues in advance and that we should not unfairly judge this at a later date with the benefit of hindsight. On the other hand, some correspondents are much more convinced that some of the current avenues of research can be judged even today as much less useful than claimed.

These worries were picked up in the Roadmap process: “There is power but also danger in the 2015 target; it refers to only one vaccine: RTS, S – Who else buys in?”<sup>36</sup> MVI<sup>37</sup> also concludes that “Classical/historical antigens are overrepresented” and that indeed the number of relevant antigens is unknown. Others worry that there is no recognition of “alternative vaccine approaches,” and that we must “ensure scientific concepts are inclusive of ‘neglected’ concepts as well as ‘leading’ concepts.”<sup>38</sup>

## **2.2. Goal-1 50% efficacy for one year: But many scientific unknowns**

The first goal sits alongside claims of multiple scientific difficulties and many out-and-out unknowns,<sup>39</sup> including:

- a) Lack of understanding of parasite-host interaction, with much of this understanding dependent on future developments in genomics, proteomics, etc.;
- b) Lack of understanding of the human immune response, both individually and in populations;
- c) Lack of understanding of selective pressure;
- d) Lack of understanding about durability of protection. What is the impact of early, effective, immunization on long-term health?;

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<sup>34</sup> MVTR p14.

<sup>35</sup> VMSR piii.

<sup>36</sup> RMSR p2.

<sup>37</sup> [www.malariavaccineroadmap.net/pdfs/trm1.pdf](http://www.malariavaccineroadmap.net/pdfs/trm1.pdf).

<sup>38</sup> RMSR p2.

<sup>39</sup> This section only considers scientific uncertainties. There are many other uncertainties (epidemiological, economic, forecast demand, etc.) impacting on the value of particular vaccine attributes at the time of use of a vaccine.

- e) Lack of understanding of the relationships among infection, severe disease, and death in different epidemiological settings;
- f) Lack of understanding of correlates of protection (though there is a discussion as to whether or not this is strictly necessary to develop a product);
- g) A heavy need to integrate into existing intervention strategies, probably much more so the lower the efficacy of a vaccine. Thresholds of optimal efficacy are therefore difficult to assess in advance, and the cost for the overall package is heavily linked to a better understanding of all of the above;
- h) Lack of a clear understanding of the predictive nature of models.

Having said all of this, however, most previous vaccines have been produced with relatively little understanding. While it is no doubt the case that we lack understanding of correlates of protection, one correspondent argued that potency assays which are surrogates for efficacy would be extremely helpful, and that there is a certain amount of confusion in discussions of “correlates” and “surrogates;” by definition, we will never know what assays correlate with efficacy until we have a suitably large database of the assays matched to efficacy trials. Similarly, we just do not know if and how much models can predict. One correspondent observed that it is better to think of models as giving us leads, and that following a lead from a model suggesting protection is arguably more likely to be productive than if the model does not provide such evidence.

**But, what is the significance of all of this?**

The key observation to take away, however, is that this lack of understanding makes it difficult to set *permanently fixed operational goals* in advance, or to exercise an early ‘option’ on knowledge. Indeed, in practically every other area of investment, such lack of knowledge would be regarded as creating a heavy ‘option cost’ from locking in early to the goals of an investment strategy – usually at a horizon of a few years, never mind at a horizon of 20-30 year. As Dixit and Pindyck put it: “When a firm makes an irreversible investment expenditure, it exercises, or ‘kills’, its option to invest. It gives up the possibility of waiting for new information to arrive that might affect the desirability or timing of the expenditure...This lost option value is an opportunity cost that must be included as part of the cost of the investment...Recent studies have shown that this opportunity cost of investing can be large, and investment rules that ignore it can be grossly in error.”<sup>40</sup> Indeed Dixit and Pindyck observe that required ‘hurdle’ rates for investors are typically three or four times the cost of capital.

An APC is an investment instrument based on investment rules with irreversibility written all over them. The difference is that the option cost is in terms of lost higher quality outcomes and lives. Indeed cost and ‘quality’ are flip sides. The observation of ‘lower quality on average’ being forced through via an APC, is linked to the fact that firms are being forced to invest ‘early’ without full knowledge of the scientific possibilities. This forces them to face higher option costs (hence finance costs) which is picked up in a lower average quality for given amount of public expenditure via an

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<sup>40</sup> Dixit, A.K., and Pindyck, R.S., *Investment under Uncertainty*, Princeton University Press, 1994, p6.

APC.<sup>41</sup> Indeed, analyzing *when* to set *operational* goals is part of the overall option pricing problem. The author has discussed option-based problems with some of those now pushing malaria, HIV, and TB vaccine APCs; the problems are acknowledged privately, but not discussed publicly. Option prices are effectively set at zero in the models used to support APCs.

### **2.3. The human immune response**

Malaria is a chronic infectious disease caused by parasites that evolve along with their hosts. A variable and complicated protein structure allows the parasite to hide immunoreactive portions and avoid the human immune system. As Van de Perre and Dedet put it: “How could such a complex infectious machinery, produced by more than 5000 genes and programmed to adapt to diverse host-cell species, such as that in *P. falciparum*, be controlled by an immune response triggered by simple antigens? Several decades of research into parasite vaccines have tried to answer that question.”<sup>42</sup> This contrasts with most other acute infectious diseases, for which it is relatively easy to reproduce the sterile immunity that follows natural infection.

One correspondent observed: “This question cannot be answered from an armchair or from a laboratory: It must be answered in the clinic and the field.” We should not underestimate the difficulties this causes for those trying to set efficient funding and incentive mechanisms. Learning in the clinic and the field is wrapped up with the levels and direction of funding, and we need to take care not to distort the one given the way it can distort the other in return. And we certainly should not trivialize the difficulties away as has been done in much of the recent economic analysis of the problem.

#### **Natural immunity**

Few, if any, individuals become completely immune to malaria, but those living in malaria-endemic regions slowly develop functional immunity through regular malaria challenge through numerous infective bites over time, and progressively acquire the ability to contain malaria parasitaemia. Once attained, immunity generally persists so long as individuals remain in areas of stable transmission. This is even the case in low transmission regions.<sup>43</sup> In high transmission areas, there is an initial phase of clinical immunity, followed by a stage of anti-parasite immunity resulting in limited parasite numbers, replication, and burden within the human host.<sup>44</sup>

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<sup>41</sup> This is then complicated by the reputational problems of producing low-efficacy outcomes. No firm would voluntarily enter into such arrangements, unless somehow they, perhaps, perceived that they had a first-mover advantage that was sufficiently large to overcome some of these inefficiencies.

<sup>42</sup> Van de Perre, P., Dedet, J.P., “Vaccine efficacy: winning a battle (not war) against malaria.” *The Lancet*, 2004, Vol. 364, pp. 1380-1383.

<sup>43</sup> Mbogo, C.N.M., Snow, R.W., Khamala, C.P.M., Kabiru, E.W., Ouma, J.H., Githure, J.I., Marsh, K., Beier, J.C., “Relationships between *Plasmodium falciparum* transmission by vector populations and the incidence of severe disease at nine sites on the Kenyan coast.” *American Journal of Tropical Medicine and Hygiene*, 1995, Vol. 52, No. 3, pp. 201-206.

<sup>44</sup> Schofield, L., “Antidisease vaccines.” *Chemical Immunology*, 2002, Vol. 80, pp. 322-342.

The nature of the induced immune response depends on many factors involving the antigen, its presentation, the host, human and parasite genetic variability, parasite-induced immunosuppression, and other factors.<sup>45</sup> Some Roadmap participants worried that “the inability of current analytical tools to permit study of more than one or a few variables at a time is a major shortcoming,”<sup>46</sup> preventing researchers from reliably knowing which antigens, adjuvants, and formulations will confer maximum protection. Others argued the need for more “mathematical modeling of parasite and immune response to quantify interrelationships and develop predictive tools.”<sup>47</sup> However, as one correspondent put it, it is not clear how helpful this would be. There is a tension, with the best sometimes the enemy of the good; sometimes we do not have the luxury of time to pin down all interrelationships before trying out approaches. The lesson is that the “approaches to be tried out” need to be decided more openly and carefully than if we had the benefit of knowing all interrelationships.

Natural immunity primarily affects the severity of disease and not infection. Some argue that an effective vaccine will need to provide better protection than naturally acquired immunity.<sup>48</sup> However, others argue that if we could accomplish through vaccination what nature does through disease – i.e. induce the state of immunity described above – millions of lives could be saved. One possible interpretation of the latest results from the GSK candidate vaccine, RTS,S/AS02A, is that it is doing just this – ‘bridging’ children over the early months and allowing them to develop naturally-acquired immunity while experiencing less disease burden. However, not all agree on exactly what is going on in this case, as we will see below.

The Roadmap recognizes that though “mechanisms by which humans acquire natural immunity in malaria-endemic areas have been partially identified, definitive protective mechanisms remain elusive,”<sup>49</sup> and that “work has been applied to understanding natural malaria immunity, including studies on differences between protected and unprotected children, but no clear answer has emerged.”<sup>50</sup> We also need much more information about immune responses in pregnant women and fetuses, in particular whether cytokines (proteins that mediate the immune response) can lead to injury of the fetus. We also have poor understanding still of the immunological immaturity of infants.<sup>51</sup>

### **Partially effective vaccines**

It is not fully clear what the impact on severity of disease would be in the short-run and the long-run of a partially effective malaria vaccine, given these limitations in our understanding. For example, a vaccine that confers limited protection (or that *seems* to

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<sup>45</sup> Mohan, K., Stevenson, M.M., “Acquired immunity to asexual blood stages.” In: Sherman, W., ed. *Parasite Biology, Pathogenesis and Protection*, 1998, Washington, DC, ASM Press.

<sup>46</sup> MVTR p23.

<sup>47</sup> MVTR p17.

<sup>48</sup> MVTR p14.

<sup>49</sup> MVTR p14.

<sup>50</sup> MVTR p9.

<sup>51</sup> As we will note below, infants are the ultimate target for a malaria vaccine, and the recent GSK candidate malaria vaccine has not been trialled in infants yet (average age so far of 3 years), though one might not have picked this up easily from the popular press coverage.

confer some limited protection) in the first year of life, may result in less protection for some in the population later, maybe even for those who received protection from the original vaccine, but who thereby failed to develop a natural long-term immune response. And what is the impact of the vaccine program on those who got no protection, and their lack of response in return back onto those who benefited from the program?

Similarly, when integrating other control measures with a vaccine, we may get responses that are not completely clear from the outset, affecting the value of the malaria vaccine being targeted. Parasite growth may be restricted by certain immune responses, but the parasite is also able to benefit from immune responses that lead to chronic infection that enhance parasite transmission to the mosquito.

For example, it has been discovered that severe malarial disease shifts from children younger than five years toward older age groups when rates of entomological inoculation fall below 10 to 20 bites per year (Snow et al. 1997<sup>52</sup>). There have also been cases where whole populations have become vulnerable to epidemic malaria following highly successful malaria control in previously high-transmission areas, because of the lower build-up of natural immunity. Mouchet et al.<sup>53</sup> detail a severe epidemic of *P. falciparum* malaria on the island of Madagascar after a highly successful program<sup>54</sup> between 1949 and 1960 – involving a combination of IRS and mass chloroquine treatment – had almost completely interrupted malaria transmission in the highland regions. Following reemergence in 1986, high death rates occurred in *all* age groups for two years until brought back under control. One correspondent observed that the Madagascar case suggests that the key to a robust solution may lie in preventing disease but not in preventing parasite exposure.

As Snow observes: “*People dying of malaria ... that’s over a million deaths a year. But there are ten times, 20 times, 100 times more people that develop severe complications of malaria that are desperately life threatening but do survive. And as part of this survival, there are risks ... from behavioral disturbances and difficulties in learning through to very severe disabilities such as spasticity, total paralysis down one side of the body ... to deafness and blindness and epilepsy. Many of those children with epilepsy may die because they fall into fires or down wells.*”<sup>55</sup>

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<sup>52</sup> Snow, R.W., Omumbo, J.A., Lowe, B., Molyneux, C.S., Obiero, J.O., Palmer, A., Weber, M.W., Pinder, M., Nahlen, B., Obonyo, C., Newbold, C., Gupta, S., Marsh, K., “Relation between severe malaria morbidity in children and level of *Plasmodium falciparum* transmission in Africa.” *The Lancet*, 1997, Vol. 349, pp. 1650-1654.

<sup>53</sup> Mouchet, J., Laventure, S., Blanchy, S., Fioramonti, R., Rakotonjanabelo, A., Rabarison, P., Sircoulon, J., Roux, J. “The reconquest of the Madagascar highlands by malaria.” *Bulletin de la Societe de Pathologie Exotique* (in French), 1997, Vol. 90, No. 3, pp. 162-168.

<sup>54</sup> Hamon, J., Mouchet, J., Chauvet, G., Lumaret, R., “Review of 14 years of malaria control in the French-speaking countries of tropical Africa and Madagascar. Considerations on the persistence of transmission and future prospects.” (in French) *Bulletin de la Societe de Pathologie Exotique Filiales*, 1963, Vol. 56, pp. 933-971.

<sup>55</sup> Snow, R.W., Kenya Medical Research Institute, 2002. Quoted in Arrow, K. J., Panosian, C. B., and Gelband, H., *Saving Lives, Buying Time: Economics of Malaria Drugs in an Age of Resistance*. 2004, Committee on the Economics of Antimalarial Drugs, Board on Global Health, Institute of Medicine of the

### **Duration of protection**

The first Malaria Vaccine Technology Roadmap goal suggests targeting a vaccine with a protective effect of only one year. The reasoning is that the most vulnerable are the youngest and that a one year effect may have high value. Infants born to functionally immune mothers, are relatively resistant to infection and severe clinical episodes of malaria for the first 6 months of life via the transplacental antibody called maternal IgG. Infants also get some protection via high levels of fetal hemoglobin. It is over the following few years that children experience greater susceptibility to severe and fatal malaria, before immunity starts to operate.

There are three main ways that malaria can contribute to death in children. First, overwhelming acute infections can kill children very quickly via seizures or coma (cerebral malaria). Second, repeated malaria infections contribute to the development of severe anaemia, greatly increasing the risk of death. Third, malaria infection in pregnant women can lead to low birth weight, with this a large risk factor for death in the first months of life.<sup>56</sup> The exact proportion of total malaria deaths in children under 5 is unclear. Snow et al.<sup>57</sup> calculate about 65 percent, while for the WHO<sup>58</sup> the proportion is much higher, at 86 percent.

However, this author has been repeatedly told by correspondents that our understanding of parasite-host interaction at both the individual and at the population level – combined with the possibilities of better vaccines (if we are not distracted from targeting them in the first place), the potential decline in effectiveness of subunit vaccines, the fact that we are interested in a joint mix of vaccine(s) and control measures, and the fact that we are adjusting all of these things under a binding budget constraint – could end up telling us that this one-year goal is *not* the most efficient target, and that it might even have adverse consequences. Again, the principle lesson is that it makes sense to keep an open mind and not to lock in just to support funding instruments like APCs.

### **Shifting the burden of disease**

There is a danger that any malaria control tool that is highly effective will impair immunity and shift the age base of cases and deaths onto those higher up the age range. While this may be perfectly efficient and within the bounds of possibilities for rich-world military personnel and tourists and others visiting malaria-endemic regions, it is likely to create extra costs and burdens on developing countries.

One correspondent, however, argued that this observation needs to be treated with a great deal of care, since propagation of such an argument had previously had a deleterious effect on the uptake of ITNs, and experience had since shown that this fear was

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National Academies, The National Academies Press, Washington, D.C. [www.nap.edu/books/0309092183/html](http://www.nap.edu/books/0309092183/html), p154.

<sup>56</sup> WHO/UNICEF. *The Africa Malaria Report 2003*. World Health Organization, Geneva, 2003.

<sup>57</sup> Snow, R.W., Craig, M.H., Newton, C.R.J.C., Steketee, R.W., “The Public Health Burden of Plasmodium Falciparum Malaria in Africa: Deriving the Numbers.” 2003, Bethesda, MD: Disease Control Priorities Project.

<sup>58</sup> WHO. *World Health Report 2002*. World Health Organization, Geneva, 2002.

unfounded, in this case at least. In the case of RTS,S, so far there is no evidence that this candidate vaccine has a selective effect on the parasite population (this was not found in the trial in The Gambia or in the Mozambique study), although the situation could be different if the vaccine were ever widely introduced. We just do not know.

### **The economic/finance point**

Yet again, the key observation is an economic/finance one. *Operationally* locking in early on a one-year duration presumes a willingness to exercise a risky ‘option’. It also forces firms to face investment risk and a range of production cost problems that have largely been unexplored, something that we will try to do in Chapter 5.

Systems that require *preset* fixed terms – maybe to feed a pre-set operationalized APC – will naturally end up being set much less efficiently given our lack of understanding of how the parasite and human immune system interact, including at the population level. This also suggests that more basic science is needed – in particular a more complete understanding of the human response to *P. falciparum*, and the way humans and parasites interact – before operationalizing 50% efficacy and ‘one year’ duration as a ‘good’ goal and targeting large purchase subsidies (indeed, as we will see, probably *all* of the available subsidy funding) via a fixed APC at it. One correspondent doubted that basic science would help much in this regard in the near term, and that the 50% goal was based on a ‘guesstimate’ of cost-effectiveness, and that we needed to be able to proceed mindful of the potential dangers but not choked into doing nothing, and mindful also of the special risks faced by firms investing heavily in malaria vaccine R&D.

## **2.4. Polymorphism and antigenic variation**

The Roadmap recognizes parasite polymorphism as a highly challenging phenomenon. The Bethesda stakeholders meeting expressed the fears that “Polymorphism creates the fear that we will develop a good vaccine, license it, and immunize infants in region. The vaccine then exerts selective pressure that leads parasites to evolve to reduce efficacy...History has taught us that malaria does evolve, and we must avoid loss of efficacy in the longer term.”<sup>59</sup> However, it also recognized that polymorphism “also presents opportunities, as polymorphic antigens can potentially become target antigens for new vaccine concepts.”<sup>60</sup>

Similarly, “antigenic variation in current parasite populations can render vaccines ineffective against certain variants, thus diluting their effectiveness.”<sup>61</sup> Antigenic variation is distinct from polymorphism; it refers to the ability of a single clone of parasites to display a variety of antigens of the same general structure but with different antigenic specificities on different cells in the population. This allows a fraction of the population destroyed by an immune response to be replaced by a fraction which has hitherto been too small to induce an immune response. The most important antigen type

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<sup>59</sup> RMSR p4.

<sup>60</sup> MVTR p9.

<sup>61</sup> MVTR p20, MVTR p31.

involved is the variable surface antigen PfEMP1.<sup>62</sup> A single parasite clone contains about 50 different copies of the gene for PfEMP1. The key fact is that the genome of the clone codes for all the variants.<sup>63</sup>

During chronic infection, each wave of parasitaemia expresses a new variant surface antigen; parasite multiplication can continue apace even when there are antibodies present, since the antibodies are targeted at the previous parasite wave.

The multistage lifecycle of the parasite generates a number of challenges:

- i) Frequently, the proteins expressed by each of these lifecycle stages are antigenically distinct. For example, if a vaccine manages to achieve high levels of antiparasite antibodies (to defend against the sporozoites inoculated into humans by the Anopheles mosquito), these antibodies generally do not recognize the asexual erythrocytic stages that follow;
- ii) For many of these genes-proteins, there is multiple allelic or antigenic variation. A single individual can be infected simultaneously with at least eight different strains all varying at critical T- and B-cell epitomes;
- iii) This is further complicated by extensive within-strain antigenic variation.

#### **Ways to tackle polymorphism and antigenic variation**

There are two potential short-term countermeasures to these problems. Either monitor changes in *P. falciparum*'s genotypes over time in vaccinated populations, and modify the vaccine. Or use multiple vaccines that are alternated on a delivery schedule to minimize the parasite's ability to evolve to avoid one particular vaccine. The author is unaware of any economic or financial analysis of the expected costs, risks, or tradeoffs of these approaches. Both countermeasures would require production capacity that may have to be planned well in advance yet be of limited and uncertain use (thus heavily raising the average production and financing costs of such vaccines, generating consequences that we will explore below). And both would present a big challenge to any incentive device, such as APCs, designed to force private firms to sink private equity finance into such activities, to be paid off ex post through product subsidies. How could such mechanisms be set even remotely efficiently and not lead to perverse incentives? The notion of holding back APC payments to see if there has been sufficient long-lasting properties of a particular vaccine is hardly worth even commenting upon.<sup>64</sup>

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<sup>62</sup> *P. falciparum* erythrocyte membrane protein 1.

<sup>63</sup> Apparently, there has been some discussion about the parasite becoming more *virulent* in the face of an imperfect vaccine (this is certainly the case for dengue virus, such that a future dengue vaccine will need to tackle all four virus serotypes). I am aware of the debate and, yet, also the uncertainty surrounding this claim. Were this to be true, it would even further complicate calculations of the value of the early less efficacious vaccine, and of how to set up funding mechanisms. However, there is some strongly held disagreement with this claim.

<sup>64</sup> A few clues for why it would not work: high compounding of capital cost at the time of such holding back (such that it would make so little sense for many products that investors would not bother investing in the R&D for them in the first place); the competence (or lack thereof) of a committee to set terms right from the start; risk of time-inconsistency if the rules are set at the start to contain flexibilities, with this undermining R&D incentives; massive rent-seeking incentives, including incentive to try to capture the pay-out scheme; high strategic value in reducing the number of competing multiple developers, hence dangers to any 'collaborative' activity; financial risk to other developers given the fixed pool of available

A longer-term measure might be to develop low-dose, whole-parasite vaccines to circumvent antigen selection difficulties and polymorphism, or to make a serious attempt at an attenuated vaccine.<sup>65</sup> But these all involve more costs and are difficult to incentivize. We find, below, that they also become more risky in light of goal one.

**Polymorphism, antigenic variation, and other scientific problems trivialized away**

It is perhaps no wonder that recent analysis in favor of setting up the funds and institutional apparatus for distributing ex post R&D subsidies via an APC has trivialized all of this scientific difficulty out of existence.<sup>66</sup> Even as recently as February 2005, Michael Kremer, the principle thinker behind such models, was still talking about *the* malaria vaccine and *the* malaria vaccine market: “Anyone developing *the* vaccine captures *the* market.”<sup>67</sup> One very senior malaria vaccine figure exclaimed in private correspondence: “There is great danger in such simplicity!”

Polymorphism and antigenic variation are difficult for scientists to deal with, and would be a huge – probably insurmountable – challenge for a pre-set size-and-time-limited subsidy scheme to have to deal with. The needed complexity of the implied ex post subsidy pattern to make any of the above countermeasures work, and hence to create ex ante incentives to invest in those measures in the first place, would be extreme. What if all the pool of subsidy has already gone when the problem starts to bite, or, more to the point, what if investors believe this will be the case and do not invest in the first place? In the absence of price signals, what is the competence of the committee running the subsidy scheme to actually incentivize behavior against polymorphism and antigenic variation, and the ex ante risk to developers that they will not be appropriately rewarded for their privately-funded activities to try to tackle these problems?

**Rent-seeking and corruption created by an APC harms efforts to tackle these problems**

Many of these scientific problems are complicated by ‘rent-seeking’ pressures. Rent-seeking refers to what happens if a large amount of economic ‘rent’ is created that firms then have an incentive to spend resources trying to acquire.<sup>68</sup> We will come across rent-seeking and corruption many times below, since these are symptomatic of ‘windfall’ subsidy schemes of the APC variety. Again, it is crucial to distinguish between competitive procurement mechanisms for already-existing products (that may involve subsidies) and APC mechanisms as genuine R&D instruments. In the latter case, vaccines

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subsidy, harming *their* incentive to invest in R&D, etc. Kremer, M., and Glennerster, R., *Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases*. 2004, Princeton University Press.

<sup>65</sup> See VNSR p27 for the details.

<sup>66</sup> A key driving paper, Kremer, M. Appendix 3 ([www.pm.gov.uk/files/pdf/Appendix%203.pdf](http://www.pm.gov.uk/files/pdf/Appendix%203.pdf)), is a remarkable example of this.

<sup>67</sup> Kremer, M., *The Lancet*, February 26, 2005, Vol. 365, p753.

<sup>68</sup> A simple example of economic rent: Imagine what would happen if a radio broadcaster announced that a pot containing a million pounds is hidden somewhere in a large London park. The efficient result may be for one person to be selected by lottery to go and find it (spending a day looking around). The radio broadcast ensures that most of the value of the pot of money is wasted on tube fares and the time of all those responding by rushing in to central London to search for it.

are supposedly costing \$1 to manufacture and most of the cost (\$14 of an overall \$15 payment, \$24 of an overall \$25 payment, etc.) per course of treatment, recorded at point of use (to help tackle the corruption), is the subsidy to cover *previous collective* R&D costs of *all* private firms and not just of the ‘winner’ firm. This is the source of the economic ‘rent’, and the fuel for corruption.

If the marginal return to rent-seeking and corruption is higher than the marginal return to creating ‘quality’ for any fixed subsidy, then economic activity is absorbed in rent-seeking and corruption costs, at lower average quality of outcome (interpreted broadly to include also any delay in vaccine discovery), and more lives are lost. Crucially, firms might rather prefer avoiding schemes that create these later incentives to rent-see and corruption, given the reputational damage caused by such behavior, and might prefer alternatives that avoid having large chunks of their (expected) R&D costs dependent on subsidies distributed at the end by a committee.

## **2.5. Subunit and combination vaccines**

At the moment, researchers have been focusing on about 12 of 40 known antigens expressed during stages of the parasite life-cycle; individual vaccine candidates designed around one or a few synthetic or recombinant antigen ‘subunits’ have been the main focus of attention. This is despite the fact that only one recombinant vaccine based on this approach – for hepatitis B – is commercially available, and the approach risks duplication and unnecessary expense. One correspondent argued that there has been an overemphasis on inappropriate antigens, particularly as a result of looking for immunogenicity in mice, given that *Plasmodium* parasites are highly specific and adapted to their hosts. Stakeholder feedback to the Roadmap argued that:

“Even vaccine-induced protection is likely to involve a variety of immune mechanisms, so concentrating on single immune responses may be inadequate.”<sup>69</sup>

“The biological complexity of the plasmodium parasite will make it difficult to achieve very high efficacy, especially for single-antigen subunit vaccines.”<sup>70</sup>

“Combination, live-vectored, or attenuated whole-parasite approaches may ultimately offer the greatest potential for highly effective vaccines capable of providing long-term protection.”<sup>71</sup>

More bluntly, other Roadmap stakeholders commented that “the 2020 [now set back to 2025] goal will require combination vaccines.”

Others, in correspondence, however argued that a recent apparently positive subunit-based result based on a limited subclass of all subunit possibilities, suggested that it

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<sup>69</sup> MVTR p25.

<sup>70</sup> MVTR p39.

<sup>71</sup> MVTR p21.

would be premature to rule out a subunit approach just yet. Others observed that all of the above may be true, but that in view of the likely cost saving of even a single subunit vaccine, we “need much more data in addition to theory,” and that it is “too early to say we will need combinations...we might or even...we probably will.”

Combination vaccines may include multiple antigens from the same stage in combination with diverse antigens from other stages to avoid vaccine failure due to polymorphism and antigenic variation in diverse parasite populations. Such combination vaccines will need good access to vaccine components and a great deal of information sharing. There are dangers that if subunit vaccines are explicitly targeted in the first goal – especially if a big reward attaches to a ‘winning’ subunit vaccine – this will disincentivize such ‘sharing’. After all, ‘sharing’ for the greater second goal already has next to no present discounted commercial value (see below), while the commercial value of not sharing is now much higher than it was before.<sup>72</sup>

### **Equity finance and combination vaccines**

If there is a strong equity finance element underlying malaria vaccine R&D (as is standard for the pharmaceutical industry<sup>73</sup>), there *are* big risks to individual investors from ‘sharing’ any information that is of a ‘public good’<sup>74</sup> nature. We will return to the issue below, but it is not clear that equity markets will price a positive collective gain in to an individual firm’s share price to compensate for the ‘individual losses’ of any privately-funded activity that is then collectively ‘shared.’<sup>75</sup> When one considers their large, fast-growing, sunk costs, is it realistic to expect firms to ‘share’ for the much more distant combination vaccine that has no commercial value? Why should firms act in ways that threaten their investments, especially if they cannot be sure of the committee running the subsidy scheme? Some firms are likely to be confused; not wanting to work on a lower-efficacy subunit vaccine but unsure if the privately-financed development of a higher-efficacy combination vaccine will be supported. Bluntly, it is not clear how combination, live-vectored, or attenuated whole-parasite approaches could really be incentivized except in a framework explicitly targeting such vaccines from the start.

The Malaria Vaccine Vision Statement observes that “Single antigen subunit vaccines alone are not enough” and that the “subunit paradigm started in 1983; it is a lot more difficult that ever imagined and *may never deliver a vaccine*”<sup>76</sup> (emphasis added). Others, however (in private correspondence), observe that only one antigen, circumsporozoite protein (CSP), has so far been systematically studied, and it has nevertheless resulted in a vaccine with some efficacy (RTS,S/AS02A), and that this suggests that this Vision Statement comment may be a little premature. The key lesson, once again is an economic

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<sup>72</sup> The rate of discounting is already high, but even *more so* once it is recognized that firms may simply not believe that they will be able to internalize the value of sharing even as sharing jeopardizes their payoffs from earlier goal 1 vaccines.

<sup>73</sup> See Farlow 2004 Section 12 (and below) for the reasons for this.

<sup>74</sup> A public good is one that is provided in the same amount to all ‘consumers’. They may each value it differently, but they face the same amount.

<sup>75</sup> Incidentally, this suggests much more attention to ‘new’ financial ‘instruments’ to encourage this ‘sharing’, cf. Farlow 2004 and 2005.

<sup>76</sup> VMSR p7.

one. The strategic decision to target subunit vaccines via goal 1 – and even to narrowly target funding *amongst* subunit vaccines – should not be taken lightly. The overriding principle should be not to narrow down too early when seemingly promising results come in from trials.

## **2.6. New technology**

Throughout its life cycle, the parasite causing malaria presents different antigens at different times to the immune system, making it highly adaptable against attack. Yet, till recently “antigen choice [for vaccine development] has been dominated by the arbitrary order in which antigens have been identified.”<sup>77</sup> The sequencing of the *P. falciparum* genome in 2002 generated more than 5,000 potential targets. Eventually this may contribute to development of vaccines, but it will take five to ten years to turn antigens into proper vaccine candidates. High throughput approaches are only just being developed and they already indicate potentially about 1,400 proteins. As Rabinovich puts it “in a single stage, three-quarters of the 684 proteins that have been identified are either hypothetical, have never been identified, or are irrelevant. We are not yet sure what we have. The question for the vaccine target, at least against something as complicated as malaria, is how to screen these proteins when complex evaluation in model systems (human or animal) is required.”<sup>78</sup>

The Roadmap recognizes that “Scientists are just beginning to apply new genomic and proteomic tools to find new vaccine candidates – with some promising results,”<sup>79</sup> and that “new tools for understanding interactions affecting the human immune response are emerging from diverse disciplines.”<sup>80</sup> Genomics is helping to clarify what the target immune response might be, though it is a long way short of a specific answer; it is stage specific and complex, and, indeed, proteomic data is indicating that more antigens are expressed in multiple stages. This again suggests that setting a low *operational* goal before all of this is understood, is bound to lead to inefficient outcomes. Fixing terms early means that results can never get better on average, in light of the unraveling of knowledge.<sup>81</sup>

Indeed, APC subsidy schemes are asymmetric in their attitude to technology. The quality bar can only ever be lowered, but never raised. When the bar is lowered, depletion of the subsidy pool is triggered or accelerated by a product below the original stipulated standard. This is explained several times in the Tremonti Report.<sup>82</sup> Unfortunately,

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<sup>77</sup> Richie, T.L., and Saul, A., “Progress and challenges for malaria vaccines.” *Nature*, 2002, Vol. 415, pp. 694-701.

<sup>78</sup> Rabinovich, R., “Progress Towards a Malaria Vaccine”, in de Quandros, C.A., Ed. *Vaccines Preventing Disease and Protecting Health*, PAHO, 2004, pp. 211-212.

<sup>79</sup> MVTR p9.

<sup>80</sup> MVTR p3.

<sup>81</sup> Again, to remind the reader, we are not talking about *inspirational* goals, but about *operational* goals that are fixed, for example, to satisfy an APC, an APC that cannot be altered to raise requirements later.

<sup>82</sup> Tremonti, G. Background Papers, 2005, p28: “Specific elements of TPPs may need to be modified, for example where significantly changed circumstances or scientific advances clearly indicate that initial TPPs are unachievable...and *only to lower TPP requirements. Increasing standards at a later date would be*

Tremonti fails to realize that whilst this asymmetry removes the risk to any one firm that the bar will be raised for it, the ability to lower the bar for any firm, forces risk on to all other firms, and that even the *possibility* of the bar being lowered undermines the value of investments.<sup>83</sup>

But exactly how high is this ‘option’ cost, given potential future technology? And, given possible technological advances, what is the point of a target to supposedly motivate investments, if investors know that it can be abandoned, and is therefore not credible?

Observe that this option cost already exists, and is probably extremely large in an area like malaria vaccine R&D, where technology is on an upwards trajectory. We discuss this in chapter 9 below. Any early investors know that ‘new’ technology will undermine their investments on average. This is an extra ‘option cost’ on top of any already high capital costs.<sup>84</sup>

Indeed, the first goal even starts to limit the expected technological discovery in the future. We are told, for example, that “Trial design should carefully consider ways to build a better understanding of *vaccine-specific* protective immune response,”<sup>85</sup> (emphasis added). Short of clinical trials themselves, there is no screening tool that gives positive predictive value that a candidate malaria vaccine will work; we have to rely on a highly empirical process driven by data drawn from clinical trials. Thankfully, compared with other diseases, malaria allows us to do challenge trials with pre-erythrocytic vaccine candidates, with the force of infection so strong that individuals are quickly able to show a response when exposed to the parasite, with indications as to whether or not vaccine candidates have an impact from trials as small as 10 or 20 individuals.

## **2.7. Evidence that a malaria vaccine will ultimately work**

This author has come across a diversity of opinion as to whether a useful malaria vaccine is ultimately achievable. On the one hand, there is “skepticism that a vaccine is

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*unfair to firms that invested on the basis of the initially-established TPPs,”* (emphasis added), though it does not seem equally obvious to Tremonti that lowering standards for a firm at a later date would be unfair to all *other* firms that invested on the basis of the initially-established TPPs. Yet again, Tremonti lets slip that he is only thinking of one firm as potentially being of interest to policymakers. Also p27: “It is important that the IAC should not, however, ‘raise the bar’, since the firms will invest on the basis of the TPPs originally defined.” And p38 “The terms of the agreement could be revised accordingly – although *not to raise the bar* in terms of the requirements for target vaccines,” (emphasis added). For some reason “changed circumstances and scientific advances” are only ever envisaged as going in one possible direction – in the direction of necessitating a lower bar.

<sup>83</sup> Why do the people who frame these documents never think through obvious financial issues like this? The inclusion of such terms makes one wonder just how many firms Tremonti had in mind. The risk is only non-existent to other firms if there are no other firms to worry about.

<sup>84</sup> This is even more reason to believe that the 6% discount rate used in the Tremonti Report for discounting future payments is so low as to verge on the ridiculous (but more on this below).

<sup>85</sup> MVTR p31.

feasible.”<sup>86</sup> On the other hand, the Roadmap files say that a “malaria vaccine appears ultimately achievable.”<sup>87</sup> This later claim flows from various observations:

- 1) We know that those in endemic regions regularly exposed to infection acquire protective immunity against severe disease and that this suggests that ultimately a vaccine may be possible. As pointed out in the Bethesda Roadmap stakeholders meeting<sup>88</sup> this is a major distinction from HIV. However, it was also commented at the UK Roadmap Stakeholders meeting that there is more agreement over the routes towards a vaccine in the case of HIV than in the case of malaria;
- 2) Passive transfer of antibodies helps protect human volunteers;
- 3) Irradiated plasmodium sporozoites protect about 90% of human volunteers from malaria challenge (though this involves a complex process over many months involving exposures to batches of live-attenuated sporozoites involving a thousand immunizing mosquito bites). We do not yet know what underlies this response, but studies indicate that it involves T-cell responses directed at parasite proteins expressed on the surface of infected hepatocytes;<sup>89</sup>
- 4) The Roadmap alludes several times to the recent GSK result of the most advanced candidate in clinical trials. For example, we hear that recent “evidence shows that a malaria vaccine that prevents severe disease and death in children under five can be achieved.”<sup>90</sup>

It is not clear to this author what *exactly* any of these observations alone proves about the ultimate achievability of a useful vaccine of any particular efficacy or duration, and especially of a goal-1 vaccine. The observations say very little about the value of 50% or 80% efficacy *per se*. If the first three observations drive thinking on ultimate achievability, and any *operationalized* target, then it is not clear that targeting a partially effective vaccine would, via its deemphasizing of the value of more effective vaccines, not just aggravate or delay ultimate achievability.

The fourth observation is based on just one study. However, some argue that this study does not show all that it claims to demonstrate or, perhaps more precisely, what certain politicians and some of the media claim it demonstrates. In addition, RTS,S has still not been trialled on infants, the ultimate target group. This is critical if the aim is to incorporate a vaccine into the existing schedule of EPI vaccines that reach around three-quarters of infants worldwide. Given the huge scientific risks still present in this case, it would be a bit extreme to bias targets, all incentives, and funding based on this.

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<sup>86</sup> VMSR p5.

<sup>87</sup> MVTR p2 and elsewhere.

<sup>88</sup> RMSR p14.

<sup>89</sup> Hoffman, S. L., Isenbarger, D., Long, G. W., Sedegah, M., Szarfman, A., Waters, L., Hollingdale, M. R., van der Miede, P. H., Finbloom, D. S., Ballou, W. R. “Sporozoite vaccine induces genetically restricted T cell elimination of malaria from hepatocytes.” *Science*, 1989, Vol. 244, pp 1078-1081.

<sup>90</sup> MVTR p4 and p5.

**Why the interest in fixing operational product- and region-specific requirements?**

We have found, given all the scientific uncertainty, that fixing product-specific and region-specific *operational* requirements for a malaria vaccine many years in advance is likely to be inefficient. Interest in doing so, and all the lobbying efforts to do so, only really took off with the interest in using a malaria APC – an instrument that cannot survive without fixed product-specific and region-specific *operational* targets. Amazingly, in light of all of the scientific unknowns and divergence of opinions, it is suggested that instead of working out whether the mechanisms we *already have* are likely to bring forward or push back the achievement of malaria vaccines, the best route is to experiment with a big pool of public subsidy and a distribution committee: “Instances in which there exist such a divergence of opinion on scientific prospects for development are especially well-suited for program such as purchase commitments.”<sup>91</sup> Farlow 2004 and 2005 argues that these are just the sorts of settings when we are least likely to know how to work out the terms of such ‘programs’ far in advance and to run the institutions needed to support them. They are essentially just an experiment. Indeed, in this vein, “Let’s just try it!” reasoned one commentator.<sup>92</sup> Politicians recently seem to have adopted the same “Let’s just try it!” attitude too.

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<sup>91</sup> Berndt et al. 2005, *ibid.* p5.

<sup>92</sup> Pierre Chirac, Book review in *Nature*, 2004, Vol. 431, pp. 629-630.

### **3. A Leading Candidate Malaria Vaccine: A Timely Case Study**

This section has its origins in a small subsection that grew as the author explored a recent case study, of the candidate malaria vaccine RTS,S/AS02A, and as feedback and ideas came in from a wide range of leading figures in the vaccine and malaria science field. As it became increasingly clear that the case study had important lessons for policymakers and funders, it also became clear that it would necessitate its own chapter.<sup>93</sup> A variety of opinions were expressed during this process of feedback, and the author can do no more than try to report them fairly and correctly, without claiming that this is a completely balanced summary of all possible views in the ‘malaria community’. Amongst those consulted, there was a spectrum from those supportive of further funding into RTS,S/AS02A right through to a sizeable minority arguing against further funding for RTS,S/AS02A. Even supporters of further funding were often candid with their critiques, and none of them expressed the more extreme position – even ‘spin’ – made by some politicians and in the media and, indeed, in some of the advocacy literature. Those asked, felt that a forum for more open debate would be very useful.

This section has three key purposes. The first – and a repeated refrain in feedback – is to highlight the need, whatever we conclude about RTS,S/AS02A itself, to avoid approaches that risk narrowing down the search for malaria vaccines and destroying more collaborative global efforts, but instead the need to strengthen approaches that keep many parallel and mutually supportive activities going, and to keep the ‘playing field level’ for all.

Second, it also becomes clear that many problems still lie ahead even for the current ‘leading’ malaria vaccine candidate, and we need to avoid the temptation of simplistic solutions. As one supporter for RTS,S/AS02A put it to the author:

“I am a supporter of the development of RTS.S but no zealot and I am uncertain if it will ever get used widely. However, the recent results show that it is a credible vaccine that could conceivably find a use in a combined malaria control strategy in some countries. I think that it is right to spend a modest amount on its further development through a series of phase 2b and phase 3 trials with the aim of licensure. The results of these studies will show whether it is a credible candidate for further much more extensive investment. I am sure that if deployed, RTS,S will have only a limited life to be replaced by a more effective vaccine...”

The issue is how to make sure that attention to one low-efficacy product does not distort behavior and harm the greater long-term goal. Tremonti argues that an APC would bring in only one or maybe two developers. The expectation<sup>94</sup> that a big chunk of the funding

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<sup>93</sup> I am enormously grateful to malaria vaccine experts for help on this. None of them should however take any responsibility for any faults.

<sup>94</sup> All the time, we are thinking of investors and their expectations, and not just the ex post outcome.

made available might go on one early low-efficacy product would not leave much, if anything, to stimulate other investors. This was picked up in correspondence. The above quote continued. "...This is often the case in vaccine development – for example the Hib polysaccharide vaccines served a useful role for several years only to be replaced by much more effective Hib conjugate vaccines a few years later and there are many other examples. It would have been wrong not to develop the Hib polysaccharide vaccine even though it had only limited efficacy and many children's lives were saved by doing this." But another correspondent argued: "The difference with Hib is that alternatives to RTS,S can be conceived, i.e. they are also in clinical development, though not in industrial development. In other words, Hib polysaccharides did not cause relative harm, but a premature RTS,S might well. This harm can be estimated globally in terms of excess mortality/year; at worst it might reach several hundred thousands." In chapter 7 we will investigate the complex tradeoff between emphasizing early low specification goals and later higher specification goals, a tradeoff that has yet to be fully explored, let alone solved. Meanwhile, this is not a time for politicians to force a solution onto this tradeoff.

A third intent is to help construct a more open debate evaluating if this particular vaccine candidate – and any that follow – is adequate for major targeting of funding (of the order of billions of dollars) to 'take it all the way to market', especially in the face of financial constraints on all other parts of the malaria and health package. Given the costs and losses elsewhere, no candidate should go 'all the way' without a very good stress-testing of its value. Neither should policymakers be egged along by language indicating that even very low efficacy is perfectly fine (e.g. statements like "Even a 30 percent effective vaccine would be highly cost-effective."<sup>95</sup>) and that there is essentially no budget constraint to worry about. Both of these views are increasingly used by some to push for an APC-based funding scheme.

There is much more behind-the-scenes debate about this than a public debate. It would be good for this discussion to be more open in every case, and not just in the case of RTS,S/AS02A. The really big allocations, and hence possible misallocations, of resources are still some years away. Now is an opportune moment to get into the regular habit of debating these issues.

### **3.1. Introducing RTS,S/AS02A**

The Malaria Vaccine Technology Roadmap observes that "recent R&D advances have caused renewed optimism among scientists that an effective malaria vaccine is feasible." Tremonti even hints that malaria is no longer in the category of a complex scientific problem: "It is financially risky to undertake early work to develop a vaccine against complex, poorly understood diseases, such as HIV/AIDS and tuberculosis,"<sup>96</sup> and "fundamental scientific puzzles still bedevil efforts to design and develop vaccines against HIV/AIDS, TB and, some believe, even malaria,"<sup>97</sup> for the first time suggesting

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<sup>95</sup> Berndt, et al. 2005, *ibid.* p19.

<sup>96</sup> I.e. Tremonti leaves malaria out of the list. Tremonti, G. Background Papers, 2005, p21.

<sup>97</sup> Tremonti, G. Background Papers, 2005, p25.

that concerns about the impact of fundamental scientific difficulties on malaria vaccine efforts is now something of a minority issue.

This pins the hope about the feasibility of a malaria vaccine on the results generated by the recent GSK Biologicals vaccine candidate RTS,S/AS02A, the leading MVI candidate. This was previously trialled on adults, and has recently been trialled in a double-blind phase IIb trial, between April 2003 and May 2004, on children in Mozambique, with 6-month results released in October 2004,<sup>98</sup> and in a single-blind follow-up, the results of which were released in November 2005.<sup>99</sup> 2022 children aged 1–4 years were recruited and 1605 (there were 391 exclusions<sup>100</sup>) were randomized to receive three doses of either RTS,S/AS02A candidate malaria vaccine or a control vaccination regimen. This candidate has not yet been trialled on the ultimate target group of infants (to be able to be administered as part of the standard childhood vaccine package).

Berndt et al. argued that “the promising results of the recent GSK trials suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought,”<sup>101</sup> even though the Berndt et al. group contain not a single malaria (vaccine or otherwise) expert. Others went even further: “Malaria Vaccine to Save Millions of Lives,”<sup>102</sup> ran one newspaper headline. “Malaria Vaccine Battle Has Been WON” (capitalization actually in the original) headlined one internet medical site.<sup>103</sup> This naïvety has a long pedigree. 50 years ago we were being told that mankind had mastered malaria: “Man’s Mastery of Malaria” ran a famous book title.<sup>104</sup>

In a similar vein, the UK Finance Minister announced days after the paper analyzing the 6 month data was released:

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<sup>98</sup> Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Milman, J., Mandomando, I., Spiessens, B., Guinovart, C., Espasa, M., Bassat, Q., Aide, P., Ofori-Anyinam, O., Navia, M.M., Corachan, S., Ceuppens, M., Dubois, M.C., Demoitie, M.A., Dubovsky, F., Menéndez, C., Tornieporth, N., Ballou, W.R., Thompson, R., Cohen, J., “Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial.” *The Lancet*, 2004, Vol. 364, pp. 1411-1420.

[www.thelancet.com/journal/vol364/iss9443/full/llan.364.9443.primary\\_research.30985.1](http://www.thelancet.com/journal/vol364/iss9443/full/llan.364.9443.primary_research.30985.1)

<sup>99</sup> Alonso, P.L., Sacarlal, J., Aponte, J.J., Leach, A., Macete, E., Aide, P., Sigauque, B., Milman, J., Mandomando, I., Bassat, Q., Guinovart, C., Espasa, M., Corachan, S., Lievens, M., Navia, M.M., Dubois, M.C., Menendez, C., Dubovsky, F., Cohen, J., Thompson, R., Ballou, W.R., “Duration of protection with RTS,S/AS02A malaria vaccine in prevention of *Plasmodium falciparum* disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial.” *The Lancet*, 2005, Vol. 366, pp. 2012-2018.

<sup>100</sup> 156 did not meet inclusion criteria, and 235 chose not to participate. Alonso et al. 2004, Figure 2.

<sup>101</sup> Berndt et al. 2005, *ibid.* p9. Though in the same *Lancet* as the first Alonso study, Philippe van de Perre and Jean-Pierre Dedet, argued that there was no reason to think things will now get easier: “The road toward a safe and efficient malaria vaccine being available and usable on a large scale...will be long and chaotic.” I have no idea on behalf of whom Berndt et al. believed themselves to be speaking. This author has found no malaria vaccine experts willing to take the Berndt et al. line.

<sup>102</sup> *The Times*, 15 October 2004.

<sup>103</sup> [www.medicinenet.com/script/main/art.asp?articlekey=39854](http://www.medicinenet.com/script/main/art.asp?articlekey=39854).

<sup>104</sup> Russell, P.R., *Man’s Mastery of Malaria*, Oxford University Press, 1955.

*“The recent breakthrough which for the first time gives us a vaccination to prevent malaria that could be ready in three to four years time is a revolution in our time.”*  
Gordon Brown, October 2004<sup>105</sup>

To which came the wry response:

*“Who has been briefing Mr Brown...?”*

Michel Pletschette, European Commission Directorate  
General for Research, 25 November 2004<sup>106</sup>

Brown further reported in January 2006 in the British newspaper *The Guardian* that: “A life-saving vaccine could soon be available for malaria to save 1 million lives each year,”<sup>107</sup> and that, in February 2006, he was going to push the G8 to pay for it via an APC.

As Snounou et al. observe: “Given the global and intolerable nature of the malaria burden to which the poorer half of humanity is subjected, and the influence of such trials on malaria control policy and budget allocations, the published trial outcomes merit critical appraisal.”<sup>108</sup> So, let’s give it a go.<sup>109</sup>

### **What is it**

RTS,S consists of a recombinant polypeptide corresponding to part of the circumsporozoite protein (CSP) of *P. falciparum* fused to the S antigen of hepatitis B virus (HBsAg), in a particle that also includes the unfused S antigen. The scientists involved believe that it generates both antibody and T-cell responses to prevent infection of liver cells and that it also destroys infected cells. Over 20 years, GSK Biologicals developed this candidate vaccine in collaboration with the Walter Reed Army Institute of Research (WRAIR). In 2001, GSK Biologicals and WRAIR entered into a partnership with MVI. The reasoning for this is summarised by Heppner et al: “The recent report that RTS,S/AS02A had a significant positive impact on clinical and severe malaria in children in Mozambique strongly support our working hypothesis that a more effective RTS,S-

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<sup>105</sup> [www.hm-treasury.gov.uk/newsroom\\_and\\_speeches/press/2004/press\\_94\\_04.cfm](http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_94_04.cfm). Contrast this with: “It could easily take a decade to develop malaria, tuberculosis, or HIV vaccines.” Kremer, M., and Glennerster, R., 2004, *ibid.* p74.

<sup>106</sup> Pletschette, M., CIPIH Open Discussion Forum, 25 November 2004.

<sup>107</sup> *The Guardian*, 11 January 2005, [www.guardian.co.uk/comment/story/0,3604,1683463,00.html](http://www.guardian.co.uk/comment/story/0,3604,1683463,00.html).

<sup>108</sup> Snounou, G., Gruner, A.C., Muller-Graf, C.D.M., Mazier, D., Renia, L., “The Plasmodium sporozoite survives RTS,S vaccination.” *Trends in Parasitology*, October 2005, Vol. 21, pp. 456-461.

<sup>109</sup> As an economist, this is a difficult and nerve-wracking task. The problem is that the economists and policy advocates pushing policy have not thought about this, even though the advice they proffer depends (or should depend) on a deep understanding of what is going on scientifically. The author can hardly criticize other economists and policy advocates for imposing solutions regardless of the underlying science, without at least attempting to understand it himself. Thankfully, there is an emerging literature and many helpful voices around the malaria vaccine community. Errors are all mine, and I would be extremely grateful to have mistakes and misunderstandings pointed out so that I can correct them in follow-on versions of this report.

based vaccine could be developed that would better meet the US Army military needs and perhaps also benefit global public health needs.”<sup>110</sup>

### **A little prior history**

After circumsporozoite protein (CSP) was identified as a dominant sporozoite surface antigen, experimental vaccines based on it were the first to be tested for efficacy in humans.<sup>111</sup> Trials of CSP vaccines have, however, proved disappointing.<sup>112 113 114 115 116</sup>

Key to the current result therefore was over ten years of work on formulating the AS02A adjuvant to enhance an immune response in this the latest and most advanced CSP-based vaccine formulation. Indeed, in naïve volunteers, RTS,S efficacy has been found to be very strongly dependent on the adjuvant,<sup>117</sup> though one correspondent observed that: “There is some limited evidence that the effect of RTS,S is not due to the adjuvant. A small number of volunteers given adjuvant alone or with another antigen were not protected, and there is now some evidence for a marker of immunity in vaccinated subjects.”

Given the potential for drift – when escape mutants are selected under vaccination-driven immune pressure – it may be necessary to combine immunogens by means of pre-erythrocytic or blood-stage immunogens with transmission-blocking vaccines. But also, because both humoral and cellular components of the immune system are needed for protection, the choice of immunogens and the development of potent adjuvants will also be equally critical. This explains a justifiably keen interest in an adjuvant. But one can already see that results that may be based on an adjuvant have to be placed in a much broader context.

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<sup>110</sup> Heppner, D.G. Jr., Kester, K.E., Ockenhouse, C.F., Tornieporth, N., Ofori, O., Lyon, J.A., Stewart, V.A., Dubois, P., Lanar, D.E., et al. “Towards an RTS,S-based, multi-stage, multi-antigen vaccine against falciparum malaria: progress at the Walter Reed Army Institute of Research.” *Vaccine*, 2005, Vol. 23, Issues 17-18, pp. 2243-2250.

<sup>111</sup> Nussenzweig, V., and Nussenzweig, R.S., “Rationale for the development of an engineered sporozoite malaria vaccine.” *Adv. Immunol.*, 1989, Vol. 45, pp. 283–334.

<sup>112</sup> Ballou, W.R., Hoffman, S.L., Sherwood, J.A., Hollingdale, M.R., Neva, F.A., Hockmeyer, W.T., Gordon, D.M., Schneider, I., Wirtz, R.A., Young, J.F., et al. “Safety and efficacy of a recombinant DNA *Plasmodium falciparum* sporozoite vaccine.” *The Lancet*, 1987, 1(8545), pp. 1277-81.

<sup>113</sup> Herrington, D.A. et al. “Safety and immunogenicity in man of a synthetic peptide malaria vaccine against *Plasmodium falciparum* sporozoites,” *Nature*, 1987, Vol. 328, pp. 257–259.

<sup>114</sup> Guiguemde, T.R., Sturchler, D., Ouedraogo, J.B., Drabo, M., Etlinger, H., Douchet, C., Gbary, A.R., Haller, L., Kambou, S., Fernex, M., “Vaccination against malaria: initial trial with an anti-sporozoite vaccine.” *Bull Soc Pathol Exot*, 1990, Vol. 8, pp. 217-227.

<sup>115</sup> Reber-Liske, R., Salako, L.A., Matile, H., Sowunmi, A., Sturchler, D., “A malaria vaccine field trial in Nigerian children.” *Trop Geogr Med*, 1995, Vol. 47, pp. 61-63.

<sup>116</sup> Sherwood, J.A., Copeland, R.S., Taylor, K.A., Abok, K., Oloo, A.J., Were, J.B., Strickland, G.T., Gordon, D.M., Ballou, W.R., Bales, J.D., Wirtz, R.A., Wittes, J., Gross, M., Que, J.U., Cryz, S.J., Oster, C.N., Roberts, C.R., Sadoff, J.C., “*Plasmodium falciparum* circum-sporozoite vaccine immunogenicity and efficacy trial with natural challenge quantitation in an area of endemic human malaria in Kenya.” *Vaccine*, 1996, Vol. 14, pp. 817-827.

<sup>117</sup> Stoute, J.A., et al. “A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. RTS,S Malaria Vaccine Evaluation Group.” *N. Engl. J. Med*, 1997, Vol. 336, pp. 86-91.

**The Alonso Result**

In late 2004 Alonso et al. reported<sup>118</sup> that RTS,S combined with the adjuvant AS02A and administered in three doses over two months, achieved, at the end of the 6 months surveillance period (starting two weeks after the last dose, hence measured at month 8.5), efficacy in children for the first clinical episode of 29.9% (95% CI 11.0%–44.8%;  $p=0.004$ ).<sup>119</sup> The average age of the children at the start of the trial was 36 months with a standard deviation of 13–14 months.<sup>120</sup> A clinical episode was defined as a child who presented to a health facility with an axillary temperature of 37.5°C or more and presence of *P. falciparum* asexual parasitaemia greater than 2500 per  $\mu\text{L}$ .<sup>121</sup>

Few children had more than one episode of malaria, and vaccine efficacy including all clinical episodes was reported to be 27.4% (95% CI 6.2–43.8;  $p=0.014$ ). At the end of the 6-month observation period (month 8.5), prevalence of *P. falciparum* infection was reported to be 37% lower in the RTS,S/AS02A group compared with the control group at 11.9% versus 18.9%,<sup>122</sup> though parasite densities were the same between RTS,S/AS02A recipients and the controls (geometric mean density 2271 vs 2513;  $p=0.699$ <sup>123</sup>). Efficacy for severe malaria was reported to be 57.7% (95% CI 16.2%–80.6%;  $p=0.019$ ).<sup>124</sup> In cohort 2, vaccine efficacy for extending time to first infection was reported to be 45.0% (95% CI 31.4%–55.9%;  $p<0.0001$ ), with 157 of 209 in the RTS,S/AS02A group and 166 of 208 in the control group having first episodes of asexual *P. falciparum*. The mean density of asexual-stage parasites at time of first infection was also essentially the same (3016 vs. 3950 per  $\mu\text{L}$ ;  $p = 0.354$ ). The number of cases of severe malaria reported was reduced by 58% (95% CI 16.2% to 80.6%;  $p = 0.019$ ). Vaccine efficacy against new infections was similar in the older and younger age groups (44.0% vs 46.5%). 15 children died during the study period. Four of those who died had malaria as a significant contributing factor and all four were in the control group, and eleven died for other reasons.

In the follow-up paper in December 2005,<sup>125</sup> during the single-blind phase, efficacy, defined as first or only episode of fever and parasitaemia  $>2500/\mu\text{L}$ , was reported as 28.9% (95% CI 8.4–44.8;  $p=0.008$ ). The case of first or only episode of fever and parasitaemia  $>0/\mu\text{L}$  was 23.3% (95% CI 2.9–39.4;  $p = 0.027$ ). The adjusted efficacy including all clinical episodes was reported as 28.8% (95% CI 6.2 – 45.9;  $p = 0.016$ ). Over the entire study period (months 2.5–21), efficacy was reported to be 35.3% (95% CI 21.6–46.6;  $p = 0.0001$ ) and for severe malaria 48.6% (95% CI 12.3–71.0;  $p = 0.02$ ).

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<sup>118</sup> Alonso, et al. 2004, *ibid*.

<sup>119</sup> In the per-protocol analysis in cohort 1, 282 children had first clinical episodes meeting the primary case definition (123 in the RTS,S/AS02A group and 159 in the control group). This yielded a crude vaccine efficacy estimate of 26.9% (with 95% confidence interval of 7.4–42.2;  $p=0.009$  [See Alonso et al. 2004, Figure 4]) and the adjusted estimate of 29.9% (see Alonso et al. 2004, Figure 3).

<sup>120</sup> See Table 1 of Alonso, et al. 2004, *ibid*.

<sup>121</sup> This case definition was established at the time of study design, before the start of the trial, based on previous background data from the site, and has been estimated to be 91% specific and 95% sensitive.

<sup>122</sup>  $p=0.0003$ .

<sup>123</sup> With  $p = 0.699$ , the two measurements are to all intents and purposes the same.

<sup>124</sup> Observe that this is a very wide confidence interval.

<sup>125</sup> Alonso, et al. 2005, *ibid*.

During the single-blind phase there were eight deaths; five in the RTS,S/AS02A group and three in the control group. Two of these deaths were judged to be related to malaria and both were in the RTS,S/AS02A group.

### **Mortality figures**

None of these mortality numbers has any statistical significance however. One correspondent observed: “It would have been useful for the p-value for these numbers being different by chance to have been presented. I guess it would be very large.” Another commented that “to assess the impact of a vaccine on child mortality would require enrollments in the range of 10,000-100,000.” As Richie and Saul, put it: “In much of Africa – which has an infant mortality of about 100 in 1,000 live births – depending on the accuracy with which a cause of death can be diagnosed, group sizes of many thousands to tens of thousands would be needed to use mortality as an end point, and this is not feasible at an early stage of vaccine development. Because there are gaps in our understanding of the progression of pathology from parasitaemia to death, our choice of end point for early efficacy studies is associated with a risk of either discarding a good vaccine because it fails to give an imperfect correlate of protection in early stage testing or wasting scarce resource by taking a poor vaccine through extensive clinical testing.”<sup>126</sup>

As with the first study, parasite densities were essentially the same at the time of the 21 month measurement in RTS,S/AS02A recipients and controls (geometric mean density 1940 vs. 1571 per  $\mu\text{L}$ ;  $p = 0.575$ ). In cohort 2, the prevalence of asexual *P. falciparum* parasitaemia was 68.8% (50 of 160) in the RTS,S/AS02A group compared with 69.4% (49 of 160) in the control group ( $p = 1.0$ ), i.e. statistically, proportionately just as many in each group became infected with *P. falciparum*.

The authors of the original Lancet paper do not themselves claim a great deal explicitly. They do say things such as “Our results indicate the feasibility of development of an effective vaccine against malaria.”<sup>127</sup> And the follow-up paper argues that RTS,S/AS02A is “a promising vaccine candidate and strongly suggests that malaria vaccines have an important role as future public-health instruments.” However, the dramatic overblown statements – such as of a 50-70% effectiveness and that a “vaccine could soon be available for malaria to save 1 million lives each year” – came from a heavy dose of watering by politicians.

### **3.2. Control group given unrelated vaccine**

Several correspondents commented on the controls used. The normal scientific methodology is, if at all possible, to vary only one parameter between experiment and control. Ideally, the controls in the trials should have been immunized with HBsAg particles formulated in AS02. Instead, in both the earlier Gambia trial<sup>128</sup> and later

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<sup>126</sup> Richie, T.L., and Saul, A., 2002, *ibid.* p699.

<sup>127</sup> Alonso, et al. 2004, *ibid.* p1419.

<sup>128</sup> Bojang, K.A., Milligan, P.J., Pinder, M., et al. “Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomized trial.” *The Lancet* 2001, Vol. 358, pp. 1927-1934

Mozambique trial,<sup>129</sup> all control volunteers were given unrelated vaccine(s),<sup>130</sup> except for the older Mozambican children who received paediatric hepatitis B vaccine, and in all cases these were formulated in adjuvants *other than AS02*, and, naturally enough, they did develop titres against HBsAg. (Alonso et al. 2004, Table 2). The use of an unrelated vaccine which can benefit the population as a comparator is a standard practice, albeit with limitations. The problem is made more difficult by the complexity of choosing appropriate case definitions.

The justification for doing this would be that giving RTS,S without the malaria component of circumsporozoite – a ‘dummy’ vaccine having all the attributes of the test article except the specific immunogenic elements – would be unethical, since it would have an unknown, possibly detrimental effect rather than a beneficial one. But if so, some correspondents argued that the authors should have provided some evidence (even from animal models would have helped) that overall stimulation of the immune system and high titres against HBsAg are not likely to confer aspecific protection against severe complications of malaria.<sup>131</sup> At the very minimum, suggested several correspondents, the trial design was limited in this respect.<sup>132</sup> One correspondent argued that this fundamental flaw made the study “rather useless.” Another, however, responded: “The trial is not useless but limited for many other reasons. Unspecific protection from these causes would always have been limited. Only a larger trial including under conditions of higher malaria transmission pressure would have been giving clearer results, also on this point.”

#### **Specific versus nonspecific immune responses**

Snounou et al. argue that this raises the possibility that the RTS,S antigen might actually target the particles and the associated adjuvant to the liver because HBsAg possesses a hepatocyte-binding site. More precisely they observe: “The trial outcomes do not, therefore, exclude the possibility that local activation of nonspecific immune responses by this strong adjuvant could have synergized with specific responses to the CSP polypeptide to eliminate the parasite. In this case, as the liver gradually returns to its normal state after the final vaccine dose, the combined ability to inhibit PE development would diminish.”<sup>133</sup> One correspondent argued however that no experimental data are provided for this hypothesis either.

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<sup>129</sup> Alonso, et al. 2004, *ibid.* and 2005 *ibid.*

<sup>130</sup> Specifically – in the case of Mozambique – because routine hepatitis B vaccination was introduced into the EPI schedule of Mozambique in July, 2001, children aged 12–24 months had already received hepatitis B immunisation. Therefore, children younger than 24 months received as control vaccines two doses of the seven-valent pneumococcal conjugate vaccine (Prenvar Wyeth Lederle Vaccines, Madison, NJ, USA) at the first and third vaccination and one dose of *Haemophilus influenzae* type b vaccine (GSK Biologicals) at the second vaccination. For children older than 24 months, the control vaccine was the paediatric hepatitis B vaccine (GSK Biologicals).

<sup>131</sup> They point out that overall protection and differences in parasitaemia levels at the onset of first attack are not significant (Alonso, et al. 2004, *ibid.* Table 3, line 5).

<sup>132</sup> Bojang, K.A., et al. 2001, *ibid.* Patarroyo, M.E., Amador, R., Clavijo, P., et al. “A synthetic vaccine protects humans against challenge with asexual blood stages of *Plasmodium falciparum* malaria.” *Nature*, 1988, Vol. 332, pp. 158-161.

<sup>133</sup> Snounou et al. 2005, *ibid.*

One way to settle this issue would be to administer the RTS,S-AS02 vaccine when transmission levels are low, and to start follow-up observation later, during the high transmission season.

### **3.3. Lack of correlation with antibody titres against circumsporozoite**

In the first Alonso et al. paper, the authors report no waning of the limited efficacy against clinical disease<sup>134</sup> along with the waning antibodies against CS (Alonso et al. 2004, Table 2) – a decay of 75% of antibody level at 6 months – while in the same period the HBsAg antibodies even go up. In the follow-up study, antibodies against CS measured in cohort 1 continued to fall during the follow-up period. Alonso et al. observe that: “In this trial, sustained vaccine efficacy against clinical malaria was observed even though concentrations of antibody against the circumsporozoite repeat region decreased substantially from the peak levels achieved after dose 3. However, nearly two years after having received the first dose of RTS,S/AS02A, antibody concentrations remained nearly 50 times higher in the vaccine group than in controls”<sup>135</sup> (geometric mean titre 14.0, 95% CI 12.5–15.6, compared to controls, 0.3, 0.3–0.3). Concentrations of anti-HBsAg antibody were measured for cohort 2, and in the RTS,S/AS02A group 173 of 176 participants (98.3%, 95% CI 95.1–99.6) remained seroprotected at month 21.

Several observed that this suggests aspecific stimulation of the immune system, and the possibility that the HBsAg antibodies themselves, play a role, rather than CS. From a biological point of view several correspondents argued that it is not conceivable how CS antibodies could protect against severity of disease other than through delaying the onset of the infection and the number of liver stages resulting from one bite, allowing the immune system more time to react to the infection. In addition, if we were looking mainly at aspecific immunity, the chances for a significant benefit of direct boosting of the specific epitope-directed immunity would be low.

However, in the follow-up, Alonso et al. argue that: “These results contrast with the duration of protection seen in malaria-naïve volunteers in the USA and in Gambian adults. They also refute the notion that protection induced by RTS,S/AS02A is mediated by some undescribed, transient, non-antigen-specific mechanism. No significant difference in the prevalence of infection at month 21 was observed in cohort 2, but this cohort differed from cohort 1 in that participants experienced substantially higher malaria transmission and underwent intensive follow-up for detection and treatment of all new infections during the double-blind phase.” Several have also agreed with Alonso et al. that the issue of a non-specific adjuvant effect seems a less likely explanation – especially after the most recent data was released.

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<sup>134</sup> Alonso et al. 2004, *ibid.* p1419: “Waning efficacy over the 6-month observation period was not noted for the primary endpoint when analysed by different methods.”

<sup>135</sup> Alonso, et al. 2005, *ibid.* p2015.

However, Alonso et al. observe that there is no correlation with antibody titres against CS: “In RTS,S/AS02A recipients, we failed to detect an association between level of CS antibody and risk of malaria.”<sup>136</sup> They also concede that the analysis was potentially constrained by the high titres achieved by nearly all vaccine recipients and the possibility that a relatively low threshold protective level of immunity might exist potentially constrained the analysis. But then the authors suggest that even the lowest titres were enough, and that – just maybe – non-measured cellular mechanisms were involved. One correspondent argued that “the scientific method would be that the most simple and elegant explanation should be followed until falsified by further experiment, and the correct hypothesis should be that CS antibodies are not involved in the marginal protective efficacy being picked up”.

In the follow-up paper, Alonso et al. are a bit more specific, arguing that: “The immunological mechanisms that underlie the observed protective efficacy of this vaccine against clinical malaria are probably complex. The RTS,S/AS02A vaccine was developed to induce both humoral and cellular immune responses against circumsporozoite protein, since preclinical data indicated that both were required for protection against infection...The very low levels of naturally occurring anticircumsporozoite antibodies in the control group confirms the poorly immunogenic nature of native circumsporozoite protein, even with substantial *P. falciparum* exposure. In this trial we did not measure cellular immune responses, but their potential role in protection is well supported by data derived from surrogate animal models as well as from a few clinical vaccine trials. We suggest that the observed vaccine efficacy results from an interplay between cellular and humoral immune responses induced by the vaccine. Both of these mechanisms might be amenable to natural boosting, and could contribute to sustaining vaccine efficacy. Future trials with this vaccine may offer the opportunity to evaluate and better understand the respective roles of these multiple factors in mediating sustained protection against malaria disease.”

One correspondent, otherwise supportive of Alonso et al., observed nevertheless that “this [claim by Alonso et al.] is as good a guess as any, but we simply don’t have the data to be dogmatic.” While, another equally senior figure argued that since sustained vaccine efficacy against clinical malaria was observed even though concentrations of antibody against the circumsporozoite repeat region decreased substantially from the peak levels, and all the evidence pointing to the fact that the antibodies being measured are not the protective mechanism, this: “Indicates clearly that the trial design was deficient – They should have measured cellular as well as humoral responses. Also there should have been an adjuvant control.” Another correspondent responded “Absolutely” to this comment and argued that the “Alonso explanation is useless. There are no recognized correlates of protection what so ever. The way to develop them goes via experimental clinical trials, explanatory trials, or hyper-empirical trials.”<sup>137</sup>

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<sup>136</sup> Alonso, et al. 2004, *ibid.* p1418.

<sup>137</sup> The same correspondent who made the observation above starting “The trial is not useless...”

Alonso et al. observe in the follow-up paper: “Although the efficacy estimate for severe malaria was higher than that for clinical malaria, this difference still could be due to chance. However, other methods of malaria control, such as insecticide treated nets, that could involve reduction in the infecting dose of sporozoites, have also yielded higher estimates of efficacy for the more severe forms of the disease than for the mild forms. This exciting possibility needs to be further explored in the case of this vaccine.” One correspondent observed: “This calls for trials evaluating a vaccine in the context of other ongoing interventions. However, since trials are limited in number for various reasons, one would need to decide first when a vaccine achieved enough as a single intervention to be evaluated in such a way. Clearly RTS,S is not yet sufficiently developed for this.”

### **3.4. Parasite density figures**

At the six month period geometric mean parasite density for RTS,S/AS02A was measured as 2271, and at the 21 month period as 1940. For the control, the corresponding figures are 2513 and 1571. In other words, density in the RTS,S/AS02A cohort started a few hundred lower than the control but ended up several hundred higher than the control, and the control group density fell by 1000, while RTS,S/AS02A fell only by about 300. This contrasts with the observation that “At month 21, prevalence of *P. falciparum* infection was 29% lower in the RTS,S/AS02A group than in the control ( $p=0.017$ ),”<sup>138</sup> since ‘infection’ refers to something else. In a much bigger study (such that these figures had statistical meaning), this would suggest that the RTS,S/AS02A group are suffering less, but that they are carrying more parasite load at the end.

One correspondent argued that from a co-evolutionary perspective this would generally be interpreted as bad news for the greater human population. Another pointed out that drug resistance is more likely to develop when parasite numbers in an individual are high, affecting how one interprets a combined package of measures involving a vaccine that does this alongside malaria drugs. However, another argued we did not have the luxury of ruling out use of vaccines *even if* this was the case – that we simply cannot wait until we have all the science in place. Nor, it was further argued, do we have the benefit of science to rule out that this co-evolutionary and resistance thinking may not be a significant effect anyway; it was pointed out that such worries in the case of insecticide-treated mosquito nets had delayed their mass roll out even though the worry had proven unfounded.

#### **Measurements of parasitaemia are imprecise anyway**

However, estimates of parasitaemia are subject to wide variation. They are, as one correspondent put it “notoriously imprecise”. The mature dividing form of the organism sequesters in the deep tissues, with only the young, so called ring forms seen on blood smears. This means that one should not really read too much into the parasite density figures for the two cohorts: “To all intense and purposes, they are the same.” On reading this, one correspondent went a bit further: “They are indeed the same.” But this creates another problem. Given that the parasite densities between RTS,S/AS02A recipients and

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<sup>138</sup> Alonso et al. 2004, *ibid.* p1418.

controls are in effect the same, how does one read in to the efficacy figures when generated on a definition such as: “fever and parasitaemia > 2500/  $\mu\text{L}$ ”?

**No statistical difference in geometric mean parasite densities**

Another correspondent observed: “At the first press conference in connection with the first publication in *Lancet*, the lack of statistical significant difference in geometric mean parasite density was commented on. The authors simply stated that the primary end point for efficacy is delay or absence of clinical malaria [defined as “first or only episode of fever and parasitaemia >2500/ $\mu\text{L}$ ”], and that the study was not designed to test density differences. The reported decline in parasite density in the two groups is compatible with age related increase in exposure and gradual increase in the ability to control parasite multiplication [The average age at month 8.5 of the trial was 44.5 months, and at 21 months was 56 months]. It is indeed disturbing that the density decreases more in the control group. It could be loosely interpreted that the control group was more capable of controlling asexual parasitaemia, which causes the disease, than the immunized group (because of the immunization), but this would require specialist statistical analysis. I think this deserves real discussion. The dogma is that children in endemic areas can first control death, then disease and finally parasites. I fully agree with [the] worries that the mean densities are fairly similar, and what is then the judgment call?”

However, another correspondent, themselves arguing that the difference are not statistically significant, observed that “It’s irrational to ‘be disturbed’ by differences that are not statistically significant at any reasonable value of alpha. One can only conclude that belief is not based on observation in such cases,” and that “I don’t know of any statistical analytic approach to address this question. It can only be addressed by increasing the power of the analysis by increasing the number of observations. This will happen as additional trials are performed.”

One correspondent, after a life-long career in malaria observed: “Truly, the differences in the two arms of the study before and after vaccination are totally unremarkable...i.e., they in no way signal an effect of any kind,” and that, spelling it out for the educated layman: “To put it in more precise terms, I would be very surprised that if the 95% confidence intervals [of the parasitaemia] values were available (and they could be calculated from the information that is available) they did not overlap extensively both in the case of the two 8.5 month data points and in the case of the two 21 month data points. Roughly interpreted, this could be taken to indicate that there is less than 1 chance in 20 that there is a difference in the true mean parasite densities in the two arms at either time. In fact, I’d expect the confidence intervals for all four data points to overlap, although I would be less surprised if the 8.5 and 21 month intervals did not (i.e., if the mean values were statistically different). Of course if the values were different at 8.5 vs. 21 months, this could be attributed to seasonal difference in transmission, etc. and isn’t relevant to the questions being addressed. To further illustrate the point, the published P value for a difference between the 8.5 month data points is 0.699 and for a difference between the 21 month data points, 0.575. These values are estimates of the probabilities that the observed difference occurred by chance. Any P value > 0.05 is usually taken as the point at which observed differences are not indicative of true mean differences in the populations under

study. None of this is to say that there are no differences...only that the evidence does not suggest that there is. A statistician would probably not think I have expressed this exactly correctly, but would agree with the overall conclusion!”

### **3.5. Case definition**

Clinical malaria was defined in the Alonso et al. study according to the first definition, of “fever and parasitaemia  $> 2500/\mu\text{L}$ .” Fever and parasitaemia below this level could be due to one of a variety of bugs, not just malaria parasites. As one correspondent put it: “Lots of kids are walking around with malaria parasites and no clinical symptoms. Hence the need for debate.” While another noted: “There is no agreed marker of vaccine protection in malaria; Alonso is using a surrogate of his own after having used another one (fever) in earlier studies. Since the results are interesting and important but far from overwhelming, it is not a surprise that the surrogate marker used here, i.e. parasite density, is also not giving very clear information. All the measurements are probably true but all the data correlations discussed cannot change anything in the modesty of the results...Since there are no agreed correlates of protection, I wonder how a regulatory agency can give the label malaria vaccine to the RTT,S product even if it is the most advanced prototype.” Another correspondent observed that “An alternative would have been to have set up a complex of parameters and compare the values via spectral statistical analysis”.

#### **The inherent difficulties of case definition**

And yet another observed that: “The problem of case definition is a very difficult one. In the context of this discussion it may be worth noting that fever is arguably a marker for illness; i.e. most people with fever don’t feel good. On the other hand, parasite density is a marker for the etiology of that illness. If the vaccine protects from fever (i.e. illness) it is providing benefit. But since a malaria vaccine won’t prevent all fevers, in order to have maximum specificity (essential to detect vaccine efficacy) the fevers not due to malaria must be removed from the tally. In practice, the cutoff density is chosen to maximize specificity.”

Obviously one of the hurdles to avoid is that of data mining. One form of data mining happens when lots of equations/regressions are run on a set/series of data. Each result on its own generates a 95% confidence interval. However, these confidence intervals only make sense if the choice of equation/regression to run is truly random. If after a range of equations/regressions are run, the data handler chooses the one most supportive of their result, the 95% confidence interval it generates means nothing.<sup>139</sup> The story is similar if a range of measures and markers are tried and then one is chosen from the set. We presume, for example, that when Alonso et al. say “We also determined VE [vaccine

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<sup>139</sup> For three meanings of data mining, see Hendry, D.F., *Dynamic Econometrics: Advanced Tests in Econometrics*. Oxford University Press, 1995, pp. 544-555.

efficacy] for other case definitions and for episodes of severe malaria,”<sup>140</sup> that they reported all the findings,<sup>141</sup> and the chosen surrogate marker was also truly random.

A further correspondent observed: “You would think that the definitions would be objective enough so there would be few occasions where a judgment call would be needed. But these things happen with some frequency in clinical trials. There could have been plain mistakes or there could have been borderline parasite counts which changed the category on final analysis.” Another observed: “There will inevitably be cases that will be classified in one category or the other when in fact the density figures are so close to the cut off that a repeat reading could easily go the other way. The saving grace is that in a study with adequate numbers of subjects the “noise” will on the average be the same in different study arms and such borderline cases will cancel each other out.”

All hospital admissions were independently reviewed by two groups of clinicians, with discrepancies resolved in a consensus meeting before the database of the single-blind phase was locked.<sup>142</sup> It would be interesting to have more details about the numbers of borderline cases. One might imagine that with parasitaemia the same, the results might be more than usually sensitive to the details of how cases were allocated. We know, for example, that the candidate vaccine was 15 times more likely to cause injection-site swelling of more than 20mm (swelling after 224 doses for the candidate vaccine, or 7.7%, versus swelling after just 14 doses, 0.5% of the control). Do otherwise trivial signs become more significant when half of the definition of the end point is effectively non-operative?

#### **End points based on elevated temperature?**

Another correspondent (head of another vaccine initiative) puzzled: “I’m getting more and more puzzled when I study the results of the RTS,S vaccine trials. Efficacy is determined by recording clinical cases (over time/the observation period) and clinical cases are defined based on parasite density and elevated temperature. There is no difference in geometric mean parasite density. The difference between the RTS,S and control groups is thus the number of cases with elevated temperature!! Strange.” Thus, an endpoint based, for example, on “time to first clinical episode of symptomatic *P. falciparum* malaria” becomes, on average, “time to first presentation of a child to a health facility with an axillary temperature of 37.5°C, with a decision made by clinicians as to which of the many possibilities, including malaria, is inflicting the child”<sup>143</sup>.

#### **Analysis suggesting that measured efficacy heavily dependent on case definition**

Recent analysis demonstrates how reported efficacies from vaccine trials may depend heavily on the clinical case definition used. The dependence is particularly striking for

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<sup>140</sup> Alonso et al. 2005, *ibid.* p2012.

<sup>141</sup> To this untrained eye, it seems that they do report all.

<sup>142</sup> Alonso et al. 2005, *ibid.* p2013.

<sup>143</sup> It wasn’t clear to this author how the specific roles of the location of health facilities in cohorts 1 and 2, and the passive case-detection in one and the mix of passive and active in the other were dealt with. But this may be more an indication of this author’s ignorance. Adjusted vaccine efficacy included adjustment for distance to health centre.

diseases such as malaria, in which no single case definition is appropriate. Rogers, et al.<sup>144</sup> used logistic regression modeling of the relationship between parasitaemia and fever in data sets from Ghanaian children. They determine the fraction of fevers attributable to malaria and model how the choice of a threshold parasitaemia in the clinical case definition affected the measured efficacy of malaria vaccines. They found that calculated clinical attack rates in their data sets varied 10-fold as a function of the threshold parasitaemia. Most striking of all, measured vaccine efficacies in reducing clinical malaria depended heavily on the threshold parasitaemia, varying between 20% and 80% as the threshold varied between 1 and 5000 parasites/ $\mu$ L: “We suggest that clinical case definitions of malaria that incorporate a threshold parasitaemia are arbitrary and do not yield stable estimates of vaccine trial end points.”

However, Rogers et al. also observe that their models are not directly applicable to a preerythrocytic-stage vaccine such as RTS,S. Although, they say, it is possible that there was a differential effect of the RTS,S vaccine on severe disease, compared with that on mild disease, “the different efficacies for mild and severe malaria may result from differences in the sensitivity and specificity of case definitions for mild and severe malaria. Validation of the models presented here will depend on analysis of the results of large-scale field trials of blood-stage vaccines.”

One general conclusion reached elsewhere in this report, is that if there had not been such a need just recently to make one study so salient and even to have it hyped by politicians and in the media, perhaps normal scientific debate about its limitations, and the evidence still needed to make a conclusion, would have been encouraged in the public eye, and critical observations would have treated as no more than normal scientific skepticism, rather than as a challenge to what politicians are wanting to do?

### **3.6. Duration of response**

At first there was some concern about the length of duration of response achieved. Smith and Milligan,<sup>145</sup> before the 21 month data were made available, pointed out that the evidence of a protective effect against malaria infection in the earlier trial in adults in The Gambia lasted for only 2–3 months, and that the new data were compatible both with sustained protection over 6 months, but also with there being little protection against clinical malaria or malaria infection for more than 3 months after vaccination. Referring to Alonso et al. 2004, Figure 4, they noted that among those who had not developed clinical disease by 3 months after vaccination, the risk of an episode of malaria in the next 3 months was similar (about 7%–8%) whether in the vaccinated or unvaccinated groups. The risk of acquiring infection by 6 months among those not infected at 3 months was also similar in both groups (about 65%). Also during the 6-month period, the numbers of children infected were similar (157 and 166, respectively). Additionally, they

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<sup>144</sup> Rogers, W.O., Atuguba, F., Oduro, A.R., Hodgson, A., Koram, K.A., “Clinical Case Definitions and Malaria Vaccine Efficacy” *The Journal of Infectious Diseases*, electronically published 27 December 2005, Vol. 193, pp. 467-473, [www.journals.uchicago.edu/JID/journal/issues/v193n3/35118/35118.html](http://www.journals.uchicago.edu/JID/journal/issues/v193n3/35118/35118.html).

<sup>145</sup> Smith, P., Milligan, P., “Malaria vaccine: 3 or 6 months' protection?” *The Lancet*, 2005, Vol. 365, pp. 472-473.

argued that there was little evidence of protection against clinical episodes of malaria other than the first; indeed, after a first episode, the rate of subsequent episodes was slightly higher in the vaccinated group than in the unvaccinated group. This can be calculated from Alonso et al. 2004, Table 3: In the vaccinated group there were 30 episodes in 19.4 person years at risk, PYAR, generating a rate of 1.5 per year. In the unvaccinated group there were 31 episodes in 27.2 PYAR, generating a rate of 1.1 per year.<sup>146 147</sup>

Smith and Milligan were at pains to point out that: “These observations are not intended to detract from the importance of the finding of the overall protection conferred by the vaccine during the follow-up period, including against severe malaria, but they do emphasize the importance of the continued follow-up of the trial population to examine longer term protection, as is planned by Alonso and colleagues.”

In the Alonso et al. follow-up, the authors however observe that “By contrast [to Smith and Milligan], the results of this extended follow-up show that vaccine efficacy did not wane and that protection against clinical malaria lasts for at least 18 months after vaccination with RTS,S/AS02A. These findings are further reinforced by the significant difference between RTS,S/AS02A-vaccinated people and controls in the prevalence of infection seen in this same cohort at the last cross-sectional survey towards the end of the high transmission season. These results contrast with the duration of protection seen in malaria-naïve volunteers in the USA and in Gambian adults. They also refute the notion that protection induced by RTS,S/AS02A is mediated by some undescribed, transient, non-antigen-specific mechanism. No significant difference in the prevalence of infection at month 21 was observed in cohort 2, but this cohort differed from cohort 1 in that participants experienced substantially higher malaria transmission and underwent intensive follow-up for detection and treatment of all new infections during the double-blind phase.”

One well-respected correspondent, considered neutral perhaps, observed “The new results are convincing that protection is sustained for many months and, as this has happened in the face of declining antibody levels, it is possible that protection may continue for longer. These new results need detailed scientific scrutiny during the coming months, and some flaws may emerge, but on the face of it they look to be convincing.”

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<sup>146</sup> Smith and Milligan also pointed out that though the prevalence of parasitaemia at month 8.5 months was lower in the vaccinated group than in the unvaccinated group in both the cohort followed up for clinical episodes and the cohort followed up for incidence of infection is consistent with a lasting protective effect of the vaccine, this is not strong evidence of such an effect because the prevalence of parasitaemia would have been affected by the early effect of the vaccine and also by drug treatments, which would have occurred later in the malaria vaccine group than in the controls.

<sup>147</sup> Vaccines against pre-erythrocytic stages are designed to prevent blood infection and so the true measure of vaccine efficacy is the induction of sterile immunity, based in the Gambian and Mozambican trials on the time to first parasitaemia as detected by microscopy. However, Snounou et al. (2005, *ibid.*) also pointed out that by the end of the 6 month observation period, the cumulative numbers of control and vaccinated volunteers who developed a parasitaemia did not differ significantly (72% versus 66%, respectively, after four months in the Gambia, and 93% versus 83%, respectively, after six months in Mozambique).

### **3.7. Protective efficacy that is not strain specific**

In another study (before the recent Mozambique phase IIb trial) Allouche et al.<sup>148</sup> explored whether RTS,S/AS02 has a protective effect only against parasites with a CSP sequence similar to that of NF54.<sup>149</sup> Samples of parasites from breakthrough infections in control and vaccine groups from a trial in semi-immune Gambian adults were genotyped at two polymorphic regions of the CSP gene encoding T cell epitopes (*csp-th2r* and *csp-th3r*) to determine if the RTS,S/AS02 *Plasmodium falciparum* malaria vaccine conferred a strain-specific effect. They found that the overall distribution of CSP allelic variants was similar in infections occurring in both the vaccine and the control groups, although the vaccine had a marked effect on the incidence of infection. Indeed, the mean number of genotypes per infection in the RTS,S/AS02 group was not reduced compared with the controls. As Allouche et al. observe “This study demonstrates that RTS,S/AS02 protected Gambian semi-immune adults against *P. falciparum* infections in a non-allele-specific manner.” In their own words (for the more scientifically minded amongst the readers):

“If RTS,S/AS02 had an allele-specific effect, a reduction in the prevalence of the *csp-th2r\*03* and *csp-th3r-03* alleles should have been observed. Given the prevalence of the *csp-th3\*03* allele (35%) and the sample size in each group, the study had 99% power to detect a two-fold allele-specific effect of RTS,S/AS02. Since the prevalence of the vaccine type at *th2r* (*csp-thr2\*03*) was 16%, the study had 60% power to detect a two-fold effect at that locus. Thus, the statistical power was very high for *th3r* and reasonably high for *th2r*, so the lack of an allele-specific effect is well supported.”

This suggests the RTS,S/AS02 vaccine candidate should be tested in transmission settings where the NF54 strain is not the predominant type.

Allouche et al. then explore another possibility, that RTS,S/AS02 reduced the genetic complexity of infection. They assessed this by investigating typing of unrelated polymorphic loci. Differences in multiplicity were found between villages, suggesting local variations in the level of transmission, and these correlated with parasite density. As they put it: “Although the vaccine reduced the incidence of infection, it did not reduce the multiplicity per infection compared with the controls. A liver stage vaccine would be expected to induce a reduction or no change in the number of genotypes depending on whether it was strain-specific, but this was not observed in this study,” and yet overall vaccine efficacy was still maintained at 34% at the end of the follow up-period in the samples they used.

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<sup>148</sup> Allouche, A., Milligan, P., Conway, D.J., Pinder, M., Bojang, K., Doherty, T., Tornieporth, N., Cohen, J., Greenwood, B.M., “Protective efficacy of the RTS,S/AS02 *Plasmodium falciparum* malaria vaccine is not strain specific.” *Am J Trop Med Hyg*, 2003, Vol. 68, No. 1, pp. 97-101.

<sup>149</sup> Remember that the RTS,S/AS02 is a recombinant protein malaria vaccine that contains a large portion of the C-terminal of the circumsporozoite protein (CSP) sequence of the NF54 isolate of *P. falciparum* fused to the hepatitis B virus surface antigen.

### **3.8. Worries about the statistics and the nature of what is happening**

Some correspondents argued that Alonso et al. used “clever statistics” to hide the fact that they were studying an essentially marginal effect. Vaccine efficacy in extending time to first infection was determined in cohort 2. The argument made by these critics is that having found a slight but statistically significant decrease in the numbers of children experiencing at least one clinical episode of malaria in the 6 month study period after the last dose in the first study – 323 children had first episodes of asexual *P. falciparum* parasitaemia, of which 157 were in the RTS,S/AS02A group and 166 were in the control group – they manage to achieve with parasitaemia related parameters an estimated vaccine efficacy for extending time to first infection of 45%.<sup>150</sup>

At the same time, like others critical of the results, they also point out that there is little indication that significant reductions in parasite densities occurred in the RTS,S-vaccinated children. Indeed, there is no difference between the groups in geometric mean parasitaemia when looking at first episodes of malaria. Nor did the incidence of first episodes associated with hyperparasitaemia (>100,000 parasites/ $\mu$ L) differ between the two groups: “This suggests that a mere numerical reduction in the inoculum (i.e. a delay in the prepatent period) is unlikely to account for a reduction in peak parasitaemia and, possibly, severe disease incidence. This seems to indicate that the onset of malaria in vaccinated children is somewhat delayed and the severity might be slightly reduced, which is an interesting enough finding in its own right, but, this is nowhere near what the press and political coverage would indicate.”

Another correspondent observed that if, the average number of infective bites per child in the study period was around 15<sup>151</sup> and the CS titres, maybe helped by the alerted immune system per se and other factors induced by an also ‘liver specific antigen’ from HepB in the vaccinated group, have reduced the number of sporozoites that made it to the liver intact by, say, 50%, this alone would be capable of explaining all the observations made. This would not even require an additional role for overall immune stimulation and aspecific or HBsAg related effects during the blood stage infection.

On this correspondent’s rather glum interpretation, the vaccine targets the massively produced smokescreen antigen on the sporozoite (that has fooled the immune system for millennia) and it helps to keep the number of liver stages below threshold. The recipient is denied, say, half of the little bit of liver stage based protective immunity during the period of elevated immune system response and CS antibodies killing half of the sporozoites during transition to the liver. Then, it helps to delay the onset of clinical problems, hence treatment and death of the patient, so that the parasite gets even more time to make gametocytes and spread to the next host.<sup>152</sup> That is, after all, its evolutionary

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<sup>150</sup> 95% CI 31.4-55.9; p<0.0001; Alonso et al. 2004 *ibid.* Figure 4 and Table 3.

<sup>151</sup> As suggested by Alonso et al. 2004, *ibid.* p1412.

<sup>152</sup> Indeed, we have long had evidence that the burden of morbidity could simply be shifted. A unique set of experiments dating back to the Second World War showed that a reduction in the number of inoculated *P. falciparum* sporozoites by at least 90% simply led to a two- to three-day increase in the prepatent period,

goal. Indeed, unlike *P. vivax*, *P. falciparum* has only recently adapted to humans and, unlike *P. vivax*, still has to find a way to deal with the problem of mortality. On this correspondent's interpretation, the vaccine helps to overcome this problem for the parasite. The issue then is what are the consequences for individuals and for the greater population. From a commercial point of view, observed this correspondent, vaccines that are marginally protective in this way might be part of a solution (involving revaccination and drugs) for tourists and soldiers, but it was less clear they would be suitable for the purposes intended here. This was also the concern of a leading medical ethicist.<sup>153</sup>

One other concern was the way that dramatic-sounding figures can be driven out of very small actual numbers. For example, vaccine efficacy in extended time to first infection of 45% was determined in cohort 2 (95% CI 31.4-55.9;  $p < 0.0001$ , Figure 4 and Table 3 of Alonso et al. 2004). This came from 157 children in the RTS,S/ASO2 group and 166 in the control group with first episodes of asexual *P. falciparum* parasitaemia.

### **3.9. Problems in generalizing results to all potential users and infants**

The study excluded children who were malnourished, had a history of allergic disease, had a packed-cell volume less than 25%, exhibited clinically significant acute or chronic disease, such as HIV that we know may lead to poor immunogenicity and reduce vaccine effectiveness,<sup>154</sup> or displayed abnormal haematological or biochemical characteristics. The results are therefore not immediately generalizable to populations having such features. This is normal for a phase 2 study. These sorts of issues will be addressed in phase 3 and especially in the phase 4. The concern here however is with the way some of these important caveats are missing from the political and media coverage of these issues.

It would be useful, nevertheless, to see the population from which the sample was drawn before these exclusions were made. If Alonso et al. hardly had to do anything to the original population to get the sample, then this would be interesting to know in its own right. And it would be further useful to compare the actual sample used with typical populations where this potential vaccine would be used. Though ignoring these features is reasonable at such an early stage of vaccine development, some correspondents felt that more information on this would be helpful to decision makers – and for media and political coverage – even at this stage. One correspondent observed that it would be very valuable to know “who were excluded. For what reasons?” Another observed “I’m sure the data exists. We should ask Pedro [Alonso].”

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with no alteration in the course of the primary infection. Fairley, N.H., “Sidelights on malaria in man obtained by subinoculation experiments.” *Trans. R. Soc. Trop. Med. Hyg.* 1947, Vol. 40, pp. 621-676.

<sup>153</sup> I would give the person away without their consent if I said more than this, and this would be unfair.

<sup>154</sup> One correspondent wondered about haematological examination included CD4 counts instead of HIV testing.

**Efficacy did not significantly change with decreasing age**

There is one generalization that is hinted at. In the first paper, Alonso et al. observe that: “No interaction was recorded between age and vaccine efficacy, suggesting that efficacy did not change with increasing age.”<sup>155</sup> Further exploratory analysis was done in the first paper on subgroups which suggested that vaccine efficacy might be higher in the youngest children. In the follow-up paper, however, Alonso et al. report (twice) that: “We noted no evidence of an interaction between age at first dose and VE, suggesting that efficacy did not significantly change with increasing age,”<sup>156</sup> and there was no subgroup analysis. The quotes in the second paper, and the lack of subgroup analysis, suggest there was lack of *significance* in any analysis Alonso et al. tried to do to find any age-related effect.

These quotes could, of course, be read the other way too – that efficacy did not significantly change with decreasing age, i.e. that efficacy rates were similar for 1 year olds and 4 year olds (referring to age at the start of the trial).<sup>157</sup> Alonso et al. seem to be hinting that the effect will not be much higher for infants – unless there is some discontinuity at, say 6–12 months. We know that if the Alonso et al. figures are sound there *has* to be some discontinuity somewhere higher up the age range, given that there is constant rate of efficacy up to 4 years, but that, eventually, this drops dramatically: “Results from previous trials of RTS,S/AS02A in malaria-naïve volunteers or hyperimmune Gambian adults suggested that protection against infection induced by this vaccine might be short-lived.”<sup>158</sup>

This is not inconsistent with a story of some sort of boosting effect to the acquisition of natural immunity (and hence with the loss of efficacy at a higher age). The Alonso et al. data suggest a linear stretch with age – then at some point a collapse; though there is no story yet to explain this. Similarly, if there is no statistically significant change in efficacy with age, this also raises issues when it comes to visualizing boosting efficacy for those of the youngest age, since this would seem to imply an ability to shift the schedule for *all* ages, when we already know that efficacy has to collapse at some age, such that the shifting of the schedule for all ages would seem to create ever-increasing conflict with the need for efficacy to collapse at some age. Having efficacy rise as children get younger would have been a very useful finding. One correspondent observed that this reiterates also that the acquired immunity developed by children as they get bitten is not the same as that conferred by the vaccine, and that this backs up the previous observation that the antibodies directed to this vaccine and to those of the naturally acquired sporozoites with CS on their surface, are not the same.

Several correspondents were very struck by the revelation that there is no statistically significant age-related difference in efficacy. But another correspondent observed “What will happen from here on out is anybody’s guess. Mine is that the differences observed

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<sup>155</sup> Alonso et al. 2004, *ibid.* p 1418.

<sup>156</sup> Alonso et al. 2005, *ibid.* p 2015, and again on 9 2016

<sup>157</sup> At the same time: “For both circumsporozoite and HBsAg, immunogenicity of the vaccine was greater in children younger than 24 months of age.” Alonso, et al. 2004, *ibid.* p1416.

<sup>158</sup> Alonso et al. 2005, *ibid.* p2016.

will persist. This is because IMO the best explanation for the persistence is that the vaccine has given the kids a jump start on developing naturally acquired immunity.” Alonso et al. indeed argue that “First, the vaccine was much more immunogenic in this study population than it was in adults, and sustained immune responses might have resulted in persistent protective efficacy. Second, the high level of sporozoite exposure that happened during this trial could have resulted in natural boosting of protective immune responses not revealed by antibody measurements.”<sup>159</sup>

### **Another problem in generalizing the result**

Snow et al.<sup>160</sup> find that the risk of death after a clinical attack of *P. falciparum* is much higher in Africa than in South East Asia and the western Pacific. They argue that the incidence of severe, life-threatening complications of *P. falciparum* malaria in Africa is at least tenfold that in similar malaria endemic areas in India and Vanuatu. Why this is so is not clear, but Snow et al. suggest that it might include better access to prompt treatment and some cross-*Plasmodium* species protection against severe disease outcomes.

Alonso et al. point out that there was “intense follow-up and early management of disease”<sup>161</sup> during the trial, unlike what would be typical in field use. Indeed, this was given as one reason – along with the fact that the average age of recipients was 3 years at commencement of the trial<sup>162</sup> – for why the incidence of anaemia was low in both cohorts.<sup>163</sup> One correspondent pointed out that in this context there is an additional sociological/health systems problem potentially offsetting a low efficacy malaria vaccine in resource-poor settings and under conditions much less ideal than those of a vaccine trial, and that may lead to slower access to treatment, slower response of parents, and more deaths. As the correspondent observed, telling (low literate and illiterate and innumerate) mothers in some of the poorest areas of the world that their child is now vaccinated against malaria along with a range of other diseases (with the various different percentages for malaria enumerated) will have a negative effect on their alertness for malaria over the following months. Key to treating severe malaria and preventing the death of a child from malaria is diagnosis and access to treatment within 48 hours. As this correspondent pointed out, how do you tell the mother of a child vaccinated against malaria that she still needed to bring her child for treatment at first signs of symptoms?

### **Anaemia**

Similarly, by the time the average age of the recipient is in the target range for EPI (and not the current average age of 3 years at first dose) the trial will be back into “the high-

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<sup>159</sup> Alonso et al. 2004, *ibid.* p 1419.

<sup>160</sup> Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., and Simon I. Hay, S.I., “The global distribution of clinical episodes of *Plasmodium falciparum* malaria.” *Nature*, 2005, No. 434, pp. 214-217, [www.nature.com/nature/journal/v434/n7030/full/nature03342.html](http://www.nature.com/nature/journal/v434/n7030/full/nature03342.html).

<sup>161</sup> Alonso et al. 2005, *ibid.* p2021.

<sup>162</sup> Alonso et al. 2005, *ibid.* p2021 “This low rate of anaemia is probably the result of intense follow-up and early management of disease and the fact that as children get older, they leave the high-risk window when anaemia is a frequent complication of *P. falciparum* infection.”

<sup>163</sup> This would also have affected the definition of severe malaria, which was a composite of measures including severe malaria anaemia. At 8.5 months the prevalence of anaemia was 0.29% (2/692) in the control group versus 0.44% (3/688) in the vaccine group (p=0.686).

risk window when anaemia is a frequent complication of *P. falciparum* infection,<sup>164</sup> with this aggravating the result. Again, this has yet to be faced. Alonso et al. comment that the rates of anaemia during the study were much lower than expected. Indeed, this “surprised” them.<sup>165</sup> They observe that at 21 months none of the 649 children in the RTS,S/AS02A group and only two of the 663 in the control group had anaemia ( $p = 0.5$ ).<sup>166</sup> This is very low, and also partly related to the average age of the children being 3 years at commencement of the trial, and hence approaching five years towards the end of the trial, with many therefore out of the high-risk window for anaemia.

This limited the ability of the trial to detect significant vaccine efficacy for that endpoint: “Intense prompting of mothers or guardians to take their children to health facilities early in the disease process might have ensured prompt treatment of malaria cases and reduced the incidence of anaemia.” Similarly, a switch in Mozambique in November 2002 to a more effective first-line treatment for malaria meant that “children who received these drugs had more rapid clearance of parasites, less recrudescence, and therefore shorter duration of infections than did children who did not receive these new drugs. Each of these interventions could have had an effect on the recorded incidence of anaemia.”<sup>167</sup>

### **GSK**

One correspondent explained: “It is certainly true that a malaria vaccine trial has two objectives at least: First, to provide high quality data supporting licensure and, second, to provide experimental data of reliable quality. In contrast to other vaccines where clinical trials are conducted to deliver data related to specific laboratory values showing the build-up of an immune response, this is elusive for a malaria vaccine as no agreed parameters on biological correlates of protection from the disease exist: The parasite biology, and the immune response to it since the disease features are too complex. This explains why the GSK trials have so many supporters, as they help to advance the scientific debate and provide data on which others can capitalize. However, GSK has taken a step further. They believe that there is no alternative to their product and that trials have to continue with more and more younger aged children so as to cover the most vulnerable part of them (the group where mortality from malaria is highest). However, there are increasing challenges regarding the understanding of the immune response in very young children including RTS,S in a mixture of EPI vaccines.”<sup>168</sup>

### **3.10. Keeping the malaria vaccine playing field open and level**

Why are these issues and counter-issues important? And why must we cross-examine things in this way? Mainly because the parasite is very ‘clever’. Just over half (948) of

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<sup>164</sup> Alonso et al. 2005, *ibid.* p2016.

<sup>165</sup> Alonso et al. 2004, *ibid.* p1419.

<sup>166</sup> Alonso et al. 2005, *ibid.* p2016

<sup>167</sup> Alonso et al. 2004, *ibid.* p1419.

<sup>168</sup> The correspondent continued, observing that some of these issues are presently addressed by regulatory authorities.

the proteins detected in proteome analysis<sup>169</sup> of *Plasmodium* have been found in one stage only, suggesting that stage-specific specialization is substantial. However, many of these stage-specific proteins are found to belong to protein families whose expression is *strategy-specific*, reflecting both conserved mechanisms of parasite development between different stages and subtle molecular adaptations dictated by specific parasite-host interactions. The evolutionary goal of the parasite is, after all, not to make as many parasites as possible in one particular host and risk killing the host.

Instead, by injecting only very few sporozoites per bite, the number of liver stages can be kept low, since these are mainly responsible for triggering pre-erythrocytic immunity. Even for appropriately activated T-cells, few parasites are difficult to find in the enormous liver. So, by keeping the numbers of liver stages lower, time to onset of first parasitaemia and the moment of reaching clinically relevant levels of parasites in the blood can be delayed too, and the course of infection and the onset of severe complications can be delayed. The immune system gets more time to react. Natural premunity to malaria is a delicate balance between the parasite and the immune system where small changes can disturb the balance and lead to clinical manifestations in previously premune people, and an overall, aspecific stimulation of the immune system can significantly alter the course of a single malarial infection.

In a new layer of parasite-human interaction, the risk is that some advocates and politicians may respond in just the way the parasite (if it had a ‘strategy’ and a PR exercise) would want them to, by issuing astonishing statements such as that this result may “suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought,”<sup>170</sup> that “fundamental scientific puzzles do not still bedevil efforts to design and develop malaria vaccines,”<sup>171</sup> that “a life-saving vaccine could soon be available for malaria,”<sup>172</sup> and, even, that we have “a vaccination to prevent malaria that could be ready in three to four years time,”<sup>173</sup> and then lobbying hard for funding structures pitched towards these early outcomes.

**No evidence things have got easier, even as the high efficacy goal is pushed off**

This author finds no evidence for the Berndt et al. claim that the Alonso et al. trials have radically altered the time-frame to a highly efficacious malaria vaccine, or reduced the cost of reaching that vaccine. Indeed, the Malaria Vaccine Vision Statement goal was that “By 2015, we will have significantly reduced death and illness in young children in sub-

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<sup>169</sup> Hall, N., Karras, M., Raine, J.D., Carlton, J.M., Kooij, T.W.A., Berriman, M., Florens, L., Janssen, C.S., Pain, A., Christophides, G.K., James, K., Rutherford, K., Harris, B., Harris, D., Churcher, C., Quail, M.A., Ormond, D., Doggett, J., Trueman, H.E., Mendoza, J., Bidwell, S.L., Rajandream, M-A, Carucci, D.J., Yates, III, J.R., Kafatos, F.C., Janse, C.J., Barrell, B., Turner, C.M.R., Waters, A.P., Sinden, R.E., “A Comprehensive Survey of the *Plasmodium* Life Cycle by Genomic, Transcriptomic, and Proteomic Analyses.” *Science*, 2005, Vol. 307, Issue 5706, pp. 82-86.

<sup>170</sup> Berndt et al. 2005, *ibid*.

<sup>171</sup> A corruption of a quote made in the Tremonti, G. Background Papers (p25) that suggests that fundamental scientific problems are no longer an issue in the case of malaria.

<sup>172</sup> Gordon Brown, *The Guardian*, 11 January 2005, [www.guardian.co.uk/comment/story/0,3604,1683463,00.html](http://www.guardian.co.uk/comment/story/0,3604,1683463,00.html).

<sup>173</sup> Gordon Brown, [www.hm-treasury.gov.uk/newsroom\\_and\\_speeches/press/2004/press\\_94\\_04.cfm](http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_94_04.cfm).

Saharan Africa due to the successful development and introduction of an affordable malaria vaccine.” During the Roadmap process, and even as the Alonso results were being reported, the ultimate high efficacy goal was pushed off till 2025.

As Van de Perre and J-P Dedet observe in their accompanying article to the original Alonso et al. paper: “In any case, the road toward a safe and efficient malaria vaccine being available and useable on a large scale, or even incorporated into an expanded programme of immunization, will be long and chaotic. Thus, for many decades ahead, the expansion of preventive and therapeutic strategies, including those new ones with an evident added value (e.g. insecticide-impregnated bed nets and treatment with artemisinin-containing regimens) should remain an utmost priority to stop the malaria hecatomb. In parallel, new drug developments are also needed to face the worldwide extension of resistance by *Plasmodium* spp. More than ever, infants, young children, and pregnant women, who are heavily affected by the direct and indirect consequences of malaria in endemic areas, deserve worldwide scientific, political, and financial commitment. Such commitment is a question of equity, of human rights, and of disease exposure for half the inhabitants of our planet.”<sup>174</sup>

### **The dangers of policy distortions**

One former malaria biology and vaccine expert<sup>175</sup> when asked to react to the current situation and after reading the paper on the Mozambique study very carefully, described the eagerness with which policymakers and politicians so desperately need something – anything – that they “look where the light is, not where they lost their keys,” and that maybe “public pressure on malaria vaccine research is driving researchers into a desperate mode where they cannot afford the same scientific rigor that they would have if as few people died from malaria as from more lucrative diseases.” One correspondent responded to this observation with his/her own observation that: “It is more a problem that the increased attention to malaria has attracted more policy-hacks, overeager to appropriate themselves with a substantial chunk of the policy debate.”

Past vaccine failures suggest extreme caution in over-hyping one particular vaccine candidate over all others, and in supporting apparently simplistic solutions to the problem. We saw this excess optimism before with respect to previous candidate malaria vaccines, such as SPf66 that after much attention proved ineffective in infants in Africa. These had plenty of hype, just no chance of the sort of large new financial payments now being floated for RTS,S/AS02A.

We also run the danger of repeating the mistakes that led to rotavirus vaccines still being unavailable in poor countries today: Glass et al. put it thus: “As the world waited for the rhesus vaccine to become a successful global product, other vaccine manufacturers were reticent to push vigorously ahead, knowing that they would arrive late to the market. They anticipated difficulty in testing their new vaccines when a licensed product was already universally recommended...The lesson from the withdrawals of the first two

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<sup>174</sup> Van de Perre, P., Dedet, J.P., “Vaccine efficacy: winning a battle (not war) against malaria.” *The Lancet*, 2004, Vol. 364, pp. 1380-1383.

<sup>175</sup> Personal correspondence.

rotavirus vaccines is that we should never count on developing one candidate vaccine alone. If multiple candidate vaccines had been tested simultaneously, at least some of these might have survived the development process and be licensed and used today.”<sup>176</sup> The whole Glass et al. article is worth reading and reflecting on for the case of malaria, since it suggests that there were complete other histories for rotavirus vaccines that were missed because of poor policy at the time.

### **A long way to go still...**

When Alonso et al. observe that “Our results indicate the feasibility of development of an effective vaccine against malaria,”<sup>177</sup> this statement relates, as one correspondent put it “only to the experimental validity, and not to the validity of their trials as part of a clinical-industrial development process...The exercise to find more long-term protected children is huge and better data than those provided by Alonso lately would require a larger trial population and consequently a much more expensive trial outlay.”<sup>178</sup> The bottom line is that a great deal more Phase 2 investigations will be needed for RTS,S/AS02A both on its own and in combination with other antigens and with alternative or additional adjuvants. It will be a long time before a Phase 3 will be justified, and then, as one correspondent put it “mega-Phase 4 studies” will be needed to assess its impact in the real world of malaria in Sub Saharan Africa.

### **So, do not distort incentives**

And all the time it will be critical to keep the malaria vaccine playing field balanced with multiple parallel activities, should this particular candidate not pan out. One correspondent observed that “GSK has asked repeatedly for more support from various agencies, including the EC, but was always discouraged by the fact that funding was conditioned on giving up the usual company monopoly rights on the design and results of the projects. Most public research funding in the world will always require a certain tranche of funding from the company itself”.<sup>179</sup>

### **Why there is so little public debate?**

There is much more critical debate behind the scenes about RTS,S/AS02A than is sometimes let on. For various reasons there seems a natural tendency for scientists to be reticent: They often draw (or seek to draw) from the same limited funding streams; there is a natural tendency not to want to be too public with criticisms of the work of colleagues; and this is science, so sometimes the unexpected happens, and risk-aversion

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<sup>176</sup> Glass, R.I., Bresee, J.S., Parashar, U.D., Jiang, B., Gentsch, J., “The future of rotavirus vaccines: a major setback leads to new opportunities.” *The Lancet*, 2004, Vol. 363, pp. 1547-1550. One correspondent observed that “Actually, this is what happened in effect, only that companies were not loquacious about it and it took some time for them to bring their products, put on the back-burner, forward again to the front-burner.”

<sup>177</sup> Alonso et al. 2004, p1419.

<sup>178</sup> The same correspondent described the Alonso et al. claim that RTS,S/AS02A is “a promising vaccine candidate and strongly suggests that malaria vaccines have an important role as future public-health instruments,” as “all rather wishy-washy.”

<sup>179</sup> The next line is “MVI is only in the role of a cash provider for GSK and serves as a transactor to Gates,” which, though only someone’s personal opinion and fair to report, sounds a bit harsh in the body of the text.

and concern for reputation may lead those involved to be guarded about comments that may come back to haunt them later. From a psychological perspective, no individual is particularly keen to pour too much doubt on something that may turn out to ‘prove’ them wrong (including if sponsors destroy better outcomes that nobody gets to see), but which does nothing to improve *their* chances of success.

This author is not a malaria vaccine scientist, and does not have a reputation in the field to sustain. Independence makes raising uncomfortable issues a little easier (but not painless). And an economist (at least this one) tends to view these issues probabilistically: Maximizing the probabilities of a good solution is the goal, and small probability unexpectedly positive outcomes should not become overweighed in policy thinking. Neither should we judge ex post with the benefit of hindsight those decisions that had no such benefit ex ante. Nor should we worry ourselves that we will be judged this way, should it thus paralyze a proper critical assessment ex ante.

### **3.11. A few closing thoughts**

When the GSK announcement was first made, it triggered a flurry of commentary from malaria experts. At the risk of taking their remarks out of context, the response to the Lancet study, in a letter to Chancellor Gordon Brown, by Professors Bob Snow and Nick White of Oxford University, stood out (these are extracts from that letter, the reader should really read the whole letter<sup>180</sup> to see the more positive remarks too):

*“This was associated with vigorous and eye-catching publicity, notably the banner headline in The Times the preceding day claiming “New malaria vaccine will save millions of children”.*

*But we have had false dawns with malaria vaccines before — and it would be prudent to be cautious. Under normal circumstances, this report would herald a concerted effort to confirm or refute the findings in different populations in different parts of Africa with studies large enough to measure the impact on mortality from malaria; one study is certainly not enough to be sure of anything. But instead, you announced a week ago that the British taxpayers would pre-buy 300 million doses of vaccine for sub-Saharan Africa, costing probably £3 billion (US\$5.75 billion).*

*... We are seriously concerned, therefore, that while millions of people suffer every year, you are proposing to allocate precious funds to a future uncertainty. This good intention is misguided. We fear you have been advised poorly...*

*The sad truth is that, despite having now developed...effective tools (with substantial support from donors such as the UK government), the international community has failed in its promise to make them accessible to people most in need. Furthermore, partnerships*

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<sup>180</sup> Full copy at:

[www.scidev.net/gateways/index.cfm?fuseaction=printarticle&rgwid=2&item=Opinions&itemid=341&language=1](http://www.scidev.net/gateways/index.cfm?fuseaction=printarticle&rgwid=2&item=Opinions&itemid=341&language=1). Snow, R., is Professor of tropical public health at the Kenyan Medical Research Institute in Nairobi and the University of Oxford. White, N., is Professor of tropical medicine at Mahidol University, Bangkok, Thailand, and the University of Oxford.

*such as the World Health Organization, Roll Back Malaria, and the Global Fund against HIV, tuberculosis, and malaria — also supported generously by the UK government — have missed opportunities to go to scale with comparatively cheap, life-saving interventions...*

*Why, then, has the UK government decided to invest in an intervention that is more expensive and less effective than bednets and effective drugs? One argument might be that the bill does not have to be paid today. And when it does, it will probably be paid to a British multinational pharmaceutical company.*

*We have truly effective measles and tetanus vaccines (they are much more effective than the current malaria vaccine), and we have had them for decades. But these vaccines still do not reach all those who need them. Together measles and tetanus kill over a million children each year (World Health Reports 2003, 2004). Similarly, although we have a pneumococcal vaccine, it does not reach anyone because it is so expensive that no developing country government can afford it.*

*The prospect of a new vaccine against a killer disease has a seductive 'high-tech', 'feel-good' allure that is appealing to donors who seek neat solutions in modern technology.*

*Yes, prevention is better than cure. But this works both ways. If we provide insecticide-treated bednets and make effective drugs available, this will also reduce the incidence of malaria, and we will achieve better effects than with a weakly effective vaccine — and importantly we will spend less money.”*

*We need to raise sufficient funds from the rich world to support scale up and deployment of what we know works best, and we must do it now.”*

### **The take-home result from RTS,S**

There have now been many well-conducted efficacy trials of various formulations of RTS,S. As Snounou et al. observe: “In the vast majority of the trials, including those in naïve volunteers, the important take-home result is not necessarily that some individuals have been protected from infection but, instead, that the induced sterile immunity failed to be sustained for a sufficient length of time in an important proportion of the recipients. In its present form, the RTS,S vaccine might prove useful for transient visitors to endemic areas, such as tourists or military personnel. However, to fulfill its humanitarian goal, the ultimate aim of vaccination against PE stages is to confer protection against malaria infections through immunization regimens that are equally suitable for deployment in infants, as part of the expanded programme for immunization, and older residents of endemic areas. Considering that proven affordable measures to alleviate suffering, such as insecticide-treated bed nets and combination therapies, are available, one important issue that the malaria community should address is when to abandon onerous development programmes that fall short of these goals.”<sup>181</sup>

One correspondent observed: “A lot more studies need to be done (and are actually inscribed into the GSK product development plan). The final aim is to integrate the

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<sup>181</sup> Snounou et al. 2005, *ibid.*

vaccine into routine childhood immunization at a very low age and there are no data available as yet if this is possible. More and more studies will be needed in lower age groups. Pedro Alonso is tenacious and paves the way for these studies by developing a trial methodology for them. However, there are still so few trials that no valid conclusion can be drawn on specific correlates let alone the values of immunizing with a one antigen construct alone when there is already evidence that the molecular immune response profile is highly variable from transmission site to transmission site.”

Another correspondent, heading another vaccine PPP, observed that “GSK deserve credit for their persistence, and MVI for their ability to invest altruistic funds. I’m convinced that [the correspondent’s vaccine PPP] would have been unable to convince [its] financial donors to allocate large amounts of money for a RTS,S vaccine, until it had been proved, beyond doubt, that it could confer malaria specific clinical protection in the target population – infants. Other vaccines have failed when tested for efficacy in infants. The current GSK/MVI clinical development strategy is to conduct several inter-linked efficacy and dose-finding studies in infant populations under various transmission intensities. This can be seen as a moderate to high risk approach, but if successful, will considerably shorten the length of time it will take to register the vaccine. Meanwhile, GSK/WRAIR/MVI are looking for additional antigens such as MSP1 and AMA1 etc. to incorporate into the RTS,S vaccine. This is a commercially feasible/acceptable strategy. If the RTS,S, on its own, fails in infants (but failure by whose definition?), I’m afraid we will have a backlash of donor skepticism and fatigue.”<sup>182</sup>

Another correspondent argued: “We should not be rejoicing about reaching the famous 30% range that was reached by earlier ‘promising vaccines’ that were tested before (partly overlapping study designers) and from which we never heard again after lots of fuss. This time the fuss may lead to an even greater distortion in the already skewed malaria funding and policy world. I wished this whole discussion went on in an open forum rather than just between selected groups. Brown won’t listen to scientists (‘just jealous they did not find this glorious vaccine’) but would listen to a public outcry.”

Another correspondent blamed the current policy environment on policy consultants: “So why all this hype? It appears that the policy consultants have discovered a new market opportunity for themselves. It is the same as the one created by sectarian cults. They create a big artificial debate on an issue where the science is inconclusive and trap profile-hungry politicians. On the other hand, GSK has also some responsibility in this.”

From an ex ante scientific perspective, without the benefit of hindsight, the best scientific strategy is to keep multiple parallel leads open, and not to risk distorting funding and destroying this. As one correspondent put it much more capably than this author, the task of funders is to “hope for the best, but plan for the worst.” This is the core argument and purpose of this chapter.

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<sup>182</sup> An engineer colleague explained to the author the collapse of interest in cold fusion research following early extremely over-hyped results that proved impossible to replicate.

## **4. Malaria Vaccines: *Part of a Malaria Control Package***

This chapter explores what happens when malaria vaccines are but one element of a larger package of measures to counter the suffering of malaria. The next chapter will look at what happens when also the cost of each portion of vaccine R&D is only one part of the overall cost of developing a malaria vaccine.<sup>183</sup> The many tradeoffs are greatly complicated by the fact that there is no such thing as ‘a’ vaccine, once and forever, as the early APC subsidy models (and politicians still it seems) presume, and because malaria vaccines may both complement and compete with other parts of an overall package of measures, and it is not always clear when one case or the other holds.

### **4.1. *The Implied mix of malaria vaccines and other malaria interventions***

The Roadmap recognizes that “rushing a vaccine to marketplace may not be justified below a minimum threshold of efficacy, *especially as it relates to existing malaria control interventions.*” (emphasis added). That is, the threshold efficacy/duration of the vaccine goal cannot be set without reference to existing and projected malaria non-vaccine interventions – including also drugs, insecticide-treated mosquito nets (ITNs), transgenic mosquitoes (driving resistance genes to malaria into mosquito populations),<sup>184</sup> chemical treatment, environmental change, and many other control options – and, indeed, other vaccine options. Malaria vaccines will have to be “developed in concert with other malaria control mechanisms or strategies,”<sup>185</sup> including other childhood vaccines, and in light of the interplay of malaria and other infectious diseases and the health systems profile.

As Arrow et al. observe: “Insecticide-treated bednets can reduce child mortality substantially, given sufficient coverage of households. Environmental measures – spraying interior walls and rafters with insecticide, reducing mosquito breeding sites near houses – also work. These measures alone are worthwhile, but partnered with effective treatment, they are synergistic, especially in areas of relatively low malaria transmission... Similar programs utilizing multiple tools are not immediately feasible in all locales, but by targeting areas where transmission has already decreased somewhat, packaged interventions can achieve additional progress and valuable lessons applicable to high-transmission areas in the future.”<sup>186</sup> Arrow et al. argue also that “effective drugs

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<sup>183</sup> It might surprise readers to discover that the models and ‘cost-effectiveness’ evidence used to support APC schemes regularly ignore this.

<sup>184</sup> The point of this research has been recently challenged in work of Ken Vernick and others (presented at Gordon Research Conference on Malaria, Oxford, August 2005) arguing that mosquitoes are already naturally resistant.

<sup>185</sup> MVTR p12 (and similarly p32, “Need to ascertain delivery strategies in conjunction with other malaria control mechanisms”).

<sup>186</sup> Arrow et al. 2004, *ibid.* p11.

combined with other control measures in well-designed, locally appropriate programs can lower the malaria burden close to zero in some places.”<sup>187</sup>

A good example of this joined-up thinking is the recent success in KwaZulu Natal province, South Africa. Here the first internationally available ACT (artemisinin-based combination therapies)<sup>188</sup> prescribed after a positive rapid diagnostic test, was combined with indoor house spraying using the insecticide DDT, and ITNs.<sup>189</sup> Within two years malaria transmission was dramatically reduced. After three years, outpatient numbers had fallen by 99% and malaria-related deaths, by 97%.<sup>190</sup> There were relatively high initial costs, but significant long-term cost savings.

### **HIV interactions**

Increasingly we are also realising that the complex synergistic interactions between HIV and *P. falciparum* are having dramatic consequences. Recent studies have confirmed an association between HIV infection, clinical malaria, and *P. falciparum* parasitemia, especially among cases of advanced HIV.<sup>191 192 193</sup> Symptomatic *P. falciparum* seems to increase HIV-1 viral loads too.<sup>194</sup> The burden of malaria in HIV-infected pregnant women is increasing, and the immune deficiency of ever-growing numbers of HIV-infected people may pose an obstacle to vaccine effectiveness because of poor immunogenicity.<sup>195</sup>

The Roadmap observes that: “The diversity of costs, delivery mechanisms, and levels of effectiveness associated with the various interventions, plus the geographic variability of malaria transmission and the diversity of health system, compound the difficulties in

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<sup>187</sup> Arrow et al. 2004, *ibid.* p11.

<sup>188</sup> Artemether-lumefantrine, or Coartem™.

<sup>189</sup> See “New drug therapy slashes malaria cases in KZN.” *Science in Africa*, June 2004, [www.scienceinafrica.co.za/2004/june/malaria.htm](http://www.scienceinafrica.co.za/2004/june/malaria.htm).

<sup>190</sup> As a caveat, see Duffy, P.E., and Mutabingwa, T.K., “Rolling Back a Malaria Epidemic in South Africa.” *PLoS Med*, 2005.2, e368. They point out that the KwaZulu-Natal results may have been influenced by a strong local economy, low transmission rates, and weak immunity, making it easier to achieve better insect control and higher levels of treatment. They therefore argue that the long-term effectiveness of ACTs in highly endemic areas has not been proven. We also know that similar resistance issues can develop with respect to nets.

<sup>191</sup> Francesconi, P., Fabiani, M., Dente, M.G., Lukwiya, M., Okwey, R., Ouma, J., Ochakachon, R., Cian, F., Declich, S., “HIV, malaria parasites, and acute febrile episodes in Ugandan adults: A case-control study.” *AIDS*, 2001, Vol. 15, No.18, pp. 2445-2450.

<sup>192</sup> Whitworth, J., Morgan, D., Quigley, M., Smith, A., Mayanja, B., Eotu, H., Omoding, N., Okongo, M., Malamba, S., Ojwiya, A., “Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: A cohort study.” *The Lancet*, 2000, Vol. 356, pp. 1051-1056.

<sup>193</sup> French, N., Nakiyingi, J., Lugada, E., Watera, C., Whitworth, J.A., Gilks, C.F., “Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults.” *AIDS*, 2001, Vol. 15, No. 7, pp. 899-906.

<sup>194</sup> Hoffman, I.F., Jere, C.S., Taylor, T.E., Munthali, P., Dyer, J.R., Wirima, J.J., Rogerson, S.J., Kumwenda, N., Eron, J.J., Fiscus, S.A., Chakraborty, H., Taha, T.E., Cohen, M.S., Molyneux, M.E., “The effect of Plasmodium falciparum malaria on HIV-1 RNA blood plasma concentration.” *AIDS*, 1999, Vol. 13, No. 4, pp. 487-494.

<sup>195</sup> Observe that the recent RTS,S/AS02A trials removed in advance all HIV positive recipients from the trial sample.

formulating appropriate policies and regulations.”<sup>196</sup> Furthermore: “Recognizing that a future malaria vaccine will be delivered in conjunction with existing malaria control strategies, more information is needed on how a vaccine may effect clinical disease and severe malaria when administered *as one component in a set of interventions*” (italics added).

As one correspondent put it to the author, much more emphasis needs to be put on “the role of the customer in deciding what he/she is going to choose to control malaria in his/her country. The choice will not be between a malaria vaccine or nothing but whether or not a malaria vaccine will be a better investment than ITNs, ACTs or indoor residual spraying, which is having a come-back. A key issue will be the added value provided by a vaccine. RTS,S may show 50% protection against placebo but will be much less attractive if it adds only 10% to the efficacy provided by a long-lasting net.”

A picture emerges of an evolving *optimal* combination of interventions, with the threshold effect for each dependent on the others. If one is pre-fixed, the others are forced to adapt *to it* even if this is non-optimal. One can only wonder how this should impact the distribution of funding over possible vaccine candidates, if that funding is very limited and via an APC mechanism.

### **The overburdening of non-vaccine components**

Control/treatment programs may in turn suffer as a result of this lack of joined up thinking: “Malaria control programs are similarly overburdened...” and “may have to divert their attention to prepare for a low efficacy vaccine as it gets near to completion.”<sup>197</sup> The malaria vaccine vision meeting wrestled with the tensions in the other direction too: “Success of other control measures to control malaria may force vaccines to compete for limited funds as control methods are purchased and deployed.”<sup>198</sup>

Imagine, for example, how setting a pre-determined efficacy and duration requirement would fit in with other recent initiatives, such as the recent signing of a Declaration to Fight Malaria in Angola, Tanzania and Uganda – where the disease is a major cause of illness and death – and the launch by the US of a program to reduce malaria mortality rates by 50% and extend preventative measures and treatment to 85% coverage in targeted countries in sub-Saharan Africa, especially amongst the most vulnerable – children under five years old, pregnant women and people living with HIV/AIDS.

Polymorphism and antigenic variation already aggravate the notion of setting a threshold (and hence an implied set of evolving vaccines) a long time in advance. In turn this also makes it difficult to work out the optimal allocation of a fixed sum of subsidy taken from a larger budget designed to cover the greater package of vaccine and control measures.

In light of these new initiatives, how does one trade-off achieving a partially effective vaccine even as it dislodges or delays higher efficacy vaccines? We find in chapter 6 the

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<sup>196</sup> MVTR p32.

<sup>197</sup> MVTR p9.

<sup>198</sup> VMSR p4.

way that recent malaria vaccine cost-effectiveness evidence has been designed to overly-justify the value of low efficacy vaccines and the use of an APC in such a way that it risks tyrannizing all other components into inefficient submission.

### **Robustness to failure elsewhere**

Since the value of an imperfect vaccine may depend heavily on its coordination with other parts of an overall package, we need to review the robustness of each part of the global solution to any other part being absent or failing. Is the 50% efficacy threshold a great deal more dependent on other parts of the package holding than 80% efficacy, say in the light of polymorphism and drug resistance issues? How much does this reduce the value of the 50% goal? Will the 50% efficacy goal remain sensible if all of the above failures are corrected, but how is it compromised if all of these failures persist? After all, we would get at least 50% efficacy from the control measures we already possess. The 2005 G8 announced the goal “to reach 85% of the vulnerable with bed nets and drugs in order to save 600,000 children's lives a year by 2015.”<sup>199</sup> How does this affect the logic of the 50% goal? How can a 50% goal be operationally and permanently fixed without these issues even being analyzed?<sup>200</sup>

This also hints at the wide range of absorptive capacity issues in developing countries when multiple new technologies are being introduced, and the way this also feeds back on the risk of developers and suppliers. Most of this was ignored in the APC literature because of the early decision to simplify to a problem where a vaccine replaced treatments.

### **EPI**

As another simple practical example of robustness, how easily would a low efficacy multi-dose malaria vaccine fit as part of the EPI?<sup>201</sup> What if other vaccines in the package are very unlike this one? Maybe the value of a malaria vaccine would be so high that breaching compatibility with EPI schedules would be justified, as pointed out by some malaria stakeholders<sup>202</sup> and we would not want to be tied to the EPI. But again, this suggests that the vaccine cost-effectiveness has to be worked out based on the package of measures and the rate of efficacy. The cost-benefit analysis of breaching current EPI conditions is much less favorable for the 50% efficacy vaccine than for the 80% efficacy

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<sup>199</sup> Prime Minister Blair, update to Parliament, [www.g7.utoronto.ca/summit/2005gleneagles/blair-parliament.html](http://www.g7.utoronto.ca/summit/2005gleneagles/blair-parliament.html).

<sup>200</sup> Given the false sense of security that a low efficacy therapeutic HIV vaccine would create, a barrage of prevention and drug treatment programs would be needed into the foreseeable future for HIV – on top of the costs of developing and using any vaccine. In particular, the benefits of low efficacy, or efficacious but short-lived, vaccines could easily be outweighed by behavioral changes, in particular an increase in the risk-taking of recipients. Meanwhile, such vaccines drain the fixed-size subsidy pool that could have gone towards those working on preventative or higher efficacy therapeutic vaccines. This too aggravates the notion that, from a very early date, a minimal (operational) efficacy could be set for a HIV vaccine, and the cost-effectiveness could easily be worked out so far in advance as to be able to set a precommitted ex post subsidy and relevant product specific goals.

<sup>201</sup> MVTR p2.

<sup>202</sup> RMSR p9.

vaccine if other treatment and control measures are in place, but we simply do not know the exact benefit.

#### **4.2. Purchasers do not drive what they get under an APC**

An approach that emphasizes the cost-effectiveness *over time* of each component of a coordinated package relative to every other component of the package does not sit well with a large subsidy attached to only one, highly imperfect, component of the package (a subsidy that is, indeed, mostly ‘windfall’<sup>203</sup> payment to a ‘winning’ firm).

Stakeholder feedback worries that it “considers vaccines in isolation – not competing with other control measures” and that the report should “restate as 50% effective as part of [an] overall control strategy.”<sup>204</sup> These worries are well-founded. *Precommitted* subsidy funds, by driving the marginal cost to purchasing countries of low efficacy vaccines much lower (as low as a dollar or so, it has been claimed<sup>205</sup>), gives such vaccines an ‘uncompetitive’ advantage against other malaria interventions. Indeed, unless those organizing the APC subsidy scheme have extraordinary foresight and credibility, this also differentially disadvantages higher efficacy vaccines if such vaccines are higher cost to develop or to manufacture compared to lower efficacy vaccines (see more on this below). The fact that the fund is sunk and *has* to be spent makes this worse. There is overuse of (low efficacy) vaccines, and burdens onto other parts of the overall package.<sup>206</sup> Let us think about this from the perspective of both the purchasers and the firms who develop vaccines.

#### **What do firms respond to?<sup>207</sup>**

What are the incentives of firms? By *not* offering firms a guaranteed payment, but supposedly facing them instead with *variable* demand generated by purchasers (the ‘Advance Market’ twist<sup>208</sup> to the APC idea), developers, we are told, will have an incentive to target useable ‘better’ malaria vaccines that are ‘wanted’ by countries. For example, if malaria treatment and prevention schemes are heavily boosted, thus making a 50% efficacy vaccine much less useful – and, *ex post*, much less optimal than it looked *ex ante* – it is claimed that firms will have a natural incentive to try to develop products of much more than the minimal 50% efficacy, realizing that they have ‘lost the market’

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<sup>203</sup> In the sense that the subsidy payment is to cover the R&D leading to the creation of vaccines and not just to cover manufacturing costs (which would not need an APC), and will be many times a firm’s actual R&D outlays if there really are multiple parallel developers.

<sup>204</sup> MVTR p2.

<sup>205</sup> And even this may be paid for from co-payment funds from outside of the purchasing countries.

<sup>206</sup> This is all compared to what would have been the case had the full costs and range of options been presented to the purchasers. It bites more, the lower the efficacy of the vaccine.

<sup>207</sup> This is all based on the notion that firms do respond. One repeated insight in this paper is that if incentives are set up to incentivize firms to behave badly, they may simply refuse to take part in the first instance, in part to avoid the reputational damage. Forcing firms to face a badly-chosen goal is neither good for those needing vaccines nor for firms themselves.

<sup>208</sup> It is just a twist, because we are already these days back – as anyone could have predicted – dealing with simple purchase precommitments (c.f. recent announcements, as evidenced below, about deals between GSK, the UK and other governments, and the Gates Foundation for a particular product).

for the 50% vaccine, even if the goal and the APC subsidy scheme allows the 50% vaccine to take all of the subsidy pool.

However, if a scheme is in place *guaranteeing* a large subsidy for each purchase of the low efficacy vaccine, developers ‘only’ need to sell 200 million treatments at a cost to country purchasers of \$1 per treatment, to take the entire subsidy pool. In the CGD case, \$3bn – but possibly a great deal higher – can be acquired by the firm for just £200m of purchaser expenditure.

### **Incentives to aim for higher are numbed**

Similarly, there is no point in this or any other firm investing in new R&D and production capacity (for a different vaccine) if the \$3bn can be had for \$200m of extra costs (supposedly the case, given \$1 per course manufacturing costs). Farlow<sup>209</sup> has repeatedly observed that such subsidy schemes force incentives onto the least challenging outcome that sellers can get away with in a self-fulfilling fashion, with this leading to poorer efficacy and duration on average per unit of funding.

Sellers also have a huge rent-seeking incentive to sell these vaccines, and a cost advantage too: If later better products that are more costly to manufacture do not get higher subsidies, then the discounted value of the per-unit revenue of sales of a firm’s current vaccine product is greater, but without any need to engage in the R&D costs needed to get the later product to market. We will also see later that if capacity – or more specifically the sunk costs of this capacity – is already in place,<sup>210</sup> the manufacturing cost structure also favors the 200m lower efficacy vaccines.

Indeed, the subsidy *should* vary (and be known to vary) across products according to efficacy, relative complexity of development, costs of production, and expected time to development, etc., but no committee could ever competently set this up in advance, and this has not even been politely discussed by APC advocates. If, in addition, the subsidy pool and the price of the product are not growing at the rate of discount used by investors, this makes the cost disadvantage of the later product even worse. A flat subsidy regardless, and a low flat price to purchasers regardless, completely numbs dynamic incentives. Since such subsidy schemes are never allowed to set efficacy and duration terms higher than the originally-set terms (but they can be allowed lower), the subsidy fund, the lack of any price signals, and the 50% goal have quashed any incentives to push for anything higher.

Observe how this is all very different from other subsidy-based schemes, such as that proposed by Arrow et al. for malaria drugs (see below). In that case, the subsidy payments take place only after firms have competed to supply, and have therefore been given strong incentives to improve on production costs and quality.

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<sup>209</sup> See especially Farlow, A.W.K., 2004 *ibid.* Section 7, Farlow, A.W.K., WHO, 2005, *ibid.* Section 3, and Farlow, *Innovation Strategy Today*, 2005, *ibid.*, p84, p104, and p110.

<sup>210</sup> This may not be the case of course.

**Do purchasers ‘decide’?**

Conversely, purchasers do not respond to the \$3bn either, but instead only to the \$200m (or not even to that, if someone else pays the co-payment). So long as it is worth more than \$1 per course to them above and beyond incidental extra costs of use (these extra costs are nevertheless high) *at the time of purchase*, they have an incentive to use the product. Contrary to the claims of APC advocates, there are *no* relevant price signals to guide buyers *at the time of purchase*. The cost-effectiveness to buyers *at the time of purchase* might be high at only \$1 per course, even if they *would have been* better off if incentives had instead been created to generate, within the same budget, a much better vaccine sooner than it will now arrive (or arrive at all).

For example, if payment for R&D is via an APC subsidy, developers will, supposedly (since it is not at all obvious, as we will see below), manufacture the low-efficacy vaccine at a dollar or so, and most of the \$15 or \$25 subsidy (or however much it turns out to be) will be to repay to the ‘winning’ developer the collective R&D costs of the multiple parallel developers (\$14 or \$24 leveraged by \$1 of payment from the purchaser). *At the time of use*, a product whose true cost of creation is \$15 or \$25 has a cost to users of \$1 or less. Clearly, the whole point of the subsidy is to repay the sunk R&D costs. However, the consequence is that the cost to the users *at the time of use* of the less efficacious component is now lower relative to alternative components of the overall malaria package that do not get subsidies, and poorly reflects the cost of creation of the low-efficacy component.

Furthermore, since the APC subsidy does not apply to other products, incentives are biased towards a package of measures that over-uses *this* component regardless of whether or not its use *at the time* contributes to the most cost-effective<sup>211</sup> overall package judged *ex ante* (i.e. the marginal impact per dollar spent on alternatives would have been higher). The reader should visualize how the problems in this section and in other sections of this report just get ever more troublesome as the subsidy gets larger and larger. How would \$50 or \$100 ‘windfall’ payment unlocked by \$1 work out in practice?

As part and parcel of this same problem, where there is a *range of vaccine efficacy* to aim for under a binding budget constraint (over vaccines and non-vaccine alternatives) but no useful price signal to purchasers of the vaccine, the decision as to whether a less efficacious vaccine is more valuable than a more efficacious vaccine, and how much of a distorted overall package to accept, has to be made *before* the investment decisions that lead to the low efficacy vaccine’s creation in the first place.

Furthermore, even if countries are aware of these inefficiencies, if they regard their individual purchases as marginal to the collective possibility of a better vaccine, they face a standard prisoners’ dilemma. Collectively they might all be better off refusing to use the low efficacy outcomes and thus not using up all the fixed pool of subsidy (and, in order to incentivize investors, they would want to credibly signal this), but if they do not

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<sup>211</sup> I.e. there is a budget constraint. We see everywhere throughout the APC literature what happens when budget constraints are dispensed with.

believe that other purchasers will do the same, then they individually have an incentive to use the ‘lower quality’ vaccines anyway, making lower quality vaccines a self-fulfilling outcome. The good vaccines are not supported in equilibrium.<sup>212</sup>

### **Countries take what they are given**

CGD heavily *relies*, in its 2005 report, on the notion that the choice of vaccine efficacy, especially the improvement of vaccine efficacy over time (i.e. follow-on innovation) – and how vaccines fit into an overall package of measures, given these APC subsidy schemes – is driven by purchasers. As Barder, Kremer and Levine claim on behalf of CGD: “The power to distribute the funds would not lie in the hands of the adjudication committee. No funds would be distributed unless and until developing countries decide that they want to use the vaccine...In particular, it [the committee] would not be responsible for allocating funds for R&D, or for deciding which company received the return.”<sup>213</sup> A DFID Briefing note<sup>214</sup> claims: “An APC aims to create a competitive developing country market for future vaccines” (rather like a developed economy drug market really?). The Tremonti Report (some of the same authors again) claims: “Donors commit to subsidize the purchase of a new vaccine if and when one is developed to meet the standards required and it is demanded by developing countries...[The actions of the committee] *replicates market conditions prevailing in developed countries...AMCs are market-based...Market forces rather than donors* determine the allocation of the additional investment on vaccine development,”<sup>215</sup> and “AMCs are a *market-based* form of public intervention. They are not a prize for the first successful vaccine developer, but an open-ended multi-year commitment that encourages entry, competition, and continued innovation. *Market forces* rather than donors determine the allocation of the additional investment on vaccine development stimulated by the AMC.”<sup>216</sup> And “It’s a *market-oriented* form of aid.”<sup>217</sup>

This ‘market’ claim is sheer myth, but the more times they are told that it is myth, the greater the emphasis those promoting APCs put on it, seemingly following the logic that if ever more assertive claims are made about the ‘*market*’ credentials of APCs, politicians and the media will be persuaded to swallow the claim whole without asking awkward questions about it first.<sup>218</sup> The Tremonti line in particular is overloaded with everything this author has criticized Kremer, Barder, and Levine for ignoring.

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<sup>212</sup> Farlow 2004, *ibid.* Part 7 explains lots of other factors pushing towards a lower quality collective result in such systems.

<sup>213</sup> Barder et al. May 2005, *ibid.* p7.

<sup>214</sup> DFID, “Introducing Advance Purchase Commitments: A package for immunization.” Consultation Note, DFID, Version 3 June 2005 (no specific author, but very reminiscent of the writings of some of the authors of the GGD Report and the Tremonti Report). [www.bvgh.org/documents/DFIDAPC2-pager.pdf](http://www.bvgh.org/documents/DFIDAPC2-pager.pdf), p1.

<sup>215</sup> Tremonti, G. Executive Summary, 2005, pi (the report even states that the size will be set large enough for only one to two developers).

<sup>216</sup> Tremonti, G. 2005, *ibid.* p3.

<sup>217</sup> Kremer, M., 19 November 2005, *ibid.*

<sup>218</sup> See Croke, K., “Using Markets to Fight Disease for Development.” *Progressive Policy Institute*, October 28, 2005.

[www.ppionline.org/ppi\\_ci.cfm?knlAreaID=450004&subsecid=900020&contentid=253603](http://www.ppionline.org/ppi_ci.cfm?knlAreaID=450004&subsecid=900020&contentid=253603).

**Outcomes are determined by the goal-setting process and the end committee, and not by purchasers**

The claim is increasingly made to shake off the fact that the main decisions framing the purchasers' heavily subsidized choices are made in the goal-setting process, and by the committee running the subsidy scheme after investors have sunk their R&D costs, with very little genuine market-based pressures at all. The myth that it is otherwise is deliberately used to detract from the weakest feature of the whole approach – that it is *not* market-based – and to deflect worries about the competence of such a committee and its ability not to be captured or corrupted. The Tremonti Report even seeks to maintain this myth that “countries decide” while also maintaining that “vaccines are bought by developing countries through a small number of international agencies.”<sup>219</sup>

It is claimed that those who set up the scheme are “responsible for specifying the goals but do not control”<sup>220</sup> the outcome, and that purchasing countries should take the blame for bad outcomes. In truth, however, whether the purchasers get 30% or 50% or 70% efficacious vaccines has nothing to do with any choice they make at the moment of purchase.

**4.3. Unbalanced subsidies harm other R&D, including R&D to tackle resistance**

Many of the other components of the overall package also require R&D for their development and improvement. As Guerin et al. observe:<sup>221</sup> “New and innovative methods of vector control, diagnosis, and treatment should be developed, and work towards development of new drugs and a vaccine should receive much greater support. But the pressing need, in the face of increasing global mortality and general lack of progress in malaria control, is research into the best methods of deploying and using existing approaches, particularly insecticide treated mosquito nets, rapid methods of diagnosis, and artemisinin-based combination treatments. Evidence on these approaches should provide national governments and international donors with the cost benefit information that would justify much-needed increases in global support for appropriate and effective malaria control.”<sup>222</sup>

**R&D to tackle resistance**

A key target of R&D is to tackle resistance. Until about 20 years ago, the drug chloroquine was the standard malaria drug. It was cheap (about 10 cents per treatment) and worked well, but chloroquine-resistant strains are now rife. However, there are new effective drugs available. When the first signs of drug-resistant malaria appeared in Asia, Chinese scientists developed a family of drugs based on artemisinin compounds made from a common shrub, the sweet wormwood, which had been used for centuries in traditional Chinese medicine.

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<sup>219</sup> Tremonti, G., Background Papers, p6.

<sup>220</sup> Barder et al. 2005, *ibid.* p3.

<sup>221</sup> Guerin et al. 2002, *ibid.*

<sup>222</sup> Guerin et al. 2002, *ibid.* p564.

To combat future drug resistance there is also the need to partner artemisinins with other anti-malarial drugs, creating what we already know to be well-tolerated artemisinin combination therapies (ACTs)<sup>223</sup> – the same approach that underlies the treatment of HIV and tuberculosis. In 2002, the World Health Organization urged governments to adopt such therapies rapidly. Scaling up the delivery of ACTs will also be extremely cost-effective, even in the most resource-poor countries.

Resistance is more likely to emerge when transmission is low, background immunity is weak, parasite numbers in an individual are high, and when there is intense drug pressure.<sup>224</sup> Emergence of resistance also depends on the properties of drugs<sup>225</sup> – drugs with long half-lives and for which resistance is conferred by single-point mutations rapidly select resistant parasites, and poor quality or fake drugs also contribute to the emergence of resistance.<sup>226</sup> Allowing resistance to develop has a wide range of follow-on costs, including increased malaria mortality and morbidity, reduced duration of clinical improvement and impaired haematological recovery after treatment. There are increased costs to the health-care system and many children never grow up truly healthy.

If resistance to artemisinins is allowed to develop and spread before replacement drugs are developed, the death toll from malaria could rise even higher. Trape et al. concluded that the development of resistance to chloroquine has resulted in a four to eight fold increase in mortality.<sup>227</sup> Guerin et al. argue that “In general, the effects of resistance to antimalarial drugs on malaria morbidity and mortality are underestimated.”<sup>228</sup>

#### **Current efforts to tackle resistance**

To meet the challenge of resistance, MMV looks set to bring forth three to four new drugs by 2010. Similarly, better combinations that reduce the number of tablets per treatment thus improving patient compliance, and fixed-dose formulations that avoid the risk of patients taking only one of the active drugs, will all contribute to reducing the risk of resistance. However, ideal combination regimens remain uncertain with much R&D needed to determine this.<sup>229</sup>

In addition, since frequent misdiagnosis complicates the appropriate use of antimalarial drugs, and over-treatment is common, much more R&D of field-adapted diagnostic tools is needed too.

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<sup>223</sup> And a need to discourage the distribution of any solo drug that might encourage resistance.

<sup>224</sup> Hastings, I.M., and D’Alessandro, U., “Modelling a predictable disaster: the rise and spread of drug-resistant malaria.” *Parasitol Today*, 2000, Vol. 16, pp. 340-347.

<sup>225</sup> White, N.J., “Antimalarial drug resistance and combination chemotherapy.” *Philos Trans R Soc Lond B Biol Sci*, 1999, Vol. 354, pp. 739-749.

<sup>226</sup> For example, fake artesunate or mefloquine have been reported throughout southeast Asia: Rozendaal, J., “Fake antimalaria drugs in Cambodia.” *The Lancet*, 2001, Vol. 357, p890; Newton, P., Proux, S., Green, M., et al. “Fake artesunate in southeast Asia.” *The Lancet*, 2001, Vol. 357, pp. 1948-1950.

<sup>227</sup> Trape, J.F., Pison, G., Preziosi, M.P., et al. “Impact of chloroquine resistance on malaria mortality.” *C R Acad Sci III*, 1998, Vol. 321, pp. 689-697.

<sup>228</sup> Guerin et al. 2002, *ibid*.

<sup>229</sup> For a review of the literature on combination regimes, see Kremsner, P.G., and Krishna, S., “Antimalarial combinations.” *The Lancet*, 2004, Vol. 364, pp. 285-294.

Another big challenge is the treatment of malaria during pregnancy, since pregnant women are the main adult risk group. Infection can result in spontaneous abortion, neonatal death, and low birth weight. Antimalarial drugs need to be safe during pregnancy. One approach has been intermittent preventive treatment, with at least two preventive treatment doses given during routine antenatal clinic visits. Another challenge is to further study intermittent preventive treatment for infants, treatments for emergency situations, and treatments for severe malaria.

Later we will discuss the importance of developing new combination therapies that do not rely on drugs extracted from plants. Guerin et al. argue: “However, no one can predict how long the present combinations will remain effective, so truly new, affordable, and easy-to-use compounds to treat malaria must be developed as well. As new drugs are developed, they should also be included in combinations. More research is needed, but this should not be an excuse for delayed action. Unless a radically different treatment strategy is adopted now, with available effective combinations of antimalarial drugs, malaria rates will continue to increase and drug resistance will worsen.”<sup>230</sup>

### **Long-lasting mosquito nets**

The recent Millennium Project<sup>231</sup> identified malaria control as a ‘quick win’, where rapid concerted action could have dramatic effects in improving people’s lives, halve the numbers of malaria attacks in young African children and save more than one in five of all childhood deaths. The report calls for the mass distribution of mosquito nets treated with a long-lasting insecticide and effective anti-malaria medicines for all children in Africa by 2007. The nets are one of the most effective ways of preventing malaria, and cost just \$3-\$4 each, and if used properly, last for at least five years. Studies find that such nets reduce malaria episodes by up to 50%.<sup>232</sup>

There are also new ways of mass treating long-lasting insecticide-treated mosquito nets (LLINs) at the factory level, to better bind insecticide to nets so that it lasts longer. These are scalable (net treatment machines come in different sizes to fit specific factory needs) and easily transferable, and this will potentially dramatically improve the supply of LLINs. Nevertheless, much further work remains to be done on new combinations of insecticides and fabrics. Deployment of insecticide-treated nets in China and Africa has been successful in reducing malaria morbidity, mortality, or both,<sup>233 234</sup> but the decrease in naturally occurring immunity impacts the medium term effect,<sup>235</sup> and the effectiveness of insecticide-treated nets varies with the rate of malaria transmission; nets do not work

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<sup>230</sup> Guerin et al. 2002, *ibid.*

<sup>231</sup> [www.unmillenniumproject.org/reports/index.htm](http://www.unmillenniumproject.org/reports/index.htm).

<sup>232</sup> <http://allafrica.com/stories/200501260806.html>.

<sup>233</sup> Aikins, M.K., Fox-Rushby, J., D'Alessandro, U., et al. “The Gambian National Impregnated Bednet Programme: costs, consequences and net cost-effectiveness.” *Soc Sci Med*, 1998, Vol. 46, pp. 181-191.

<sup>234</sup> Utzinger, J., Tozan, Y., Singer, B.H., “Efficacy and cost-effectiveness of environmental management for malaria control.” *Trop Med Int Health*, 2001, Vol. 6, pp. 677-687; Lengeler, C., “Insecticide-treated bednets and curtains for preventing malaria.” *Cochrane Database of Systematic Reviews*, 2004, Issue 2.

<sup>235</sup> Druilhe, P., Renia, L., Fidock, D., “Immunity to liver stages.” In: Sherman, I.W., ed. *Malaria: parasite biology, pathogenesis and protection*, 1998, Washington DC. American Society for Microbiology, pp. 513-543.

well in many areas of low and unstable transmission, and/or where malaria vectors bite in the early evening and morning.<sup>236</sup> More information is needed on the relation between the extent of community-wide use of insecticide-treated nets and malaria morbidity, mortality, and transmission.<sup>237</sup>

### **Environmental management**

A recent systematic review<sup>238</sup> of 40 studies that emphasized environmental management interventions against reported clinical malaria variables as outcome – interventions such as measures aiming to create a permanent or long-lasting effect on land, water, or vegetation to reduce vector habitats, methods creating temporary unfavorable conditions for the vector, and modifications of human habitation – argues that malaria control measures built around environmental management are “non-toxic, cost-effective, and sustainable.” In 16 studies that applied environmental modification and in eight studies on modification of human habitation, the risk ratio of malaria was reduced by 88%<sup>239</sup> and 79.5%<sup>240</sup> respectively: “We conclude that malaria control programmes that emphasise environmental management are highly effective in reducing morbidity and mortality. Lessons learned from these past successful programmes can inspire sound and sustainable malaria control approaches and strategies.”<sup>241</sup>

### **Distorting non-vaccine R&D incentives**

A heavily-subsidized partially-effective malaria vaccine would have a negative impact on R&D incentives for non-vaccine R&D by making the value at the margin of investments in these other R&D routes weaker and more uncertain.<sup>242</sup> In addition, the marginal cost in the field of doing some alternative investments is also effectively higher in comparison to purchase of a low-efficacy vaccine.

All these problems are further complicated by the fact that an APC-subsidized vaccine is supposed to fall – *legally* according to the APC contracts – in price to about \$1 in the long-run.<sup>243</sup> More on this below, but the upshot is that this forces vaccine firms to scale

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<sup>236</sup> Kroeger, A., Gonzalez, M., Ordonez-Gonzalez, J., “Insecticide-treated materials for malaria control in Latin America: to use or not to use?” *Trans R Soc Trop Med Hyg*, 1999, Vol. 93, pp. 565-570.

<sup>237</sup> See “Scaling up insecticide-treated netting programs in Africa.” Roll Back Malaria, August 2002, [www.lshtm.ac.uk/dfid/malaria/Acrobat%20documents/scaling\\_up\\_itn\\_programmes\\_strategic\\_framework.pdf](http://www.lshtm.ac.uk/dfid/malaria/Acrobat%20documents/scaling_up_itn_programmes_strategic_framework.pdf).

<sup>238</sup> Keiser, J., Singer, B.H., Utzinger, J., “Reducing the burden of malaria in different eco-epidemiological settings with environmental management: a systematic review.” *The Lancet Infectious Diseases*, 2005, Vol. 5, Issue 11, pp. 695-708.

<sup>239</sup> 95% CI 81.7-92.1.

<sup>240</sup> 95% CI 67.4-87.2.

<sup>241</sup> Keiser et al. 2005, *ibid.* p695.

<sup>242</sup> Remember, again, that we are distinguishing ex post and ex ante thinking. There will always be a distortion, but what we are looking for is the globally optimal price distortion – hence why we would be interested in not bluntly fixing efficacy without regard to its marginal impact on other components of an overall package.

<sup>243</sup> Though this author argues that, if anything, the incentive to drive this price down will now be weakened given a range of limiting factors, including the dangers of a sole supplier, the higher likelihood that the vaccine will only be of short-lived value making it less cost-effective for firms to install capacity to drive price down, the low level of competition in the end market with reduced cost pressure, the lack of

up even a low efficacy product to achieve the \$1 price even as it puts better products and alternative technologies at an artificial disadvantage.<sup>244</sup>

#### **4.4. Unbalanced subsidies create coordination difficulties**

There is a more subtle distortion, and yet more reasons to doubt the ‘countries decide’ claim. Some components of a control package need coordination across countries and regions. For example, as well as drugs, the value of ITNs, a transmission-blocking vaccine, DDT, or transgenic mosquitoes (see the critical comments elsewhere and in the literature about the possibilities of this working) rises as more countries or regions coordinate on the use of the technology.

Bednets not only reduce the number of infective bites for a given mosquito population but have important mass insecticidal effects. It is already the case that even in areas where the benefits are great and bednets have been deployed through national programs, community uptake has been disappointing: Sustainability is already an issue. Rabinovic lists the potential benefits of a transmission-blocking vaccine but observes that these strengths are complicated by the ultimate goal: “the need to immunize – not just vaccinate – virtually every person in a community, regardless of age or other conditions, to benefit not the individual but the community.”<sup>245</sup> Transmission-blocking simply could not work in a high-transmission areas without extremely good coordination. Resistance of vectors to insecticides is also increasing, further strengthening the case for coordinated use.

Yet, if a mechanism allows countries or regions to choose whether or not to take part in a particular technology and to use other financially-favored technologies instead (inferior vaccines that supposedly countries can ‘choose’, courtesy of an APC, at \$1 per course) the failure of these countries to coordinate on the first technology will increase the risks to other countries of using that technology, and force these other countries into sub-optimal choices themselves. Imagine the cost disadvantage caused by a poorly-fitted subsidy to a non-transmission-blocking vaccine and the potential destruction of value of a transmission-blocking vaccine – with this possibility feeding back to undermine incentives to develop transmission-blocking vaccines in the first place. Bluntly, it is not possible to have components of a package that requires coordination sitting alongside components that allow countries to deviate from coordination at heavily-distorted subsidized prices: The inferior route is always self-fulfilling.

Given that a pre-commitment to buy a highly-imperfect vaccine will need a lot of supportive control measures, the upshot is that the unequal pattern of subsidies may end up forcing those working on malaria control measures to cooperate against their will with

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technology transfer, etc. More on these issues below. The \$1 has recently been revised up to \$6, and, indeed is made indeterminate in some of the recent discussion. It is after all, indeterminate in practice.

<sup>244</sup> Of course, firms are supposed to factor the obligation to keep supplying at \$1 into the expected overall rewards including rewards from making the early sales. We later see that this is very tough to imagine firms doing.

<sup>245</sup> Rabinovic, R., *ibid.* 2004, p210.

a vaccine (based on RTS,S?) that they would otherwise not have chosen. The author recognizes the need to cover the sunk costs of R&D but argues that since the ex post subsidy is already *sunk*, the overall package is biased, ex post, away from activities where subsidies are *not* already sunk (or are non-existent<sup>246</sup>), forces costs on to others, and gives too much of a bias towards the use of low efficacy vaccines.

In turn, overall measures of cost-effectiveness and efficacy end up much lower than claimed. Perhaps the notion of a package of measures has become increasingly downplayed in part because its recognition would lead to increased questioning of an elaborate ex post subsidy attached only to one component, and more questioning of the efficacy of that component?

#### **4.5. The impact of market and delivery risks on vaccine R&D incentives**

This lack of ‘package thinking’ shows up strongly in some of the suggestions made to ‘drive’ the APC subsidy scheme. For most underused vaccines and vaccines very close to market, a key objective is to *remove* market risk and to drive price lower.<sup>247</sup> Indeed, this is the whole point of recent initiatives like IFFIm, and we are starting to realize that it is proving to be a great deal more challenging in the recent cases of pneumococcal and rotavirus than we had thought would be the case.<sup>248</sup> Current APC thinking however sees all kinds of risk, including and especially *market and delivery risk*, put back on to developers and recovered in the subsidies they receive. Depending on the quality of health systems, demand building and the demand forecasting abilities of public bodies, firm response (including worries about the impact on reputation if not responding to an apparently ‘generous’ incentive) becomes very sensitive to this risk.

The argument made by APC advocates is that developers *should* face ex post ‘market risk’ because it helps to drive ‘effort’ and their choices of what vaccine leads to follow based on the pre-set ‘quality’ rules, and that it helps to stop the pool of subsidy from draining into the hands of those producing low efficacy products<sup>249</sup> and disincentivizing higher efficacy products. After all, an APC is a variable R&D subsidy (supposedly), with variation of subsidies across firms done, we are told, via ‘purchaser choice’. However, to the extent that purchasers behave dysfunctionally (on top of the distorted price signals we discussed above, and, indeed, aggravated by the lack of a price signal), firms will face risk in the ratio of subsidy they receive to the quality of ‘effort’ they put in and the quality of ‘choice’ of vaccine leads they make. To the extent that this risk cannot be diversified away (below, we show that this risk, unlike that of the underlying scientific risk, *cannot* be diversified away) this risk has to show up in lower R&D intensity for any level of subsidy.

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<sup>246</sup> Observe the way that newly-initiated non-vaccine subsidies would absorb part of their effort correcting for this distortion, though they have the disadvantage of needing to be negotiated and paid *after* the original sunk vaccine subsidies that ignore this effect.

<sup>247</sup> See Farlow, *Innovation Strategy Today*, 2005, *ibid.*, Section 3 for historical case studies.

<sup>248</sup> [www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069\\_pf.html](http://www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069_pf.html).

<sup>249</sup> More of this self-fulfilling effect later.

### **Dysfunctional markets**

These are markets where ‘market risk’ is to say the very least ‘noisy’, and markets inefficient, even positively dysfunctional:

- 1) These are resource-poor market settings;
- 2) Most country-level users are relatively uninformed about current vaccines never mind about expected future vaccines – a crucial requirement for efficiency via ‘purchaser choice’ over time in a model with a limited pool of subsidy;<sup>250</sup>
- 3) There are no marketing budgets (though one would hardly believe it from some of the literature);<sup>251</sup>
- 4) Vaccine usage needs a good distribution system, with such systems generally *not* under the control of vaccine companies;
- 5) There are very heavy knock-on costs to purchase decisions;
- 6) There are multiple organizational problems;
- 7) There is a severe lack of qualified personnel on the ground;
- 8) There are multiple political interests;
- 9) There are cultural barriers;
- 10) Most purchase decisions in developing country markets are made by governments and sponsors, not by individuals;
- 11) The correct price signals for buyers – the true opportunity cost of vaccines of alternative efficacy when compared also to non-vaccine products and control methods – do not exist. Lack of response to the true costs is compounded by the high rent-seeking incentives of i) sellers who have plenty of ways to ‘encourage’ decision-makers to take their vaccine over the malaria products of other firms, whether vaccine or otherwise (even more so if the ‘other firm’s’ vaccine or drug does not yet exist), and ii) possibly governments (on behalf of their own companies), and iii) sponsors (who wish to have something they can call a ‘result’ from their policy initiatives, even as it risks distorting the overall package of malaria control). This introduces risk into the ratio of subsidy a firm receives relative to the quality of ‘effort’ and ‘choice’ of product the firm makes, reducing the firm’s R&D incentives;
- 12) This perception of low market demand “has been compounded by the lack of accurate demand forecasts”;<sup>252</sup>
- 13) It might be argued that facing firms with these risks of distribution/market failure will make them work on products that are usable in dysfunctional settings, but this incentive only works up to a point. The danger is that a firm gets good or bad take-up of its product unrelated to the quality of the product and the effort and investment that went in to it. Again this expectation lowers the profit of such markets;
- 14) Much of the country ‘choice’ takes place many years after the firm’s choices. It is hard to imagine a firm facing dysfunctional markets being

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<sup>250</sup> See Farlow, 2004, *ibid.*, Section 7, which also discusses some of the political constraints.

<sup>251</sup> Though the equivalent of some form of ‘marketing budgets’ might go on rent-seeking.

<sup>252</sup> VMSR p5.

prepared to ‘bet’ on them being much less dysfunctional in 20 or more years time when making investment decisions *today*.

**Health experts worry about field uptake: Malaria APC advocates make it core to efficiency**

So while Roadmap participants and many public health experts worry about ‘field uptake’, the APC literature makes ‘field uptake’ part of the R&D repayment mechanism. As CGD Working Group member Donald Light put it after withdrawing his support: “No time was spent understanding the organizational, political, and cultural barriers to effective delivery of the vaccines, only purchasing them. Rather than actually delivering vaccines to people, is a windfall purchase the real goal here? As an expert in health-care delivery, I could not endorse a report that ignored these issues.”<sup>253</sup>

**Part of the ‘like a market’ myth**

The only reason the APC literature incorporates a key role for market and delivery risk is to avoid connotations of a ‘committee’ deciding how much subsidy each firm would get, and to avoid having to justify how the committee would allocate the subsidy. It sounds better if this is left to ‘the market’, however dysfunctional that might be. But as Kaper et al. put it “The struggle to protect human health from an infectious disease hardly ever ends with development of a good vaccine.”<sup>254</sup> It seems pointless to link reward for the development of a vaccine to this struggle after a vaccine has been developed. All these expected failures increase the costs of R&D by increasing risk,<sup>255</sup> thus reducing the impact per dollar of an APC.

The APC subsidy literature brought ‘delivery’ in at a very late stage, and still continues to treat developing country markets pretty much as if they are just less financially endowed versions of richer country markets. Tremonti still maintains, rather startlingly, that a malaria APC “replicates market conditions prevailing in developed countries...Market forces rather than donors determine the allocation of the additional investment on vaccine development.”<sup>256</sup> And Barder has gone as far as to assert that these schemes are just like “the incentives that produced almost all the drugs on the shelves in one’s local pharmacy.”<sup>257</sup>

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<sup>253</sup> Light, D., “Making Practical Markets for Vaccines: Why I decided that the Center for Global Development Report, Making Markets for Vaccines, offers poor advice to government and foundation leaders.” PLoS Medicine Volume 2, Issue 10, October 2005, e271, <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020271>

<sup>254</sup> Kaper et al. 2005, *ibid.* pp. 4-5.

<sup>255</sup> It is widely recognized that costs of delivery of an AIDS vaccine are especially problematic since it would require large scale adult and adolescent vaccination in high prevalence countries, something very unlike anything done before, and costly distribution to high-risk groups in lower-prevalence countries.

<sup>256</sup> Tremonti, G. Executive Summary, 2005, pi. The Tremonti Report recognizes that APC-supported vaccines will require “capacity to administer AMC-supported vaccines” (including anti-corruption mechanisms given the corruption pressures such schemes create) and a range of “complementary capacity-building interventions” (Tremonti, G. p12), but then ignores the risk implications for those investors dependent on APCs for their investment returns.

<sup>257</sup> Quoted in Zandonella, C., “If you build it, they will pay.” IAVI Report, July-August 2005, Vol. 9, No. 3, [www.iavireport.org/Issues/Issue9-3/iavireport\\_aug\\_final.pdf](http://www.iavireport.org/Issues/Issue9-3/iavireport_aug_final.pdf). One might well dwell on the question: ‘Pay for what?’

### **A tradeoff**

There is an inherent tradeoff in all this – so far mostly unresolved. We want to give firms ‘effort’ and ‘quality’ incentives, but there is little point in facing them with all these layers of risks, since these risks simply feed back to harm R&D incentives in the first place. But, if firms are not made to face *some* market ‘risk’, and a large subsidy is paid to them regardless of vaccine ‘quality’ and uptake, it risks paying for a product that is less useful and that gets low take-up for some reason that was not captured in the product specifications at the start, and it also risks the mechanism falling into the hands of a limited number of players. Yet, the APC has no other way to create incentives. The alternatives are either through committee ‘dictat’ at the end,<sup>258</sup> or through some other mechanism used to control ‘quality’ en route, but with less subsidy at the end. This alternative will be discussed further in Chapter 8 below.

### **Or is it just a ruse?**

Or maybe our concerns about ‘dysfunctional markets’ emanate from a clever ruse? One possibility, of course, is that we are first told all about the role of country purchasers. We then worry about the dysfunctionality of ‘markets’. Some firms avoid getting involved. But the one firm that does manage to negotiate a deal and push a vaccine through is then essentially not bound by any ‘market’ discipline at all as sponsors push to get the firm’s product used as much as possible. The ‘purchasers decide’ notion becomes just another part of the marketing exercise for the APC idea, and created to avoid awkward issues about who drives the outcome and what the true market forces are.

### **Delivery: A Key part of a package of measures**

Both the Roadmap and the APC literature have tended to treat the end market and delivery conditions as more separate from R&D decisions than is justified. Since the value of a vaccine is part of a package, the value of which depends on coordination, vaccine R&D incentives will be a function of delivery issues. As one correspondent put it to the author: “This [delivery issues] needs more emphasis than is often given in these kinds of discussions. I have just come back from Niger where EPI coverage is less than 20% and coverage in adjacent northern Nigeria (population around 100 million) is even worse. Investing in malaria vaccine development is a waste of time until steps are taken to sort this out.”

Again we find that investors are *not* put off just by the ‘potential’ size of markets *per se*. Their ability to benefit from any given potential market is a function of a huge range of failures. Current APC logic relies on all the other components of a package of measures being in place and delivery failure problems being overcome, but ignores them in calculating its own terms and likely strength. Simply making an incentive ever bigger to absorb all these risks and failures is not obviously the most efficient way to overcome them. A more sensible route is to prioritize tackling these dysfunctional problems first.

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<sup>258</sup> Though we already realized that even the ‘market based’ mechanism is framed and driven by the committee.

**Why force all R&D repayment through quantity of purchases anyway?**

At a much more fundamental level, is there any logic for why the value of a firm's malaria vaccine R&D should all be related to the amount of a vaccine used anyway? As various malaria experts have pointed out to this author, given the complexity of the malaria problem, the incomplete understanding of the interaction of the parasite and humans, and the need to integrate imperfect vaccines into larger packages of measures, it may not be optimal to roll out en masse early low-efficacy vaccines across many markets.<sup>259</sup> Such vaccines may be highly valuable in showing the way for later vaccines, with the faults they reveal helping in the design of better vaccines. Low sales of these vaccines and greater sales of later vaccines may be more optimal from a health perspective, but, according to current APC thinking, this will reverse the required rewards for the developers. The only way around this is to encourage over-use of the low efficacy vaccine, or for those setting up the APC to know how to work out 20 plus years in advance the prices and quantities to, somehow, give developers a fair return.

Observe also that without a true price signal to purchasers and with a fixed pool of subsidy, there is much less incentive to 'delay' sales till later and use licensing of the early technology to achieve later sales through later 'better' vaccines. Unlike in a standard market, a firm does not get a higher price for a better vaccine later nor a new 20 year patent in eligible countries if the subsidy pool has gone. The greater sales of later 'better' vaccines required to make the licensing optimal are much less guaranteed. If it only costs \$200m to drain the \$3bn subsidy pool, better to drain the subsidy pool sooner rather than later.

**Firms do not want to face ethical dilemmas to make sales**

Incidentally, this is a comment on the behavioral decisions firms would be forced to face, and not a comment on their ethical approach to business. Why should firms be forced to try to get a vaccine used in many more countries and/or regions than is optimal, in order to get a fair return (because the committee failed to achieve it)? Why should they face the rent-seeking incentive and have to engage in corruption to do so, given that they face customers who have the 'wrong' price signals? What are the ethical implications of facing firms with this dilemma? If firms do not like being backed into a corner – with heavy sunk investments and imperfect vaccines that should not be used en masse, yet there are distorted price signals and rent-seeking pressures in that direction – they may simply resist getting involved in the first place.<sup>260</sup>

**APCs are too blunt to link rewards to true 'worth' of products**

The truth is that blunt subsidy schemes such as APCs will not link rewards to the true ultimate worth of products, and the investments of firms. Many highly worthwhile breakthrough – but low-use – products therefore risk not even being created via this

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<sup>259</sup> Similarly, in the case of partially-effective HIV vaccines, if any significant number of countries roll out mass vaccination, each purchase generates a large windfall subsidy payment for a firm that is drained from the subsidy pool, even if the vaccine is ultimately low value and less subsidy is left in the pool for later developers.

<sup>260</sup> Remember that the investment decision has to be thought through ex ante in the light of all of this, such that certain acts, such as rent-seeking and corruption, might be profitable ex post but not profitable ex ante.

route. Low roll-out would rule out early R&D cost repayment via an APC once a vaccine is ready. Even a few years delay destroys much of the commercial value of a vaccine (real capital costs are mounting at 8%-11% or more depending on the figures one uses).<sup>261</sup> How is a link between the value of a vaccine and the subsidy a firm receives maintained in such a complex setting?<sup>262</sup> Firms cannot simply market an imperfect malaria vaccine like a new anti-obesity drug. The notion of giving purchasers the ‘freedom’ to buy up to 200 million doses at the ‘wrong’ price, exhausting the total subsidy pool, may simply be plain wrong scientifically, economically, and ethically.<sup>263</sup>

Indeed, we found that to mitigate the consequences of polymorphism and antigenic variation, we will have to be careful how vaccines are rolled out, monitoring genotypes of populations as population coverage increases, and, as just one method, using “vaccines that are alternated on a delivery schedule to minimize the parasite’s ability to evolve resistance to one particular vaccine.”<sup>264</sup> Linking rewards to how many purchases a firm can make hardly makes sense in such a complicated scientific setting.<sup>265</sup>

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<sup>261</sup> Again, this may be worse for HIV. Many of the projections this author has seen visualize a ten year roll-out.

<sup>262</sup> This is probably worse for HIV. The first vaccines are likely to increase time between infection and onset of symptoms. How is the subsidy payment for such vaccine to be set so as not to disincentivize other privately-funded developers? In particular how does ‘too much’ subsidy not go on such vaccines? The argument would be that any firm that ‘learns’ off the first vaccine can be locked into contracts to pay for this value, but it is not clear how easy this is to do in the case of vaccines as complicated to develop as malaria, HIV, and TB.

<sup>263</sup> This may well be worse for HIV. Imagine a vaccine costing a few dollars to manufacture but generating \$15-\$20, or much more, per purchase in windfall subsidy on each sale (the approximate current IAVI proposal), an amount that is lost to the subsidy pool for future vaccines. Imagine a program trying to target vaccines at high-risk populations at a few dollars per purchase, but with \$20 windfall profit per purchase. How is it done without data corruption, overuse, or rent-seeking? Ordinarily, the full \$25 or so would be up for payment *each time*. But in this case, a few dollars will leverage \$20 or so from the *sunk* subsidy pool (and it is somebody else’s loss if better later vaccines are not derived because firms believe that the subsidy pool will be dissipated too early). Maybe IAVI has visions of a hyper-controlling monitoring regime to control this behavior? Maybe revaccination and booster programs are part of that same regime? We also know that low- and high-prevalence countries would use a partially effective vaccine very differently (Esparza, J. et al. “Estimation of ‘needs’ and ‘probably uptake’ for HIV/AIDS preventative vaccines based on possible policies and likely acceptance.” *Vaccine*, 2003, Vol. 21, No. 17-18, pp. 2032-41). Low-prevalence countries will concentrate on targeting high-risk individuals, while those countries with higher prevalence (with more than a couple of percent of the population) will attempt a catch-up program across adults and adolescents. The issue then will be how rapidly firms scale up production and supply. One of the problems with the lack of a price signal is that no signal is provided to enable the efficient distribution of potentially limited vaccine supply over these different scenarios, and the dangers that since purchasers pay the same price regardless, vaccines will not get directed at the use that gets overall greatest value out of the of them. In particular, if the optimal scenario has high-burden countries getting treatment first, what is the price signal (or rationing scheme) to prioritize purchases to them first? If mass vaccination absorbs the entire subsidy fund ‘too soon’, this will increase DALYs, but cost per DALY will be dramatically higher – indeed several times higher. Once the collapse of research for follow-on vaccines, consequent on this expected collapse in subsidy pool, is also factored in, this will send the cost per DALY even higher (again maybe several times higher). This may particularly aggravate situations where a vaccine is still not fully certain in its impact.

<sup>264</sup> MVTR p21.

<sup>265</sup> Observe how many of these problems are already part of the system, and are part of the reason why firms do not invest.

There is also a general consensus that a stream of follow-on vaccines will be needed over 20 plus years; how a subsidy pool could spread efficiently over time if ‘purchasers drive’ things – given all the failures listed above – is anyone’s guess. The issue then becomes how the developers of the early vaccines can reach through, via contracts, to the sales of later vaccines, and how this might be upset if early knowledge is more freely available to later vaccine developers.<sup>266</sup>

#### **4.6. Problems with trust: The case of polio**

The success of a malaria vaccine program will depend on maintaining trust. This not only relates to currently existing vaccines, but even more so to second or third generation vaccines, that will need to be trialled even as first generation products are in use. Recent problems with polio provide valuable lessons.

Polio is a virus which is spread mostly by feces and can lead to paralysis and death. In 1988 the WHO launched a drive to eliminate polio by the end of 2005. A program of mass immunization reduced the number of cases from 350,000 a year to about 1,200 cases a year. To try to hit the target, and stamp out polio for good, two to three years ago international health agencies pushed ahead with a \$2 billion campaign, the largest of its type ever. The program hit problems when government officials in northern Nigeria suspended the program after rumors that the vaccine caused sterility and AIDS. Health workers sent in to vaccinate children were even being stoned and taunted. The Nigerian program was eventually resumed but the damage was done to the whole region. Polio rebounded in northern Nigeria and spread to at least 17 other countries that had been till then polio-free. Sudan – a major crossroads between Africa and the Middle East – suffered a massive outbreak, just four years after eradicating polio.

Fighting diseases through vaccination requires the full support of the people in regions where the diseases impact. And this requires trust. How does trust work when a vaccine is costing a dollar or less to manufacture but attracting \$15 or \$25, or even more, ‘windfall’ subsidy to its seller when it gets used? How do concerns about lack of trust when using ‘early’ vaccines feed through to second and third generation vaccine trials?

#### **4.7. Safety and liability issues impact R&D incentives**

Liability issues remain a problem and, to developers, a big risk.<sup>267</sup> The Durban Malaria Vaccine stakeholders meeting urged the need to emphasize safety and pharmacovigilance much more, and wondered how safe a partially effective vaccine would be as part of a package of measures.<sup>268</sup> It is notable that those in a high prevalence setting were much more clued up to this than many policymakers who seem more happy to push

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<sup>266</sup> Observe that even if these mechanisms are in place, the mechanism may still face firms with an incentive to supply ‘too many’ markets, to the extent that the CGD logic of payment related to quantity of purchases holds.

<sup>267</sup> VMSR (p5) talks of “Vaccine safety issues.”

<sup>268</sup> VMSR p13.

forward with a partially effective malaria vaccine justified on the basis of what we will shortly see is highly dubious recent cost-effectiveness evidence. They also tend to downplay liability issues for partially effective malaria (and HIV and TB) vaccines by reference to vaccines for other conditions, such as flu where the epidemiology is very different.

For malaria, the build-up (or failure to build up) of natural immunity is an extremely complex issue into which to insert a partially effective vaccine. A partially therapeutic HIV vaccine would be a whole other ball game from a flu vaccine.<sup>269</sup> Even in the much simpler case of smallpox, Kaper et al. 2005, observe that “Today, safety concerns would make a program like the smallpox eradication effort much more complex.”<sup>270</sup> Furthermore, “Strict attention to individual rights practiced today would prevent widespread application of a vaccine like vaccinia, the smallpox vaccine, which carries a number of health risks.”<sup>271</sup>

It is not clear that this liability issue has been satisfactorily resolved, and how this will impact the cost-effectiveness of vaccines of different effectiveness, nor how it affects the cost-effectiveness of an overall intervention package containing a partially effective or short-lived vaccine or a vaccine that loses effectiveness over time due to polymorphism or antigenic variation. This author has seen no analysis even attempting to articulate what the implications would be for cost-effectiveness of a 50% (or 30%) efficacious goal rather than an 80% goal, once safety and liability issues are properly factored in, and hence how it will affect commercial incentives (and hence, even more, the cost-effectiveness of the vaccine<sup>272</sup>). A global solution will need liability risk to be quantified – according perhaps to vaccine efficacy – apportioned and dealt with clearly and effectively from the start.

### **How is liability apportioned?**

When the CGD tried to work out how to do this for a malaria vaccine,<sup>273</sup> a two stage approach was suggested. First, until an eventual supplier was designated, the sponsor(s) should fully indemnify the committee running the malaria vaccine subsidy scheme and this committee would be “subject to legal challenge where necessary”<sup>274</sup> in the jurisdiction chosen for the contracts (the US, when it is ever specified) – even though the sponsor(s) lose control over their funding (for the sake of the credibility of the scheme) to a committee with discretion. However, since not many pharmaceutical firms would savor the PR disaster of suing the Gates Foundation, the World Bank, the US or any other Government, or a PPP (if it is acting as a sponsor),<sup>275</sup> this apportionment of liability would not exactly be credible. Furthermore, if the APC subsidy fund is only a small

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<sup>269</sup> Kaper et al. 2005, *ibid.* p2, comment that “Although it is far from clear which H5N1 strain to target in making an avian flu vaccine, let alone how to finance it, produce it, and ensure its safety, many scientists and public health authorities are optimistic that an H5N1 vaccine is within reach.”

<sup>270</sup> Kaper et al. 2005, *ibid.* p3.

<sup>271</sup> Kaper et al. 2005, *ibid.* p3.

<sup>272</sup> Since this risks sending capital costs rising.

<sup>273</sup> Though the details were left out of the contract term sheets attached to the CGD Report.

<sup>274</sup> Barder et al. May 2005, *ibid.* p6.

<sup>275</sup> Indeed, this point applies to any discretionary mechanism going through these entities.

portion of the overall costs of development and production of a vaccine, this runs the risk that liability risks would be heavily leveraged onto the shoulders of the last-stage sponsors (such as the Gates Foundation or World Bank). It is difficult to imagine the Gates Foundation lawyers letting that one through.

Second, the eventually designated supplier is supposed to “defend and indemnify” the sponsor and members of the committee: This has equally as many problems. Only the world’s largest companies will be able to participate in such arrangements (even if they wanted to). And there would be reliance on third parties, such as the WHO, to help in the decisions driving the distributions of the subsidy payments, but who would nevertheless be expected to relinquish all decision-making powers to the controlling committee. It is not clear what would happen if liability problems flow from *discretionary* decisions of the committee, and are therefore *not*, strictly speaking, the fault of a firm; this would require suing the original sponsor. Sponsors must also share some liability for ‘due diligence’ in the setting up of such programs to make sure that such programs will work as suggested and, indeed, not fail. If, for example, an APC collapses through no fault of firms trusting in the program to work, but because of negligence of those setting it up, it should be possible to sue sponsors.

It is difficult to imagine – supposedly in order to achieve ‘credibility’ – that sponsors, especially foundations and their legal advisors and the WHO, would permanently relinquish key decisions to a committee or committees with discretion to lower standards, fail to work out the exact legal status of these new institutions alongside already existing institutions, and yet leave the issue of liability risk entirely unresolved.

The problem with liability risk is just another reason why the private sector does not invest in complex early-stage vaccines, such as malaria, HIV, and TB, and *especially* only partially effective, and ‘therapeutic’ vaccines. Failure to contractually cover liability risk has doomed previous proposals. Project Bioshield no longer treats liability risk in the fashion just described for malaria, HIV, and TB vaccines. Masking this with ever higher product subsidies is not the most obvious solution, and just aggravates other problems (like the reputational risk firms are forced to face).

#### **4.8. Why did purchaser co-payments stay as key to the working of an APC?**

In APC models of just a few years back it was proposed that developing countries should *pre-sink* their co-payments to ‘commit’ themselves to an APC subsidy scheme, and to force them to face a “market test.”<sup>276</sup> Farlow 2004 Section 7 argued that this was a very bad idea, since the sunk nature of co-payments would create all kinds of perverse incentives and would generate corruption and self-fulfilling pressures that would tend to push for a lower quality outcome. Sunk co-payments have now been dropped.

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<sup>276</sup> Kremer, Appendix 7, No. 10 Policy Unit.

However, in spite of the risks of unbalanced subsidies and the dangers of using small co-payments to unlock large windfall payments, the notion that co-payments will ‘drive’ outcomes has nevertheless remained in the CGD-inspired literature. In private correspondence, a variety of senior vaccine and industry figures have expressed grave concerns about the corruption inherent in such arrangements. Another leading figure wrote “CGD speaks of markets and does not distinguish from distribution volumes. A vaccine will cost only a fraction of the vaccination. It is utopist to extend the concept of markets to areas where no purchasing power for health exists.”

There are several possible reasons for why the co-payment arrangements stayed:

- 1) The advocates of such schemes do not understand the problematical issues. If so, this is hardly encouraging to private investors;
- 2) It is completely key to the notion of the mechanism not being a first-come first-served prize, and therefore key to follow-on incentives, and the generation of ‘quality’. And key to the whole payment not going into the hands of one ‘early developer’. As Tremonti puts it: “A prize would not incentivize the development of subsequent, second- and third-generation products...”<sup>277</sup> and an APC “would not create incentives for second and subsequent vaccine developers: and it would require a very detailed specification of the product in advance...An AMC, by contrast, would only oblige the donor to pay a top up on vaccines *for which there is a demand from developing countries*, which ensures that there is a *market test at the time the vaccine is produced*.”<sup>278</sup> We already saw that this is a pretty thin myth. Those setting the scheme up, and the committee at the end of the whole endeavor have to frame everything to drive follow-on innovation, if follow-on innovation is possible at all,<sup>279</sup> by first setting and then manipulating the price-quantity envelope – the initial and tail prices – in light of expected development and production costs, expected science many years from now, developing country public health needs, what they believe will be an acceptable level of risk for industry, and their understanding about industrial organization of the industry both now and in the future, and a whole range of other factors. If the reader thinks about it for a few moments, they quickly start to realize the fallaciousness of the Tremonti claim that an AMC does *not* have to set up “a very detailed specification” in advance and that ‘quality’ is driven by a “market test”;
- 3) It allows for the impression to be created that purchasers drive quality and have a ‘choice’, even if they do not, with the side-benefit that if the result is bad, purchasers can take the blame; it is what *they* chose. In particular, if the payment all ends up going to the developer of a low-efficacy product, advocates can justify this outcome as what the purchasers wanted;
- 4) It is a convenient excuse to let APC advocates off the hook, given that they have still not worked out who else will drive quality, or, indeed, have any notion of how it would in practice be achieved. They can avoid also all of the institutional

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<sup>277</sup> Tremonti, G., Background Papers, 2005, *ibid.* p7.

<sup>278</sup> Tremonti, G., Background Papers, 2005, *ibid.* p7.

<sup>279</sup> There is a whole range of industry expectational issues, which are all most likely to fail to drive the needed follow-on investments.

- issues of how this would be done, by alluding to the notion that it is the ‘country purchasers’ and not these institutions that drive the result;
- 5) If, instead, poor countries were to face the *whole cost* of vaccine development at the time of purchase (they could, for example, be given an overall malaria budget and decide how much of it to use on the vaccine, and how much to use on other parts of the malaria ‘solution’) then if the vaccine is of very low efficacy and not worth using, purchasers could get to choose to spend their budget on malaria drugs and alternative non-vaccine technologies. However, with the co-payment subsidy scheme in place, the less efficient solution of the vaccine can be pushed through more easily;
  - 6) It helps APC advocates ignore delivery issues. Tremonti observes that “An AMC is a tool to provide financing...[but that] Strong health systems and appropriate national planning and budgeting are imperative if the AMC is to have an impact,”<sup>280</sup> ignoring the fact that private financiers are being asked, via the APC scheme, to shoulder the risk of the uncertainty of all of this;
  - 7) Bluntly, while sunk eligible country co-payments had to go because of their inherent faults, the greater reason – why large subsidy funds themselves should not be sunk – could not be abandoned, since that would have removed a key strand of reasoning legitimizing APC thinking;
  - 8) It is all part of the same ruse we discussed above. There really is no intent for co-payments to drive anything. The producer who captures the APC first, gets to dominate the result (either by being the only vaccine that gets developed, or by destroying the chances of getting a vaccine), and countries pay what gets forced out of the APC-based scheme.

We end up with a mechanism (according to CGD reasoning) involving:

- 1) Multiple individual country purchasers;
- 2) Facing highly dysfunctional distribution and health system pressures;
- 3) Supposedly driving multiple generations of follow-on innovations and all the required investment to do this (think of the needed investor expectations);
- 4) Via their individual ‘demands’ for vaccines;
- 5) Drawn from a range of both existing vaccines and not-yet existing but fully-known-about future vaccines;
- 6) Paid for from a limited, depleting (as soon as any developer starts to draw off it), and possibly too small, subsidy pool;
- 7) At hugely subsidized prices;
- 8) With ‘winning’ firms then tied in to supply at cheap prices the same product for ever (or till nobody wants it any more).

How in touch with practical reality is this?

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<sup>280</sup> Tremonti, G. Background Papers, 2005, *ibid.* p13.

#### **4.9. Emphasizing an overall malaria control strategy is good for vaccine R&D incentives too**

This suggests rethinking current advocacy efforts. The low level of current funding for treatment and prevention and research into alternative non-vaccine malaria technologies, is often treated as fact enough to justify advocacy of the setting up of APC subsidy schemes for ‘a’ malaria vaccine. The real issue, however, relates to the overall size of the fund to tackle malaria – with the optimal split across vaccine R&D, prevention, control and so forth, being a separate independent issue in which all interventions compete fairly in policy makers’ minds. Meanwhile, it is a fundamental mistake *not* to state the vaccine goals without reference to an overall control strategy.

Constant allusions to vaccines making other components redundant and therefore not competing with them<sup>281</sup> may even weaken the overall impact of the vaccine R&D effort, since this attitude will lead to insufficient emphasis on supportive measures and developers of these being disincentivized. These other components have failed in the past, and yet, according to the first goal of the Malaria Vaccine Technology Roadmap, they must now be relied upon as part of the goal-1 package. Indeed as this report goes to press, the Global Fund for HIV/Aids, TB, and Malaria meeting in London, has managed to raise barely half of its target. This hardly suggests that vaccine mechanisms – generating, say, 50% efficacy vaccines – that will rely on coordinated treatment and prevention programs will be able to rely on the funding for this.

#### **Many deaths down to failure in prevention and treatment**

Indeed, much of the death toll from malaria in Africa can be accounted for by failure of prevention and treatment. As the Malaria Vaccine Technology Roadmap<sup>282</sup> points out, malaria deaths are on the rise and progress is hampered by shortages of trained staff, inadequate healthcare systems, growing drug resistance, and insufficient funding for existing prevention and treatment. This hardly augers well for partially-effective vaccines. It also suggests that if the Roadmap is targeting an 80% vaccine for 20 years off, with 20 to 30 million malaria deaths between now and then, and a quarter of a trillion dollars worth of economic losses over 20 years in Africa alone,<sup>283</sup> there might be some sense in getting treatment and prevention up to the level where 50% or more of deaths, and much of the debilitating consequences of malaria, can be prevented with the technology we already have, and working on R&D to maintain and improve this, and working out how vaccine(s) fit in with this, instead of constantly justifying ever-lower efficacy vaccines on the back of this failure.

Neither does it make sense to justify deliberately targeting a low-efficacy vaccine on the grounds that access to medicines, insecticide-treated bednets, and other interventions that can be effective in controlling malaria remain limited, if such a vaccine will then have to

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<sup>281</sup> Such as “This avoids the need to choose between research on new vaccines and current needs, such as increasing access to existing vaccines, or fighting malaria, tuberculosis, and AIDS using existing technologies,” in “A World Bank Vaccine Commitment.” Glennerster, R., and Kremer, M., April 2000, p4. [www.iaen.org/files.cgi/80\\_kremerglenn.pdf](http://www.iaen.org/files.cgi/80_kremerglenn.pdf).

<sup>282</sup> MVTR p1.

<sup>283</sup> \$12bn per year. See references above.

rely on a range of such non-vaccine measures to have any chance of succeeding, and that will see the needed level of expenditure on such measures have to rise dramatically. Given resistance issues, this attitude isn't particularly helpful. A poorly efficacious vaccine, the impact of which collapses, may even aggravate this coordination. Indeed, one barrier to collaboration is the "View of [the] scientific community and funders regarding drugs and other control methods (e.g. bednets)."<sup>284</sup> Paradoxically, a greater emphasis on an overall control strategy might benefit the setting of vaccine research priorities.

From recent policy announcements, action on treatment and prevention for malaria, has thankfully, moved rapidly up the policy agenda.<sup>285</sup> Will the converse result be a reassessment of the appropriate vaccine goal to operationally target?

Most of all, it seems odd to generate cost-effectiveness evidence of the high value of a vaccine, only then to then excuse policymakers for doing little to tackle access to other interventions, but instead using the low level of funding for all components of an overall malaria control package as a clarion call for justifying a favored mechanism, with claims such as: "In the absence of an incentive of this sort, there is unlikely to be sufficient research and development into vaccines and medicines,"<sup>286</sup> or, better still, that not using the chosen approach is equivalent to doing nothing (clearly those who disagree with the logic of the malaria APC scheme must be suggesting "doing nothing"), "*waiting for a vaccine to be developed*,"<sup>287</sup> 'living with the status quo', and condemning millions to death.<sup>288</sup>

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<sup>284</sup> VMSR p6.

<sup>285</sup> [www.reliefweb.int/rw/RWB.NSF/db900SID/HMYT-6G2JQ4](http://www.reliefweb.int/rw/RWB.NSF/db900SID/HMYT-6G2JQ4). *ibid.*

<sup>286</sup> CGD, March 2005, *ibid.* p39, and see also p35: "Direct funding of research and development in neglected diseases is beneficial, but is not on sufficient scale significantly to overcome the market reality." See also Kremer, M., and Glennerster, R., 2004, *ibid.* Chapter 9, especially pages 93-95, and p87: "At present, funds are not sufficient to pursue enough of the possible avenues of research." When Farlow et al. critiqued the low level of funding into PPPs, instead of taking sides with them, this was used by CGD to make a case against them (Barder et al. *ibid.* p3, and see below). Farlow, A.W.K., Light, D. W., Mahoney, R. T., Widdus, R. "Concerns Regarding the Center for Global Development Report 'Making Markets for Vaccines'," Submission to Commission on Intellectual Property Rights, Innovation and Public Health, WHO, 29 April 2005.

<sup>287</sup> CGD, March 2005, *ibid.* p60.

<sup>288</sup> Kremer, M., and Glennerster, R., 2004, *ibid.* pp. 125-6.

## **5. Minimizing Malaria Vaccine Development and Production Costs and Securing Long-Term Supply**

The development of vaccines for malaria is a complex process involving many players and stages. It is not possible to cover every aspect here. For a much more thorough overview of this multi-stage subtle process in the cases of malaria and HIV, and for good detail on the players and capacity, see Widdus, R., 2005.<sup>289</sup> Two of the biggest weaknesses in the malaria vaccine R&D literature at the moment are:<sup>290</sup>

- 1) A reliance on presumed low production prices to make R&D pull mechanisms work in the first place (to the extent that these are *advance* mechanisms and *not* real-time procurement mechanisms) without any analysis of where these low production prices will come from;
- 2) No notion of how to discipline long-term product costs, and how to ensure long-term supply; in particular, the possibility that the mechanisms and market structures needed to help drive production costs lower in the long-term might conflict with some of the instruments used to repay R&D investments. The problem, we find, is made greatly more difficult by the fact that we are dealing with a range of potential product efficacy, necessitating generations of products.

### **5.1. The challenge of low costs**

The Malaria Vaccine Technology Roadmap participants wondered whether a vaccine could be produced ‘affordably’ for Africa at all. There is no point in having a weakly-efficacious vaccine that costs too much to develop and manufacture, or that uses up a great deal of the budget for other parts of a combined package of measures, resulting in cutbacks for other measures,<sup>291</sup> or that during its development makes heavy demands on limited field trials capacity raising the real opportunity costs of other potential vaccines. Indeed, some expressed “concerns over the likely costs of malaria vaccines in relation to the funds available for health in endemic countries.”<sup>292</sup>

The Roadmap points out that “production costs are likely to be high, particularly for combination vaccines. Malaria vaccines will likely cost dollars per dose, rather than pennies. Efforts to minimize the cost of production should commence early in the R&D process.”<sup>293</sup> Roadmap participants pointed out that “Subunit vaccines will need to be highly multicomponent” and there were worries about this “increasing [the] cost out of

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<sup>289</sup> Widdus, R., “Key Stakeholders and Funding of HIV and Malaria Vaccines: Considerations in selecting appropriate instruments for accelerating the public health impact of vaccination in poorer countries,” WHO Commission on Intellectual Rights, Innovation and Public Health, 2005, [www.who.int/intellectualproperty/submissions/WiddusMay05.pdf](http://www.who.int/intellectualproperty/submissions/WiddusMay05.pdf).

<sup>290</sup> This section contains comments that sometimes conflict, mainly because there are a range of possible responses, and we (or, more likely, I) do not really know which will come to dominate. The greater specific knowledge of some readers will enormously clarify the likely predominance.

<sup>291</sup> Relative to the optimal package that might have been possible otherwise.

<sup>292</sup> VMSR p6.

<sup>293</sup> MVTR p40.

[the] range of affordability.”<sup>294</sup> This chapter is interested in knowing how the two goal approach of the Roadmap, malaria science in general, and the presence of a malaria APC, might affect costs of vaccine production – both the development costs and the manufacturing costs once developed.

## **5.2. APC contracts to repay malaria vaccine R&D costs?**

The Roadmap is shaping up to contain two goals, and there is growing pressure to pay for at least one of them<sup>295</sup> via a ‘novel procurement mechanism’ based on product subsidies. We therefore need to specify exactly what this novel mechanism is. Kremer, Towse, and Williams, distinguish between an ‘advance contract’ in terms of a multi-year commitment to purchase a product that *already exists*, and an ‘advance contract’, an APC, in terms of a commitment to purchase a product which *does not yet exist*. The latter is an entirely different proposition from the former.<sup>296</sup> Indeed, many features of the former will clash with features of the APC now being proposed for malaria, as we will shortly discover. Kremer, Towse, and Williams, take great pains to clarify that though “the idea of advance purchase commitments may seem similar in flavor to some things that are already being done in practice,” these advance contracts are entirely different and have never been tried before.

It is critical to realize that APCs are *sunk subsidy* schemes, with *pre-fixed* terms, since this is central to explaining what generates most of their faults. ‘Rent-seeking’ distortions flow from this, as does the predisposition to low efficacy outcomes, and crowding out, and a range of other practical problems. We now discover that APC subsidy proposals are likely to be self-defeating since they put too little emphasis on both short- and long-term production prices. In turn, this feeds back to undermine the incentives to do R&D in the first place, and therefore increases the tendency to low quality outcomes.

But first, how do APC subsidy schemes work if the intention is to use them according to the second Kremer, Towse and Williams definition of an ‘advance contract’? We need to clarify this before we can analyze production cost issues on their own.

### **All must sign on**

According to the CGD, sponsor(s) of such schemes and all current vaccine developers are supposed to sign-up to the scheme at the start (or within 36 months of its initiation). This would involve the signing-up of the 100 or so current trials being run through eight different funding organizations: NIH and its intramural Malaria Vaccine Development Unit (MVDU), the European Commission (EC), the European Malaria Vaccine Initiative (EMVI), the Malaria Vaccine Initiative (MVI), the United Nations Development Programme (UNDP)/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, the United States Agency for International

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<sup>294</sup> VMSR p6.

<sup>295</sup> It should be both, but we’ll come to that later.

<sup>296</sup> Kremer, M., Towse, A., and Williams, H., “Briefing Note on Advance Purchase Commitments.” 19 DFID Health Systems Resource Centre, May 2005, p13.

[www.who.int/intellectualproperty/submissions/MichealKremerKTW\\_CIPIH\\_submit\\_2.pdf](http://www.who.int/intellectualproperty/submissions/MichealKremerKTW_CIPIH_submit_2.pdf)

Development (USAID), and the United States Department of Defense/Naval Medical Research Center.

The later entry of other developers would be policed by the committee running the APC scheme *before* such developers would be allowed to engage in vaccine R&D. This is so that they do not get the competitive advantage of going unmonitored before signing on in the hope of claiming the subsidy. Those conducting current vaccine trials and failing to sign-on and those initiating future vaccine trials without prior permission from the committee are barred access to the ‘eligible’ markets controlled by the committee.

The key role of contracts came about because the original claim that an APC would not need resources to be put aside in advance was found not to be true without such contracts in place first.<sup>297</sup> Tremonti has recently confirmed this problem, by suggesting a variety of payment routes into an APC, some involving early-loading of funds even into an end-loaded malaria APC scheme, if contracts cannot be made watertight across all developers.<sup>298</sup>

### **All must be monitored**

All actual and potential developers agree to be monitored by the committee controlling the scheme, otherwise those running the scheme have no way of knowing if it is working and whether they have to alter the terms. In particular, we still have no idea how to actually set the size of a malaria APC, yet we also know that trying to alter the size later creates perverse incentives.<sup>299</sup> All firms are supposed to report truthfully in their periodic progress reports (though nobody has yet explained how truthfulness is enforced).

To economize on monitoring, the original idea had been that an auction would be used to keep the mechanism on course, and the use of an auction would avoid those running the scheme from having to know lots of information in advance in order to set ‘size’. After this was abandoned as unworkable, it became clear that heavy monitoring would be needed instead, and that a great deal of information (or guesswork) would be needed in advance to set ‘size’. The Tremonti Report makes this very clear.<sup>300</sup>

### **An opt-out by sponsors?**

Currently, the proposal is that sponsors have an opt-out if monitoring shows that the contracts are failing to stimulate ‘enough’ privately *funded* research. However, the status of the opt-out is a little unclear at the moment, and the concept of ‘enough’ is largely impossible to define, since judgment can only really be made after a result or failure to get a result. If there is no opt-out, there is a danger of being stuck with a scheme that isn’t

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<sup>297</sup> Of course, if there was a genuine ‘market’, none of these contracts would be needed. This is yet another reason why it is wrong to suggest that APC schemes are just like “the incentives that produced almost all the drugs on the shelves in one’s local pharmacy,” (Zandonella, C., 2005, *ibid.* quoting Barder, O.).

<sup>298</sup> Actually, Tremonti is a little unclear. Even if everything is tied down in contracts from the start, countries may still find that APCs are treated as a financial liability. The fiscal scoring of APCs (how they are treated in national accounting) is still not resolved.

<sup>299</sup> Indeed, if firms *think* that terms might be changed afterwards.

<sup>300</sup> See for example Tremonti, G., 2005, *ibid.* p11.

working and all the costs of running it and the perverse affects it has on remedial activities to get around it. But if there *is* the possibility of an opt-out, this may put investors off, making collapse more likely anyway. If funders do decide later to opt out of the scheme, it is unclear how much compensation they would pay to those who invested on the basis of the claim that the scheme would repay them their investments (on average).

### **What the ‘winner’ gets**

As Tremonti observes, the problem is that one price is seeking to do two things – to provide a return to companies and to regulate access to any resulting vaccines. The solution proposed is that a committee determines the allowed price and quantities each firm gets on early purchases to determine investment return to each firm, with contractually agreed prices even before R&D is performed to solve the long-term access problem. As Tremonti puts it “The specific risk and challenges for the development of each new vaccine require the design of a separate AMC mechanism for each target disease, incorporating an estimate of the [additional]<sup>301</sup> market size necessary to stimulate *additional* private sector investment and accelerate the development of the target vaccines.”<sup>302</sup> Tremonti, as CGD, skirts around the notion that the estimate should be based on the “specific risk and challenges for the development of each new vaccine”, i.e. on R&D costs and not just on revenues. Yet, we have no handle on such cost data.

Supposedly, for the sake of efficiency, a winner (or winners) is repaid *all* of the privately-funded (and *only* the privately-funded) R&D costs (including *all* capital costs) of *all* firms (both the successful and the unsuccessful) and *only* the cost of private firms, since the time the promised subsidies were announced (and *only* since they were announced) and *only* for eligible markets covered by the scheme. Those not privately financed should not get anything, otherwise they harm those who are privately financed and who are relying on the APC subsidies to repay their R&D costs.<sup>303</sup> It is a subsidy scheme after all, and all these ‘others’ must not be allowed to ‘crowd out’ the payment to private investors.

‘Capital costs’ refers to the costs of the finance used, and includes the required return to cover *all* risk being borne, including any risk *created* by the committee-run mechanism itself (i.e. ‘capital cost’ does not refer to physical real capital investment). This author argues that this ‘mechanism risk’ is likely to be especially great.<sup>304</sup>

Firms are paid if they meet the criteria of the original contract, though in all the versions so far presented, the committee is allowed to waive conditions. Requiring less from developers is always allowed, but never requiring more.

### **Top-ups, subsidy redistribution, and a committee resetting terms later**

Given the potential difficulties of setting terms and creating better follow-on generations of products (there being no price signals to guide this), more recent versions of the

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<sup>301</sup> The additional market assessment requires an assessment of the total market.

<sup>302</sup> Tremonti, G., 2005, *ibid.* p.ii.

<sup>303</sup> In the expected sense, i.e. many times their out-of-pocket costs.

<sup>304</sup> Farlow, A.W.K., *Innovation Strategy Today*, 2005, *ibid.* Sections 2.5 and 2.6.

proposal claim the committee running the scheme would hold back on subsidies to early products in order to leave something in the subsidy pool to be available for later follow-on vaccines to create incentives for *their* R&D and for top-up subsidies to any firm that makes “a vaccine that meets the technical specification, and which improves on any existing vaccines that meet the specification.”<sup>305</sup>

Tremonti now argues that the committee is also allowed to reset terms if costs come in higher than expected: “Ultimately, the COGs [Cost of goods] will determine whether the firm will lose or gain at the AMC guaranteed price and in the post-AMC supply and price agreement. The higher the COGs, the less attractive given AMC terms become, up to the point where the AMC would need to be re-evaluated and possibly increased.”<sup>306</sup>

Tremonti does not explain how this increase could be done from a fixed subsidy pool without reducing the level of subsidy available to other later developers, or how new top-up funding would be created via the political process to increase the size of the subsidy pool to maintain balanced incentives. Neither does Tremonti explain how a firm already getting rewarded with a subsidy payment that is a large multiple of out-of-pocket R&D costs and many times its COGs, would be able to argue for payment increases to cover extra COGs on the notion that these extra COGs undermine its *ex ante* profitability. The only way to explain the above quote is that Tremonti seems to be reasoning (like Hurvitz on behalf of CGD as discussed shortly) that there are very few firms present, and maybe even just the one, and that the APC is mostly to cover the COGs of that one firm. But this runs counter to the claim that APCs are R&D instruments: If an APC is only an instrument to cover COGs, why would it need to be set 20 plus years in advance, and why would prices be fixed?

### **What happens to IP?**

The privately-funded firm gets the IP to the vaccine<sup>307</sup> and ‘eligible’ and ‘non-eligible’ markets face very different pricing strategies. If only ‘poor’ countries are eligible, middle income and higher income countries would face monopoly prices.<sup>308</sup> The more that middle income and high income countries are included, the bigger the APC subsidy pool has to be and the greater the dangers of ‘crowding out’.<sup>309</sup> It is difficult to imagine the US or UK or any other administration making the ‘size’ of the subsidy pool big enough to absorb all potential markets and to cover all potential R&D so as to absorb and ‘neutralize’ this entire crowding out problem. An APC potentially leaves its winner with all the subsidy and all the property rights for a malaria vaccine for South East Asia for example, even if the success of the vaccine was heavily dependent on publicly/foundation funded research and access to the results of trials conducted in such countries.<sup>310</sup>

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<sup>305</sup> Barder et al. May 2005, *ibid.* p9.

<sup>306</sup> Tremonti, G., Background Papers, 2005, *ibid.* p21.

<sup>307</sup> Under the current proposal.

<sup>308</sup> I.e. tiered monopoly prices. Indeed, due to market segmentation, prices may even be higher than they would have been without the subsidy scheme applying itself in the eligible markets.

<sup>309</sup> See Farlow, A.W.K., *Innovation Strategy Today*, 2005, pp. 92-97, and further below.

<sup>310</sup> With the problem compounded for South East Asia if the Kerry-Lugar Bill goes through and it really does favor US firms in the way it seems to be set up.

What are the likely effects of APC subsidy schemes on the production costs of malaria vaccines? And how might the nature of goal-1 and goal-2 affect this?

### **A word of warning**

Before seeking to answer this, we should observe that none of the analysis will make any sense at all if an APC is really just a Rube Goldberg machine; that is a machine that does something extremely simple, but does it in as many complex steps as possible. There are yearly ‘Rube Goldberg machine’ contests.<sup>311</sup> The challenge for the 2006 contest is “to cut or shred into strips five sheets of 8 ½ by 11, 20-lb. paper individually with a shredder and place the shredded paper in a recycle bin in 20 or more steps.” If the whole point of an APC is just to pay off one major vaccine developer, that happens to be the first to have anything to be paid off, with none of the contract features actually ever used, and none of the subsidy reallocation going on as hypothesised, then a great deal of this report is picking over, with increasing amazement, the pulleys, wheels, cogs, and levers of a Rube Goldberg machine. For now, we will take an APC as seriously intended as an R&D repayment scheme across multiple private-financed developers.

### **5.3. Worries about costs undermine R&D incentives**

It would be fair to say – as CGD themselves once said – that “*it is difficult to predict which technologies will succeed and hence hard to anticipate the cost of production.*”<sup>312</sup> However, the whole logic of the APC literature, *as R&D literature*, is that developers expect a malaria vaccine can be manufactured cheaply and – highly important for investors and those designing the overall size of the subsidy pool and its distribution over developers – that this<sup>313</sup> is *known* in advance, and that the development costs of ‘winning’ developers is a fraction of the overall APC payment. Costs also have to be known relative to vaccine efficacy. If follow-on or goal-2 vaccines are more costly to develop and manufacture, the per-unit subsidy on them should be greater. Though the way this is to be set should not distort and reduce incentives to cut costs. So far this has not been worked out in any of the literature, and is an almost impossible feat to achieve in terms set in advance.

It is striking that not once does the uncertainty about costs – R&D and manufacturing costs – appear in any of the underlying models used to support APC advocacy, nor in any of the cost-effectiveness analysis, nor in the final CGD report. Figures of \$1, or so, average manufacturing cost per course of malaria vaccine have been proposed,<sup>314</sup> indeed in reference to the manufacturing costs of *early* users of malaria vaccines, and seem to be

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<sup>311</sup> [www.rube-goldberg.com](http://www.rube-goldberg.com) for some pictures of such machines.

<sup>312</sup> CGD, Feb 2005, p57 (not in final report).

<sup>313</sup> I.e. the expectation over the efficient cost of production. It is perfectly possible for costs to come in higher or lower than expected, on the presumption that firms can hedge against this. The issue here is the mean of this distribution, and also whether firms believe that the distribution over costs is disciplined in the direction of lower mean costs or not.

<sup>314</sup> Sachs, J., and Kremer, M., 1999, *ibid.*

key to the CGD thinking on long-term pricing.<sup>315</sup> The manufacturing cost of many current vaccines in volumes above 10 million units is very low, between one and five cents. But new-age biologic vaccines might cost much more, as might combination vaccines. As Light observes: “The CGD price of \$1 per course is quite high compared to many generic vaccines and for many poor governments. But then, it might not cover the costs of a technically expensive vaccine.”<sup>316</sup> Indeed, the \$1 has since been revised up to \$6.

From the firm’s perspective it is the early sales that are key to the success of an APC subsidy scheme, since only these attract the subsidies. From the sponsor’s perspective, the low-cost long-run sales are key to the long-run success of the scheme. However, this chapter finds that expected problems at the manufacturing stage, and high expected development costs, feed back to undermine R&D incentives. Indeed, it is fairly standard in economics that poorly designed and operated subsidies may simply generate wasteful behavior and reduced incentive to cut costs. It should not surprise us that this happens in this case, with the added hazard that this feeds back to weaken R&D incentives.

### **Some reassuring words?**

We have been told not to worry about these cost issues. As Hurvitz put it on behalf of CGD: “Manufacturing costs [and the rest of the quote implies development costs too] will not be an issue with respect to a qualified product for so long as it is subject to the price guarantee...If a developer produces a vaccine that is more expensive than \$15 per course, they are unlikely to want to avail themselves of the Advanced Markets mechanism (as this guarantees the price at \$15). They would be in the same position as they are now, of seeking to negotiate an agreement with recipient countries and donors. The Advanced Markets commitment makes them no worse off than they would be in the absence of the commitment.”<sup>317</sup>

### **A simple example**

It is worth running a simple example to show why this is faulty economic reasoning. We remember that, so as to encourage multiple parallel developers, most of the APC subsidy is supposedly to repay to the ‘winning’ firm or firms all of the out-of-pocket R&D costs and capital (i.e. finance) costs, *of all developers* and not just the manufacturing and R&D costs of the ‘winning’ firm or firms.<sup>318</sup> In particular, there would be no point fixing prices and setting complex subsidy rules 20 years in advance just to cover the costs of the ‘winning’ firm – and indeed it would be very counterproductive.

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<sup>315</sup> See Nancy Birdsall, on behalf of CGD to US Senate Foreign Relations Committee, May 17, 2005 (see below). Though, recently, this has been revised up to \$6 per course according to MVI and the UK’s Department for International Development.

<sup>316</sup> Light, D., 2005, *ibid.*

<sup>317</sup> Hurvitz, J., CIPIH Forum, 16 December 2004. The notion that “they would be in the same position as they are now” is not strictly so if the \$15 (or \$25, etc.) was already much more than they could get facing recipient countries and donors now. If they breach the \$15 (or \$25, etc.) they *are* worse off, since the relevant comparator at that point in time is not what they would have got without the scheme.

<sup>318</sup> Though there is an overlap, since production facilities often have to be put in place for producing trial vaccines, that might also be used as facilities for producing eventually-purchased vaccines.

Imagine, for simplicity, that a firm<sup>319</sup> is developing a vaccine that is highly likely to cost \$15 per course to produce, especially for the crucial early sales that attract the ‘early sales’ subsidy (for example a three-dose malaria vaccine at \$5 per dose). These early sales are ‘critical’ to the firm since there is little benefit in achieving lower production cost in the way-off distant future when the allowed price is very low. If there is \$3bn in the subsidy pool, 200 million courses of a vaccine costing \$15 per course will drain the entire subsidy pool, leaving *nothing* to incentivize any R&D by multiple parallel developers and – if having multiple parallel developers was crucial to success in the first place – then creation of the vaccine in the first place.

Indeed, should any firm ever develop a vaccine, it would get stuck with a commitment to supply long-term at a legally-binding cheap price<sup>320</sup> (that it may not be able to achieve anyway) if it had been foolish enough to have claimed the ‘subsidy’ in the first place. The possibility of a waiver may reduce the worry of this, but, as we will see below, the waiver undermines incentives to cut cost and risks delays and loss of access of the poor to long-term cheap products,<sup>321</sup> and advantages bigger, more influential, players too.

What if the subsidy pool is bigger? Say \$6.25bn (one of the original early CGD figures for malaria)?<sup>322</sup> Is this not a ‘good deal’ even for the firm with production costs of \$15 per course? It might seem so. Assuming, for simplicity, the firm is allowed to be a sole winner of the entire subsidy,<sup>323</sup> \$6.25bn minus \$3bn still leaves \$3.25bn of ‘profit’. This is more than the firm’s private out-of-pocket research costs. It is even better if half of the firm’s costs were subsidized by tax breaks and other push devices and the appropriate multiple of these has not been extracted in the payment to the firm from the subsidy pool.<sup>324</sup> It is also more than enough to cover the firm’s capital costs. But, again on the presumption that the intent is multiple parallel developers and creation of the vaccine in the first place, it is still not a financially sound deal!

### **We are looking in the wrong place**

We are concentrating on completely the wrong decision problem. What matters is the investment decision *before* R&D costs are sunk, before *any* firm knows who will ‘win’. At *that* decision point, the expectation of a \$15 cost takes \$3bn out of the \$6.25bn fund. If the fund was set right at the start with most of the \$6.25 needed to incentivize the R&D of multiple parallel developers needed to generate the one ‘winning’ ‘good’ vaccine, this leaves far too little to motivate firms to bother investing in the first place – they would end up collectively *subsidizing* vaccine development and production – and the vaccine does not get created in the first place. We will shortly see the way the cost-effectiveness

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<sup>319</sup> One can also imagine several firms, each concerned whether capacity can be put in place to generate vaccines at a low enough production cost to make the R&D worthwhile.

<sup>320</sup> Though the APC literature has increasingly fudged this issue, as we will see below.

<sup>321</sup> Its presence makes any commitment to long-term supply and low price ‘time-inconsistent’.

<sup>322</sup> These figures taken from Farlow 2004 and 2005 based on CGD figures.

<sup>323</sup> Supposedly, this is not guaranteed.

<sup>324</sup> See Farlow, A.W.K., *Innovation Strategy Today*, 2005 *ibid*, pp. 94-95, for why a multiple of any push funds should be extracted and not just the push funding/tax-break an individual firm has received. Again, this is because we are treating it as if the APC is drawing in private finance to do R&D and not as an instrument to cover production capacity and manufacturing costs. More on this below.

evidence developed by supporters of malaria APCs, such as Berndt et al. (2005), has even been done to indicate that even this non-creation would be picked up as highly cost-effective.

**Lower incentives to push costs lower**

Of course, if the firm *has* invested in R&D and has a malaria vaccine, then *ex post* it is rational to manufacture at up to \$15 per course and take the \$6.25bn, even if this is not *ex ante* rational. Indeed, the firm's incentive to push towards lower manufacturing and distribution costs is much reduced:

- 1) It risks the firm delaying getting its allocation of the subsidy pool, or of the firm ever being rewarded any subsidy, by taking too long. Capital costs are growing heavily the more it delays sales. The suggestion in the literature is a nominal 11% to 15% per year. If the firm cannot cut costs quickly enough, it would be better to take the subsidy;
- 2) Most of the purchase price is economic rent to the 'winning' firm. It may be more profitable therefore to invest in rent-seeking to make more sales at a given cost than to cut costs. For example, if the firm has got costs down to \$5, but not \$1, it gets \$10 'windfall' subsidy on each sale anyway, even if this is not *ex ante* optimal. At this stage of the game it is highly profitable, in the *ex post* sense, to take the subsidy. Another way to view this is that it is not 'dynamically consistent' to presume cost cutting rather than rent-seeking at this stage in the development process.
- 3) The firm has some incentive to cut costs to benefit its bottom line, but by this stage it is only competing 'against itself' in pushing its own costs lower, and it is not competing on price in the market;
- 4) Since it is crucial that the mechanism have 'additionality' (the firm sells at higher prices in 'non-eligible' markets) the firm has to have tight hold of key IP and know-how and has to try to keep prices high in these other markets, and it is thus more difficult for competitors, needing access to the firm's vaccine IP, to drive production prices lower;
- 5) It is a sole supplier. This will reduce incentives to cut costs quickly for all the standard reasons such as 'X inefficiency' etc.;
- 6) If all the fund has gone on high development costs and high manufacturing costs, firms still get valuable IP (for use in other markets not covered by subsidies), but this is an 'over-reward' given the firm's own R&D put in to win it, and given the 'quality' of the outcome.

This is another route to lower efficacy vaccines for any given expenditure of public funds.

**A paradox**

There is a paradox here, that will tend to undermine pre-set APC schemes: The knowledge that there will be less competition to drive prices lower at the manufacturing stage (and in the R&D stage) will reinforce the notion that vaccines will *not* cost \$1-\$2 per course to manufacture in the crucial APC subsidy-paying days. This undermines by backwards induction the incentive to engage in R&D in the first place.

The problem is especially severe in the case of goal-2 vaccines as defined in the Malaria Vaccine Technology Roadmap. To the extent that the goal-2 vaccines are likely to be a great deal more costly to develop and manufacture than goal-1 vaccines, this reduces even further the value of any fixed-size subsidy pool 'set aside' for the goal-2 vaccine. Indeed, just the uncertainty over cost could wipe out even the low commercial value remaining in goal-2 (if there is any) after already very heavy discounting.<sup>325</sup> This further tips incentives towards the goal-1 vaccine.

**Some figures:**

Let us try some stylized figures to illustrate the point. Let us be really generous and allow for a malaria vaccine to be priced at \$25 per course of treatment. At horizons of interest (10 to 20 years), would it be outrageous to suggest that the \$25 would need to break down as follows if it is to work via an APC solution:

\$1-\$2 for production and distribution;  
\$6-\$ for *private* out-of-pocket R&D costs;  
\$16-\$18 for the cost of finance?

Let us say there is 50% 'crowding out'.<sup>326</sup> This would mean that about \$3 of the \$25 would go on genuinely new *private* out-of-pocket malaria vaccine R&D costs.

These are very, very rough figures, since paucity of information is such that we really do not have much of a handle on these issues. Venture capitalists (VCs) have told the author that these are being generous to the out of pocket R&D cost component, and that VC costs would gobble up most of the subsidy. VC costs are high anyway: There are big risks from the APC mechanism, and the science means there is a large 'option price' element in early R&D, etc.

Are these even remotely realistic figures? To the extent that they are, if it is not obvious that a vaccine could be manufactured for a dollar or so in the crucial early days, it is not realistic to expect private finance to be drawn in and for there to be multiple private malaria vaccine R&D programs.<sup>327</sup> These proportions are completely the converse for currently existing vaccines, and, indeed, for many late-stage vaccines, and this may point in the direction of commitments to competitively procure and to separate R&D issues more from production issues, instead of the provision of large ex post R&D subsidies along the lines of CGD to cover all parts of the problem.

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<sup>325</sup> High risk of science, high risk of collapse of coordination, high mechanism risk generated by mechanisms such as APCs.

<sup>326</sup> Explained below, and in Farlow, A.W.K., July 2005, *ibid. Innovation Strategy Today*, pp. 92-97.

<sup>327</sup> In the case of currently existing and late-stage vaccines, we find: Much lower capital costs because of much lower risk, especially risks of the mechanism itself; much less crowding out (because of the ability to use competitive tenders and other 'separation' devices to just repay the extra private costs incurred); greater ease at setting efficient terms (because of competitive tenders and other devices to reveal information, and good information on technology, etc.); and, for purchases of underused vaccines, price disciplined (or, at least potentially) by competitive tender, competition, access to IP, etc.

**All the fund absorbed by one firm then?**

The Hurvitz statement is not only poor economic reasoning, but it is also very puzzling in other ways. The by-gones-are-by-gones nature of R&D is such that even if the overall costs including R&D are greater than \$15 per course, firms will still avail themselves of the contract so long as the *manufacturing costs* of the malaria vaccine are below \$15 and they have no more lucrative markets to sell to elsewhere. So, the statement must be referring to *manufacturing costs* exceeding \$15. But, if so, with contract terms set on the basis of, say, 10 or more firms competing, why would those setting these contracts ever entertain the notion that manufacturing costs per course of treatment could be 30 to 50 times the out-of-pocket R&D costs of the winning firm?

The notion that manufacturing costs of *up to* \$15 are *not harmful* only makes economic sense if the subsidy is being lined up for *one firm alone* to take, with a large proportion of the payment allowed to go on the high costs of that firm for maybe not a particularly highly efficacious product, with the firm getting the IP too. In this case, anything up to \$15 makes perfect economic sense. However, this, supposedly, is not the intent of such schemes, slows down vaccine development, and raises the chances of feeding all of the subsidy to a lower quality, lower ‘quality’, result.

Like Tremonti, Hurvitz seems to be reasoning on the basis of a procurement scheme to cover manufacturing costs of a limited number of players – perhaps even just the one firm – rather than in terms of an R&D device. An ability to pitch for a lower efficacy requirement would be especially helpful in this regard. Similarly, by appropriate strategic positioning (certainly not by openness and acts of ‘sharing’ as discussed below) a large firm with a low efficacy vaccine is perfectly capable of surviving with high production costs eating up most of the subsidy.

**Paying the manufacturing costs of one big firm is not the point of the exercise**

The original claim was that “A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more.”<sup>328</sup> At least the Hurvitz claim highlights this underlying intent and the problem with this thinking. It also describes the firm as facing an option that they can take advantage of only if it suits them at the time.

The only conceivable justification for price-fixing would be that it has a major impact on R&D incentives, by encouraging multiple parallel privately-funded developers. Once commentators concede that any subsidy thus created may simply get used up in production costs, the whole point of price-fixing has become self-defeating. In place of 10 or 20 or more firms and one high quality winner – but a struggle to get the subsidy scheme to work – we end up instead with fewer numbers of firms, lower quality and higher prices justified.

It also seems perverse to be discussing partially efficacious vaccines as part of a package, to then allow production costs of those vaccines to become very high, and to allow high-

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<sup>328</sup> Kremer, M., No. 10 Policy Unit, Appendix 1, p9.

cost low-efficacy products to compete (temporarily) against much cheaper non-vaccine alternatives on the basis of most of the high production costs of the high-cost vaccine having been subsidized.

#### **5.4. Incentives to drive costs lower will increase the value of R&D**

APC advocates (Kremer et al., CGD, Berndt et al., IAVI, Tremonti, etc.) insist on doing all analysis – including fixing the size of the subsidy pool and cost-effectiveness analysis – on the basis of complete certainty of low short- and long-term production prices. Kaper et al. observe: “A number of outstanding questions about the cost and efficiency of producing these [malaria] vaccines persist, but the potential health and economic benefits of a good malaria vaccine are immense.”<sup>329</sup> Unfortunately APC advocates concentrate almost entirely on the latter observation and ignore the major hurdle of the former.

The problem is that by attaching payment for the R&D part of the process to the purchases of the ‘winning’ firm, the risks of the manufacturing part of the process get fed through to the R&D part of the process. Some separation of the two would help. This is not likely to be easy. First, while some shielding of the R&D from the risks of manufacture might reduce the risks and costs of R&D, expected R&D costs *should* feed into R&D decisions, and R&D decision-makers should share some of this risk. Second, given capacity issues, this is one area where risky R&D is often bundled with manufacturing capacity anyway.

This creates the interesting possibility, however, that if R&D investors (both private and public) can believe that manufacturing cost of the vaccine can be pushed lower, and there is more pressure on keeping development costs down, and, if they can pick up the benefits of this in payments for their R&D investments, then more investors will invest in R&D in the first place. Thinking about ways to have more firms active in the end market, might be good for those who invest in R&D too! Mechanisms less prone to generating sole suppliers – and rent-seeking and insufficient price pressure – may thus generate more R&D activity. This needs much more exploration. It suggests that the R&D ‘player’ should not be the only potential player at the end. If this player is *not* made to rely on all its expected R&D costs (including attrition rates, risk, etc.) being paid through ‘quantity times price’ in the end market via an APC, may this be more possible? Would it be helpful to use PPP approaches with more access to IP at the end, but with more of the costs of the R&D (how much?) already cleared from the system en route? None of this has been explored recently given the overemphasis on ‘sole-supplier’ or ‘few-supplier’ set-ups inherent to APC thinking.

#### **5.5. Goal-1 vaccine costs**

A two-goal approach adds to this problem. Many of the problems of the APC subsidy scheme and the scientific challenges discussed above show up as extra fixed costs – that

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<sup>329</sup> Kaper et al. 2005, *ibid.* pp. 12-13.

is costs that add much more to average costs the fewer the number of units of vaccines they are spread over. This affects the average costs of goal-1 and goal-2 activity, and further feeds the conundrum of how much to devote to goal-1, and how much to devote to goal-2. Intuitively, there is a part of the APC that is required to incentivize R&D and a part to pay the production costs. If production costs rise, the APC needs to adjust upwards to keep the R&D part constant.<sup>330</sup> None of this has been modeled, again, in part because of the crowding out of interest in these practical issues by the attention to idealized APC approaches. In this section we just discuss the economic principles.<sup>331</sup>

### **5.5.1. Capacity issues push up average costs**

There are a huge range of issues impinging on average costs of malaria vaccines – especially early vaccines. The average (expected) fixed cost of goal-1 specific R&D<sup>332</sup> and average expected fixed manufacturing costs, will be higher because these fixed costs will be spread over fewer purchases; we are referring to goal-1 after all and a product that is supposed to be superseded.<sup>333</sup>

Capacity takes years to put in place. What are the risks that unless the firm can be sure that it will be the only possible supplier, putting the capacity in place would be too risky for short-lived vaccines? In particular, it may be optimal to only have low-level roll out of useful goal-1 vaccines, but as a result these are higher average cost vaccines. How are subsidies adjusted for this? Or do firms ‘overdo’ sales of goal-1 vaccines, exploiting the fact that the marginal cost to purchasers is very low (\$1 even)? But this is unethical and raises problems with incentives for follow-on vaccines.

Firms may not believe that the goal-2 vaccine will be achieved and/or they may believe that the subsidy pool will all go on the goal-1 vaccine anyway. This might suggest that they should invest anyway in capacity for the low efficacy goal-1 vaccine. However, the uncertainty created by the presence of goal-2 will likely dictate that it is better to have a lower capacity and a higher average cost of production and fewer sales spread over more years, than to try to put in place capacity to hit high heavily-subsidized sales straight away, with a firm finding itself stuck with long-run supply contracts, and sponsors with the option to end the contract for a ‘better’ goal-2 vaccine anyway.<sup>334</sup> Past vaccine ‘successes’ relied on incentives to install capacity quickly and for use quickly. How is

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<sup>330</sup> Though it may have to rise higher still if higher production costs also cause more technological costs on the R&D side. This problem also makes setting the overall size of APCs even more difficult. See Farlow 2004 Section 6.

<sup>331</sup> Done here, with an extremely simplistic understanding of expectations.

<sup>332</sup> I.e. we are allowing for some goal-1 investment to be usable for goal-2, though we also realize that it has very low value indeed given the *extra* ten year horizon. There is a tradeoff somewhere in here: For investment that has value for goal-2, the greater will be its current expected value if goal-2 is nearer to goal-1, but the lower therefore will be its expected value for goal-1.

<sup>333</sup> Though firms may also put in capacity to deter others and to exploit the ability to ‘rent-seek’ the subsidy pool; hence why only ‘supposed’.

<sup>334</sup> Similar capacity issues impinge on trial capacity. We hear that a high priority is to “substantially increase and sustain trial capacity in endemic countries,” and to spend more on “designing, testing and improving regulatory pathways for trials.” (MVTR p28).

this altered if there are different efficacies of vaccines and a set of pre-fixed efficacy ‘goals’?

Even if the first goal in the Roadmap is achieved (by no means a foregone conclusion) not enough firms may be prepared to get involved for a vaccine that they expect to be less long-lived or, in the case of HIV, less therapeutically useful<sup>335</sup> and this will undermine forces otherwise generating lower product prices. This might also create a problem if the perception is that “a vaccine exists” and a firm is criticized for not producing enough, even though, in truth, to do so would require too much capacity compared to the long term optimal level. The less the time between goal-1 and goal-2, the higher these fixed costs of goal-1, and the lower the incentives to innovate to reduce costs.

Indeed, we saw above how some current R&D pull proposals (such as the CGD’s APC) build quantity uncertainty in – but this will drive up expected average costs. Such approaches create a fundamental conflict. Control over ‘quality’ of the whole development process via ‘acts’ in the end-market conflict with the need to get the manufacturing costs lower which may rule out such ‘acts’. A mechanism that disciplines ‘quality’ *en route* may be better able to achieve larger capacity, multiple suppliers, and lower prices – and, we saw above, stronger R&D incentives – than a mechanism that disciplines ‘quality’ via holding back in the end market.

### **5.5.2. Higher production costs because of low follow-on incentives**

Creating competition for later-generation products and competition between developers of current vaccines is “very important if we are to secure the availability of effective vaccines at affordable prices.”<sup>336</sup> While Barder et al. claim that “an APC *can be designed* to create incentives for new products and competition,”<sup>337</sup> it is now widely recognized that non-market incentives, such as APC subsidy schemes, threaten to stifle a range of follow-on activities, including those that would help to decrease average production costs. One of their side effects is that they distort the price signal that would have incentivized firms to innovate to cut costs and/or to replace earlier developers.

*“Advance purchase commitments may also stifle incremental innovation. Because they create a ‘winner takes all’ solution, it would be difficult for incremental, follow-on competitors to emerge, thus dulling the benefits of competition on cost and improvements. The innovation that wins will crowd out competing inventions because it is being given away free by the public sector. This ‘crowding out’ effect means that no improvements will be made to the winning formulation, and this may have negative consequences for resistance and effectiveness in subpopulations.”*<sup>338</sup>

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<sup>335</sup> There are also issues related to liability risk.

<sup>336</sup> Barder et al. 2005, *ibid.* p2.

<sup>337</sup> Barder et al. 2004, *ibid.* pp. 2-3 (emphasis added).

<sup>338</sup> International Policy Network, “Incentivising research and development for the diseases of poverty,” 2005, p15.

### **5.5.3. Less incentive to lower costs for less efficacious products**

Lowering costs of manufacture is itself a technological endeavor in need of R&D. It is not clear how much incentive there is to lower the costs of production of a less efficacious goal-1 vaccine or vaccines of limited life-span anyway. Intuitively, one would imagine that the incentive to invest in the capacity and research needed to make the product cheaper is lower for less efficacious vaccines than for more efficacious longer-lived products, since the cost saving is able to be spread over more units of vaccine in the latter case. It is probably fair to conclude that lower efficacy also means less incentive to drive production costs lower. But again, this has been totally ignored in the cost-effectiveness evidence.

### **5.5.4. The high 'global' costs of goal-1 vaccines due to the technical challenges of the malaria parasite**

Many of the activities discussed in the science section above pertaining to goal-1 vaccines – such as modifying a subunit vaccine to overcome polymorphism and antigenic variation, or using multiple vaccines alternated on a delivery schedule to minimize the parasite's ability to evolve resistance – end up requiring a lot of expensive ongoing modification, new and expensive technology, and/or vaccine production capacity,<sup>339</sup> even as large investments are needed for goal-2 vaccines. The more difficult combination vaccine route involves generating something that is already much more complicated and higher cost but requires less of these modifications.

None of this has been costed into the two-goal approach, let alone even visualized under an APC for malaria. What exactly is the tradeoff? How do investors simply not end up believing that they will ever get a 'fair' return to their investments, and so not carry out the required investments in the first place? This is on top of the costs and risks of combining the eventual vaccine with control mechanisms. Once again, this suggests that cost-effectiveness figures used to support goal-1 vaccines have not been completely worked out yet.

### **5.5.5. Higher costs because of rent-seeking and other strategic behavior**

It is always better to compete for a contract *before* sinking costs. Current APC logic is that firms sink R&D costs first, and then risk having to compete twice. First, at the R&D stage. Second, at the committee/purchasers stage. The principle that 'investment by-gones are investment by-gones' means that it is always worth spending up to the value of the second stage in 'rent-seeking' behavior to acquire its value (see the Glossary for a reminder of terminology). In such situations, firms expect to face a negative rate of return from the overall project, and will therefore try to find ways to reduce needed rent-seeking costs as early as possible (for example, by narrowing down the number of other firms).

Again, we find that a fixed-size, time- and quantity-limited subsidy pool intensifies the problem. Unlike patents, under an APC the first to market is likely to get all of the

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<sup>339</sup> Including all of the risk of such capacity showing up in finance costs and financial option values.

subsidy pool if it can hold off ‘follow-on’ vaccines just long enough. Even better if it can create the reputation for this; it becomes self-fulfilling since other firms hold off investment and the first firm gets the subsidy pool sooner. With standard patent-based systems and marketing, firms can more easily agree to split the market, so there is incentive to share/license/split the higher price for the better product. This has all gone with the lack of a price signal. Since firms can do nothing to affect the price, but can affect their share of the pool of subsidy via quantity, much of the competitive impetus (and cost-cutting impetus) may get absorbed in rent-seeking instead. There are strong incentives for the first-generation developers to block (advertently or inadvertently) second generation vaccines (via not ‘sharing’ IP, know-how, etc.). This all drives average product prices higher.

Firms can try to influence purchase decisions through, for example, illegal kickbacks and bundling of products to hide discounts. There are sanctions against the former – if detected. There are fewer sanctions against the latter, and it is difficult to detect. This biases APC schemes against small biotechs (since they cannot bundle and cannot hide other subsidies), not-for-profits (who may not be allowed to behave in these ways), and emerging developers. Again, *expectations* of this will disadvantage the latter groups when trying to acquire the original finance for R&D.

If there is an incumbent firm, its best bet as a way to reduce its own later rent-seeking costs (that will only serve to drive later average costs higher) is to signal/ behave in ways to increase the expected risks of other firms. The result is that no second firm bothers to enter whatever the size of the commitment. The ‘winning’ firm saves on rent-seeking costs. Product prices are higher. But to the extent that this is all understood from the start, R&D incentives for any given size of subsidy are lower, average vaccine quality is lower, and vaccine development slower.

One solution might seem to fix terms at the start to make it clear that no amount of lobbying/spending at the second stage will change the payouts. However, fixing terms contradicts the need for discretion in the hands of the committee running the subsidy scheme, given that the science and costs are highly uncertain, if not simply unknown, and because it is difficult to set terms efficiently once and for all. Terms would become mechanistic, based on expectations at the very start, and science that is 10-20 years out of date.

Again, the key point is not that certain players are able to engage in rent-seeking more than others, but that even rent-seeking firms might in the first place prefer to avoid being put in such a situation, and will therefore prefer to avoid schemes that force this on them. Here, the added twist is that it eats into costs.

#### **5.5.6. Higher costs because of weak distribution and health systems**

Under CGD-style and Tremonti-style APCs, quantity is not guaranteed, making scale up difficult to judge. Either firms scale up production facilities but then face uptake risk and hence higher average costs that way. Or they hold back scaling up, facing higher average

cost because of the lower scale.<sup>340</sup> Historically, uptake has been slower than predicted for a wide range of reasons, especially weak distribution channels and EPI management problems. Industry has a dim view of demand forecasting, and regularly finds that the public sector has been overly optimistic. Regular sustained uptake of current vaccines would strengthen the systems for new vaccines.

### **5.5.7. Liability worries raise costs**

The more that liability issues are unresolved, the less incentive firms will have to scale up capacity to push average production costs lower.<sup>341</sup> It really is not appropriate to compare the case of flu to the case of 30% efficacious malaria vaccines and partially effective therapeutic HIV vaccines.

### **5.5.8. Higher costs of a ‘global’ package**

From the policy-maker’s perspective, the issue should be the ‘global’ average cost of the vaccine. We really do not know the costs imposed on other components of the malaria package (especially one-off costs) of having to coordinate with a lower efficacy goal-1 vaccine. And there are plenty of secondary costs that do not get picked up in the firm’s bottom line average cost either. For example, “long-term follow-up of trial subjects is also extremely important [and costly] to identify potential secondary effects,” and guidelines to improve trial design will “also increase the costs associated with an already expensive activity.”<sup>342</sup> These add to the average expected costs of using low efficacy vaccines, though it is not clear to what degree these costs show up in the bottom-line of goal-1 developers (and not the bottom-line of sponsors) or governments of developing countries.

Yet again, this suggests that we still do not have adequate *global* cost-effectiveness analysis.

### **5.5.9. Conclusion**

Once we combine rent-seeking with the problems of generating low production costs (especially the uncertainties of follow-on and goal-2 vaccines) we see the risks of an industrial structure that collapses down the number of sellers, whose high price products, on account of high average production costs and ‘rent-seeking’ costs, absorb most (in the limit, all) of the subsidy pool. Throw in a waiver to get out of having to supply the long-term market, and this is an even more likely outcome. Ex ante, it becomes difficult to imagine multiple parallel privately-funded R&D investments. Overall, R&D intensity is yet again slower, vaccine discovery delayed, and the likelihood of accepting a lower efficacy product, or getting no product, increased.<sup>343</sup>

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<sup>340</sup> And potential loss of repayment via an APC if take-up problems are resolved.

<sup>341</sup> And the, by now, standard observation that it eats in to the expected subsidy leaving less over to stimulate initial R&D investments.

<sup>342</sup> MVTR p31.

<sup>343</sup> Farlow, 2004, *ibid.* Section 10 looks at a range of industrial organization issues.

To repeat what should be obvious by now. All extra expected average production cost feeds back to weaken R&D incentives for a fixed size subsidy pool. The assertion that vaccines will be generated costing \$1 or so to manufacture – even for the first vaccines produced – has no basis in data, though it is key to selling APCs. Given the risk that by being false, it undermines R&D, the claim needs to be investigated more thoroughly. Similarly, the notion that R&D costs will be disciplined needs more thought.

This is part of a general problem with poorly-designed subsidy schemes. While, ex post, R&D subsidies help to avoid time-inconsistency, they run the danger of losing the value of competition and price signals, and other natural market disciplining devices, to push costs lower.

### **5.6. When legally-binding long-term supply contracts undermine R&D incentives**

As one way to ensure long-term supply after all of the fixed pool of R&D subsidy is gone, one suggestion is to legally bind firms from the start – even before they sink R&D investments into malaria vaccines – to supply at a low price in the long-term. In fact, this is key to the CGD claim that this approach removes previously experienced access problems for ever. DFID explains: “Once the initial market commitment has been realized and R&D investments recouped,<sup>344</sup> the company agrees [i.e. legally from the start] to supply at an agreed lower price. An APC therefore builds in a commitment to long-term sustainable pricing.”<sup>345</sup> As Nancy Birdsall put it to the US Senate: “Part of their legal agreement would be that once 200 million doses, in this example, had been bought, they would reduce the price indefinitely, going forward, and promise production indefinitely, going forward, at \$1 per immunized person.”<sup>346</sup> It seems that even as late as mid-2005, the \$1 long-term production cost and the notion that long-term secure supply and access was as simple as a contract detail set twenty years in advance was seriously being justified at the highest of political levels.

#### **Tremonti allows prices be set after R&D costs are sunk**

As Tremonti puts it: “To ensure public health impact... firms that participate in the AMC must commit to supply subsequent doses at a lower price, or to license other producers to do so.” According to Tremonti, “two stage pricing to ensure sustainability”<sup>347</sup> is key to the proposal, and (somehow) this has to reflect the scientific challenges and production costs of the vaccine at hand, and be set in such a way as to strike a balance between the “public health goal of sustainable supply and the need to establish a sufficient return on the investment of successful vaccine developers.”<sup>348</sup> Given the difficulty of doing this, we are then told that this price structure can even be set much later, after firms have sunk their R&D and manufacturing costs! According to Tremonti<sup>349</sup> this “requires either fixing

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<sup>344</sup> Of course, this is a hypothesis, and not a fact.

<sup>345</sup> DFID, June 2005, *ibid.* p1.

<sup>346</sup> To US Senate Foreign Relations Committee, May 17, 2005.

<sup>347</sup> Tremonti, G. Background Papers, 2005, *ibid.* p37.

<sup>348</sup> Tremonti, G., 2005, *ibid.* p8.

<sup>349</sup> Tremonti, G., 2005, *ibid.* p8.

the lower price ex ante, or agreeing in advance on a process to determine it when more information is available on production costs [even if there is only one firm involved].” Or “an alternative option could be to design a formula for the long-term price of the vaccine which guarantees the cost of production while creating an incentive [but without explaining how, given that many competitive features are missing] to keep it as low as possible.”<sup>350</sup> Again, that Tremonti worries so much about setting allowed *costs* later (via a committee that is allowed to change the allowed price later), points up the fact that Tremonti, once again, seems to be thinking of APCs as instruments to cover manufacturing costs of limited numbers of suppliers and not as R&D instruments.

Indeed, Tremonti explains, “another noteworthy task of the IAC<sup>351</sup> will be suggesting [to] donors the split of each AMC commitment between the unitary prices and the number of doses,”<sup>352</sup> to determine the payoff to each player, in order, supposedly, to balance all the different incentives. Though, yet again, no details are spelt out as to how this could conceivably be done without harming cost-cutting incentives and competition in the industry, dealing with all the asymmetric information problems, and preventing mechanism capture and the risk of disincentivizing a range of vaccine players.

Nevertheless, and in spite of all the scientific and informational problems, we are told that this pricing structure “*can be designed* [it is not explained how]<sup>353</sup> to maintain incentives in continued research on new and improved vaccines even after the first vaccine meets the scientific requirements specified in the AMC.”<sup>354</sup> Incidentally, this role for the committee was a little less obvious in the original CGD papers, which tended to emphasize the notion that the payoffs to each player would be set in the rules in advance and driven by purchasers, and not involve too much the committee at the end. At last, Tremonti is recognizing the impossibility of doing this.

**But the supply commitment was in return for the promise of a short-term advantage of initial sales at high prices and getting the IP**

This ‘legal’ obligation – supposedly enforceable in a court of law, usually in the US when ever specified – is in return for the short-term advantage of initial sales at very high, heavily-subsidized, guaranteed prices that generate a ‘windfall’ profit,<sup>355</sup> and also in return for getting valuable IP (especially for use in ‘non-eligible’ markets). The notion is that having taken all of the subsidy pool and the IP, it would be a disaster for sponsors if

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<sup>350</sup> Tremonti, G. Background Papers, 2005, *ibid.* p18.

<sup>351</sup> The committee running the subsidy scheme and determining payments at the payout stage. This was called an ‘Independent Adjudication Committee’, IAC, though the independence of any such committee is far from clear. It has since been argued that “adjudication” sounds a bit too legal and disciplinary. However, if the committee is to do its job – and have the necessary teeth – this terminology has to have some resonance.

<sup>352</sup> Tremonti, G., 2005, *ibid.* p11.

<sup>353</sup> Phrases like “can be designed” are liberally sprinkled all over the Tremonti report even though the authors who advised the inclusion of such phrases know that such design challenges have not even been looked into yet.

<sup>354</sup> Tremonti, G., 2005, *ibid.* p8.

<sup>355</sup> As always, the author is visualizing what would happen if there were multiple parallel developers, since the science dictates that this would be needed, with a ‘winner’ or ‘winners’ getting a large multiple of its own out-of-pocket R&D costs.

the firm ‘abandoned’ the poor eligible segment of the market, either in order to supply part of the (much) more profitable non-eligible segment (which may have a particularly profitable segment, and given that there may be limited capacity and limited ability to supply all segments), or simply because the firm had failed to get costs low enough, with no back-up mechanism for the eligible segment. It can take 5-7 years to set up vaccine capacity; spare capacity can hardly be created by sponsors to hold in reserve to supply the long-term eligible poor market if the original firm abandons it. This long-term, supposedly legally-binding, commitment to supply at a very low price for ever is key to ensuring access in the long-term under APC schemes. Certainty of low long-term prices is also key to sustaining vaccination programs in all countries, low-income or otherwise.

The need for a legal contract term to cut prices and to supply vaccines in the long-term arose because it was recognized that it was the only way to secure long-term supply for eligible markets, given that the ability to make firms compete at that stage had now been reduced by the presence of the subsidy scheme and its pre-committed subsidy price, and by an industrial structure more geared to sole suppliers. It was also included by CGD and Tremonti because without it the APC would have looked decidedly threadbare on a key practical issue.

But is this legal threat credible? Will it work? Are legal agreements better at driving long-term supply and low prices than access to technology and genuine competition? On both counts the rest of this section finds the idea lacking. It is an easy fudge of a complex and difficult problem.

### **5.6.1. This cannot be done**

CGD suggests that the original malaria contracts determine, at the time of signing, the ‘guaranteed’ long-term price, or an ex ante methodology for determining the long-term price, and that all firms be legally tied in to such contract terms even before investing in R&D. As CGD puts it: “In any event, setting the ongoing supply price is a *critical component* of the advance market commitment,” (emphasis added).<sup>356</sup> And “Setting the long-term base price is a *critical component* of the advance market commitment,” (emphasis added),<sup>357</sup> and completely key to the claim that such schemes are the way to end ten to fifteen year delays in access to new vaccines.

Others argue this ‘critical component’ would fail.<sup>358</sup> No such methodology for setting long-term price years in advance of product development exists. Extensive exploration of the issue by the NIH in the early 1990s concluded that it was extraordinarily difficult to compute or even lay out a methodology for computing the price of an unknown product given the difficulty of knowing in advance the manufacturing complexity of any vaccine discovered, and that competition policy and commercial law may preclude engaging in activity that could be seen as price fixing and/or a subsidy to a favored firm.

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<sup>356</sup> CGD, April 2005, *ibid.* p107.

<sup>357</sup> CGD, April 2005, *ibid.* p47.

<sup>358</sup> Farlow et al. 2005.

Second-generation vaccine costs are even more difficult to work out in advance than first-generation vaccine costs. CGD was advised that malaria vaccine production costs could range from \$0.50 to \$15.00, and that no such guarantee could be inserted into contracts. Indeed, this “critical component” was left blank in the CGD contract term sheets, *even as* the notion of a guaranteed \$1 production cost was being promoted in the US Senate.

The long-term price can only be set on the basis of estimated future manufacturing costs. A tall order. If the price is set early to supposedly encourage firms to cut costs<sup>359</sup> – by, for example, their choice of technology – it will defeat the whole object of the exercise if it is set too low or too high. If it is set too low, firms cannot beat it and their R&D is disincentivized. If it is set too high, too much is paid relative to what could have been.

### **Tremonti suggests more manipulation**

Various solutions are suggested to get around this problem. Tremonti suggests either to leave determination of the tail price till production is in place, or to fix a price, and monitor and correct the price mid-course. Once again, both solutions are seemingly based on the assumption that an APC is not an R&D instrument over multiple parallel developers. But both of these solutions simply generate a range of new problems:

- 1) Industry may fear opportunistic behavior, given the large sunk costs they have to sink to get to this decision point, with this intensifying as the number of parallel developers increases;
- 2) Given the state of incomplete contracting and the fact that industry has more information on costs, firms will manipulate cost accounting and elevate the costs attributable to this product (with this giving advantage to some firms over others, in particular larger firms over smaller firms concentrating on just this product with fewer ways therefore to hide and manipulate their costs);
- 3) It leaves the overall level of financial commitment unclear, with this either harming follow-on innovation (given worries that the limited funds will be depleted by allowing higher costs to an overly-expensive early product) or requiring politicians to take on a more open-ended financial commitment.

This is another case where the benefits of true competition have been ignored, in this case both to drive the ‘tail price’ lower, but also to reveal it.

### **Reasons to delay or to deny to eligible markets**

One danger is that firms will simply delay or slow supply at the short-term price, perhaps because of limited capacity<sup>360</sup> to avoid having to supply at the long-term price ‘too soon’ (e.g. while they supply a more lucrative non-eligible market first). There is also an extra incentive to do this if the low long-term price risks pushing prices down in non-eligible markets. Given the forced requirement on a firm to supply at a low (say, \$1) price after making all of its allotted subsidized sales, there may be some logic in siphoning off the subsidy pool over several years rather than achieving the large scale required to take it

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<sup>359</sup> We already saw that this was problematic from an R&D perspective.

<sup>360</sup> There is an option cost to putting capacity in place. If no other firm is obligated to supply, the firm is hardly likely to work to supply *all* the eligible market first.

early and then having to supply at the long-term low price and being forced to sink the costs to achieve this. Or it may simply not be in a firm's interests to supply one set of markets at an extremely low price whilst still in patent elsewhere, realizing that the low price market may act as a reference price for higher price markets.<sup>361</sup> One can imagine the political scenarios too (e.g. in the case of HIV, with Russia<sup>362</sup> forced to pay a high monopoly price while a hyper-cheap product is on sale in a much poorer market).

### **A price discontinuity**

Observe also the discontinuity in price, dropping at 200m sales from \$15 to, say, \$1. Those sales very close to the 200 millionth sale may have very expensive consequences once manufacturing costs are fully explored. Indeed one can see that, as sales rise, if it is proving difficult to achieve the low required price, there is logic in slowing production to hold off having to supply the 200 millionth purchase and hitting the discontinuity. There is a standard monopoly problem in here. The marginal profit to one more sale falls and may become negative well before the 200 millionth sale, once the impact on profit of the sales beyond the 200 millionth is factored in. The long-term legal commitment feeds back to reduce early quantities, raise early production costs, and, indeed, undermine R&D incentives in the first place.

This is all dependent on the state of competition in the industry – but this can be controlled by any sole winner – and the state of any waivers on long-term supply. Intuitively, a firm that was not getting production costs low enough, would not be keen on another firm pushing the fund over the 200 millionth sale forcing the first firm to supply at the low long-term price. We are reminded of the assertion in some of the cost-effectiveness evidence (Berndt et al) that delay hardly impacts cost-effectiveness of a malaria APC.

Incidentally, *all* firms who benefited from APC subsidy payments should be obliged to supply at the long-term low price. If this is not rigorously applied (and expected to be applied) the legal obligation would be unfairly applied and give some firms a competitive advantage.<sup>363</sup> Even those who never achieved high enough capacity to get price low enough before the subsidy pool ran out, should be obliged to continue supplying at the low price. But who will enforce this?

### **5.6.2. What if long-term price does not go low enough?**

If the winning firm's production cost does not come in low enough – say a firm has got costs down to \$10 but no lower – or if a firm simply 'prefers' not to sell to 'eligible' countries at the long-term low price, it is argued that contracts would allow sponsors to 'acquire' the right to produce the vaccines instead, with this threat acting as a disciplining device on long-term manufacturing costs. However, this will not work, and may even backfire:

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<sup>361</sup> This would also lead to reluctance by firms to give cost information in any methodology that tries to set a 'reasonable' long-term price, late on in the decision process.

<sup>362</sup> Russia would be part of the base market on which, supposedly, the subsidy contract 'creates' an additional HIV vaccine 'market'.

<sup>363</sup> With the others, no doubt, seeking redress.

- 1) The supplier is required to turn over IP to the sponsor, even if the supplier may not have the right to sublicense all the IP;
- 2) The sponsor will have difficulties acquiring ‘know-how’ and production capacity. If the supplier has all the know-how, how is the sponsor to get it? The presence of know-how (extremely important for biological products) makes many disciplining threats non-credible (e.g. compulsory licenses if vaccine developers refuse to supply);
- 3) The supplier must still be allowed to retain IP rights to ‘non-eligible’ markets – but this creates conflict. Since IP and know-how barriers have been principal causes of delay in achieving flexible, cost-effective manufacturing and quick access to vaccines for the poor in the past, it does not make much sense to make the control of IP and of know-how part of a threat mechanism to drive ex post contracts;
- 4) There are supply shortages and damaging access delays. The sponsor is hardly likely to put in capacity in advance of taking over the right to produce, especially if it is not clear that it will need to produce. Such capacity would anyway raise average costs, and would have to be paid from a separate budget to any subsidy payments. This all mitigates against using the threat and this feeds back to harm price-cutting efforts;
- 5) There are reputational damage issues for both supplier and sponsor(s);
- 6) The threat undermines incentives to invest in vaccine delivery systems;
- 7) The threat undermines incentives to invest in vaccine R&D;
- 8) The sponsor may anyway find itself in a similar position to the firm, unable to get production prices any lower, and having missed out on earlier cost reducing opportunities.

### **Penalties to force good long-run behavior?**

Alternatively – and the reader can tell how desperate the argument is becoming, to wriggle out of every new hole in the CGD and Tremonti logic, and to appeal to politicians, oblivious to investors and financial markets – CGD suggests “other penalties” to force compliant long-term behavior. However, though “other penalties” such as “liquidated damages provisions” imposed on the supplier are proposed by CGD in the contract term sheets attached to both the CGD and the Tremonti Reports, the term sheets leave the details blank.

This new threat may also backfire. The paradox is that unless firms can be sure of generating low manufacturing costs, using legal threats to prevent firms from abandoning poor markets in the long-run (especially if threat provisions are as vague as CGD makes them) will undermine the original incentive to do R&D.

It can also create the perverse incentive not to supply eligible markets in the first place or delay supplying eligible markets in order to delay the threat.<sup>364</sup> Intuitively, firms will not be subject to any penalties if they never supplied via an APC in the first place or delayed supplying (say if they have richer markets to deal with first, and know that other firms

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<sup>364</sup> This is more likely for HIV than for malaria one would presume, though it is not clear.

will regard it as too risky to try to develop a product to take the APC early<sup>365</sup>). This also weakens incentives to invest in vaccine delivery systems in eligible countries.

Every legal advisor this author has discussed this with<sup>366</sup> says that such threats in contracts at 20+ year horizons are simply not used. They could never be credible, and no firm would tie itself down like this even before investing in R&D. Firms would in particular keep away in the first place from sensitive and emotive market situations where ignoring a legal obligation – to supply vaccines – after a big-looking reward (which may still not have been adequate in the ex ante sense) or facing damage provisions, would make them look ‘bad’. Several correspondents observed that instead of an economic, finance, or health-systems solution, CGD each time plumped for a legalistic solution.

### **The presence of threats alerts us to a big problem**

The heavy use of threats and counter-threats on long-term supply in the CGD and Tremonti schemes at least reveals a recognition that such schemes may suffer the inherent fault of struggling to create long-term supply and low-cost access, and create the risk of delays. How do production costs get low enough to supply the ex post market? What happens if the threats do not work? A mechanism that relies on this presumption in order for it to work should be treated with a great deal of caution, indeed skepticism. It may say something that 8+ years since the idea first surfaced, the only way found to force low long-term prices out of these models is through contractual threats. And even more worrying that the contract writers do not then have a clue how to write the terms of such threats.

Yet the claim is *still* made that “Public and philanthropic funding of research does not directly ensure access” but that an APC subsidy scheme “would *guarantee* that after a pre-determined number of doses had been purchased the price would fall to a sustainable level in the long run,” and that this would “end the delays which prevent vaccines from reaching developing countries once they have been developed.”<sup>367</sup> Increasingly, this is argued as one of the innovative merits of these schemes. Tremonti argues: “There has been a long delay before vaccines that were developed for affluent countries became available at an affordable price in poor countries. More than a decade after the development of vaccines for Hepatitis B and Haemophilus influenza B... these vaccines are still not widely available in the developing world.”<sup>368</sup> Zandonella, on behalf of IAVI, argues that “AMCs might help vaccines reach developing countries sooner, avoiding millions of needless deaths that can occur when a vaccine is too expensive for developing countries. A vaccine against *Haemophilus influenzae* serotype (Hib) developed in the mid-1980s is still too expensive for use in many low income countries and an estimated 4.5 million unvaccinated children have died from Hib-related disease over the last decade.”<sup>369</sup>

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<sup>365</sup> The first developer still has an option on the APC.

<sup>366</sup> Well, it hardly counts as discussion when it is dismissed straight off.

<sup>367</sup> Barder et al. p3.

<sup>368</sup> Tremonti, G. Background Papers, 2005, *ibid.* p5.

<sup>369</sup> Zandonella, C., 2005, *ibid.* p19.

Observe that the term ‘AMC’ is supposedly referring to an R&D device, and not to a large procurement fund with scale economies and competition on prices. So, Zandonella is discussing *long-term legally-binding contract terms* set *even before* embarking on R&D, as key to saving millions of lives. We failed before because we were just too hopeless in getting firms to sign APC-style contract terms to supply Hepatitis and Hib vaccines at \$1 per course for ever, before they even started work on the R&D. Why did we slip up so miserably when the solution was so eminently “simple, easy to understand, and practical to implement”<sup>370</sup>?

### **Hib demonstrates what a bad idea this would have been**

Incidentally, the Hib case shows just what a bad idea it would be to expect firms to sign such long-term legally-binding contract terms even before they would be allowed to do vaccine R&D. If firms really did not believe that Hib would become as cheap as stipulated in the Hib APC or that other failures would intervene to prevent sufficient use of Hib to drive prices that low, expecting firms to sign such deals would have killed incentives to do the R&D in the first place. An R&D device could hardly “help vaccines reach developing countries sooner” if it had already killed off incentive to develop those vaccines in the first place. Again, we are reminded of the cost-effectiveness evidence (see the next chapter) used to justify a malaria APC that says that even this is still a highly cost-effective outcome.

### **5.6.3. Long-term price and follow-on issues**

What is the sense anyway in *forcing* on firms the legal requirement to supply a goal-1 malaria vaccine at \$1 – and to have to put in the capacity to do so – if the vaccine is supposed to be superseded (but may not be) by a follow-on goal-1 or goal-2 vaccine that will take the market?

On the one hand, this forces inefficiently large capacity and costs on inferior vaccines. This is even worse for the firm if a ‘winning’ vaccine was not even a particularly ‘big’ winner, in the sense that it was only allowed a minority portion of the total subsidy pool, so as to leave enough in the pool to incentivize follow-on activity.<sup>371</sup> Now, the firm is supposed to be legally obliged to supply at low price for ever, even if the firm was paid little of the total subsidy pool in the first place. And what if a firm argues that it is being forced to keep supplying, unprofitably, a vaccine because no vaccine came along to replace it, and that this is the fault of those running the subsidy scheme for getting terms all wrong and disincentivizing ‘better’ vaccines in the first place? The firm would have a good case for not being tied into the long-term low-price supply obligation.

On the other hand, it forces superior vaccines to compete against low efficacy vaccines that have been set ‘artificially’ low prices by this forced obligation to supply at a low price. In other words, the price signal to help incentivize even better follow-on vaccines has gone too.

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<sup>370</sup> Barder, O., CIPIH Forum, 19 November 2004.

<sup>371</sup> There is no presumption in this author’s mind that this would ever work; here it is treated as how an idealized model would have to work.

Either way, it is not obvious that forcing firms, even before investing in R&D, into these long-term supply deals is not just a very bad idea. The notion is really only included for APC advocates to avoid an even bigger set of problems regarding long-term supply, that would expose serious problems in the logic of their thinking.

### **Problems allocating limited supplies of particular vaccines**

The arrangements for follow-on might also harm early vaccines if a follow-on better vaccine is created, and also create reputational damage all round. Normally, an early product might be able to compete on price and preserve some share of market even if a superior product comes along. Indeed, in a situation of limited capacity this might make sense, as a way to spread purchases across the limited capacity, with price used as an allocating device. Now, with all firms competing at the same price, why should any buyer have anything less than the latest ‘new’<sup>372</sup> vaccine? Absent price signals to allocate purchases, who rations the vaccine and forces the ‘inferior’ vaccine onto purchasers?<sup>373</sup> Who takes the PR consequences? The Gates Foundation? The World Bank? Or, would the use of a ‘price signal’ to allocate be just as problematic?

This is further complicated by the fact that fixing long-term low price would give a perverse incentive to not work on vaccines the long-term production costs of which are likely to be high, but instead to concentrate on vaccines the long-term production prices of which are likely to be low. But this gives even more impetus to less complicated vaccines over more complicated combination vaccines. How does one generate different allowed prices and quantities through a committee based on differences in the complication and costs of the underlying technologies in order to give developers a ‘fair’ (expected) return

## **5.7. The destructive impact of a waiver on long-term supply obligations**

As Hurvitz puts it “the contract is *intended* to give developers the incentive to create a low cost vaccine that meets the technical specification, *if at all possible*,” (emphasis added).<sup>374</sup> As the next example of the desperate measures needed to wriggle out of every logical problem newly created in response to the previous logical problem, one suggestion of a way to avoid the negative consequences onto R&D incentives of the use of legal threats and damage provisions written into contracts years in advance (at least the

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<sup>372</sup> Which does not have to be the most perfect, just the most perceived perfect (in informationally poor settings there may be herd effects, informational cascades, etc. picking off vaccines).

<sup>373</sup> The reader can think of what happens when the latest Christmas toy craze hits the shops. Absent any price signal, how are purchasers supposed to be incentivized to purchase less-popular toys? They show up in queues (that act as a form of rationing device via the cost of queuing, with coordination failure creating large externality effects between those queuing, with this absorbing the value of any economic rent) and hassled store managers.

<sup>374</sup> Hurvitz, J., CIPIH Forum, 16 December 2004. Incidentally, this is another of those statements where we are much more interested in the likely actual practical implications and not the easily verbalized ‘intentions’.

damaging nature of such provisions is realized), is to allow the requirements to supply long-term and at a low price to be waived if low price does not prove possible!

However, the whole point of the legally-binding requirement was because the mechanism was creating a sole-supplier or too few suppliers, getting ‘windfall payments’, and the only way to stop this from reducing price pressure and harming long-term supply was to give the supplier(s) a legal obligation and an incentive to seek ways to cut price. In the Zandonella and Tremonti and CGD quotes above, these *long-term legally-binding contract terms* were praised as the key to saving millions of lives. These terms should hardly now be up for waiver or renegotiation.

A waiver therefore creates the worst of both worlds. On the one hand, the ‘committed’ long-term low price undermines competitors and disincentivizes them from investing in order to compete against the original firm on price (price competition needs investments and the APC contracts have made these investments risky and much less valuable), so the original firm *itself* has to be *legally* tied to long-term price to give *it* incentives to cut prices. On the other hand, if this firm knows that this obligation can be breached, then the incentive to find ways to cut long-term price is wrecked,<sup>375</sup> and, meanwhile, no alternative to the sole supplier is put in place to drive efficiency on price, to supply the market and to ensure long-term access at a low price if the legal requirement is breached.

### **The strategic use of waivers**

In addition, the presence of waivers is far more likely to give a strategic advantage to larger, more influential, firms. Smaller, less influential players would surely expect to be held much more to their contractual obligations, especially if allowing small firms to be ‘let off’ via a waiver is detrimental to larger more influential competitors. Meanwhile, larger players have more resources to lobby for a waiver (it is a valuable form of rent-seeking). Just the expectations of this, will feed back to raise risks and hence the financial costs of smaller players.

What if a waiver is allowed? Who will supply the vaccine cheaply enough to provide long-term supply? An APC clamps down on generic versions,<sup>376</sup> and generics may regard the risk as so high, and the capacity so uncertain that they will not have put in place the capacity to supply at low long-term price anyway. In addition, so as not to harm follow-on products, first generation products that fail to achieve long-term low prices will not be able to be so easily replaced with lower priced generics. Who supplies to make up for any collapse in long-term supply?

Furthermore, this supply commitment, and low price, was also supposed to help give countries incentives to invest in systems to use vaccines in the long-term. These countries are harmed in the process of the waiver and their behavior in expectation of this will

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<sup>375</sup> If there are several firms, the equilibrium may be that if other firms are not investing to lower the long-term price then it is less optimal for this firm to do so too, with this behavior increasing the chance of a waiver.

<sup>376</sup> Remember that the ‘owner’ of an APC-financed vaccine needs to protect the non-eligible markets from generic versions that may undermine it.

further undermine R&D incentive. When countries make investments based on secure vaccine supply at an affordable price, should this be based on a contractual threat that is then allowed to be waived? Would not real competition be better than ‘competition’ by a non-credible legal process?

Besides, if the ‘winning firm’ developed a product on the back of sponsor funding (of, say, trials on children in Africa), but they are then allowed to abandon the poor market, or only to supply it after a long delay, because their costs are not coming in lower than \$15 (or \$25), it is a disaster (remember, they get to keep the IP). Why should they be allowed to get out of providing the vaccine to a poor market because they did not push their costs low enough?

### **Reputational damage**

Given all these gyrations over long-term price, and the supposed needs of firms to set up internal mechanisms to push price lower to avoid “liquidated damages provisions” and other “penalties” (though these were surely not to be taken seriously?<sup>377</sup>), how many firms will want to enter such a highly sensitive area with all these problems waiting in store for them, replete with reputational damage? These penalties got mentioned in the CGD contracts but have never been spelled out. How many hundreds of millions or billions of dollars of penalties would in truth be stipulated in the contracts for failing to supply long-term?

Maybe the reason we ended up with non-credible inserts into R&D contracts and waivers was to avoid having to think about a major practical problem – long-term supply and price – even as the proposed contracts are set so as not to drive costs low enough for long-term supply. Maybe going back to first principles on just why this situation might arise might be damaging to some of the assumptions of those lobbying hard for APCs? Better perhaps just to presume, and reassure, that the contracts can take the strain?

It may make more sense, yet again, to think much more about ways to enable product manufacturing costs to be pushed as low as possible as quickly as possible, and avoid mechanisms that rely on sole suppliers and legal obligations on sole suppliers. Instead we are told that “the price would be reduced to an affordable level as required by the contract. This would ensure that the market exclusivity did not become a barrier to access to low cost vaccines.”<sup>378</sup> And the APC cost-effectiveness evidence and the calculated size of the overall needed subsidy pool have all been based on this assumption holding too. This should have warned us of the problems being ignored. Cutting corners like this is just not good enough.

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<sup>377</sup> At the very least, these are time inconsistent (economists would say ‘not subgame perfect’).

<sup>378</sup> Barder et al. 2005, *ibid.* p6.

### **5.8. The problems of ‘top-up’ production subsidies and of flexible costing rules**

If all threats and waivers fail, one other possibility might be to allow firms to put in a later claim for more funding above and beyond what they received from the APC subsidy scheme. However, at the time of this later request, firms will have sunk heavy investments and will face the risk of time-inconsistency from funders<sup>379</sup> and yet suffer a great deal of reputational damage in the process of trying to get a fair risk-adjusted payment.

Imagine, to simplify thinking, if there is a sole ‘winner’ of the \$3bn subsidy pool (and none of the subsidy pool is being held back for follow-on purchases) but production costs are coming in at £15 per course, requiring, say, \$6bn to cover both the £3bn cost of manufacture of the 200million early courses, and \$2.8bn as the fair risk-adjusted pull R&D subsidy.<sup>380</sup> From an ex ante perspective (before they invest in vaccine research) this would require a sole-winning firm to expect to request billions of dollars of top-up payment in addition to the original \$3bn pull subsidy, even if they had spent just a few hundred millions of dollars on out of pocket R&D costs themselves. No firm is going to invest ex ante knowing this, and the potential reputational consequences. Besides, knowing the political constraints on funding, firms would find it hard to believe that more funding would be forthcoming – especially if advocates are seeking fresh funds to incentivize the 80% follow-on malaria vaccine for which no subsidy funds are left in the subsidy pool.

#### **A flexible rule for long-term price?**

Another possibility suggested is to allow firms not to have to face a pre-set low price, but instead to face “a formula based on actual costs, or some hybrid approach.”<sup>381</sup> But this also generates a range of problems. There is less incentive to lower product prices, and it is less clear how competition would work to lower long-term prices (the firm owns the IP). It also creates problems with the funding once the subsidy pool has gone. Does the US Treasury top the fund up via an extension to the Kerry-Lugar Bill? Does the US Senate agree to this in advance? It also risks using up all subsidy funds, not tying developers in to supply at long-term low prices beyond the time the subsidy pool has gone, having no alternative locked in place, still leaving a problem with long-term funding, and undermining R&D incentives into the bargain.

If the choice on how to set up this “formula” or “hybrid approach” is left open, it becomes yet another strategic variable to rent-seek, with the usual asymmetric impact on different players. But if it is fixed in advance it will need a great deal of information and become inefficient. If it really is “difficult to predict which technologies will succeed and hence hard to anticipate costs of production,”<sup>382</sup> how could such rules ever be set up in

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<sup>379</sup> Or they did not sink the required investment so as to try to force more funding out of funders – in which case, early products are extremely expensive to manufacture (no scale economies) and greater delay has entered the system.

<sup>380</sup> The original \$3bn minus the supposed \$200m to cover manufacturing costs of the ‘winner’.

<sup>381</sup> Barder et al. 2005, *ibid.* p5.

<sup>382</sup> CGD, Feb 2005, p57 (comment removed from final report).

advance? And if prices are not set in advance, it ceases to be an APC subsidy scheme, somewhat defeating the whole point of the exercise.

Yet another suggestion is to link long-term price to ‘cost-effectiveness’ and ‘affordability’ of a vaccine<sup>383</sup> – a polite way of saying that inefficiency and high prices, will be tolerated so long as a vaccine is ‘valuable’ (though try pricing computers, phone services or bottles of water by this methodology).

Why all these gyrations? Why can’t price competition be treated as just as important in the case of vaccines as it is in any other market? There is never any story in this literature as to who pays any higher prices, and why this market should be allowed to become so inefficient compared to just about any other market.

This extra cost ought to show up as an extra cost of any finance mechanism based upon it, making the APC approach less cost-effective than other approaches that do not rely on this inherent inefficiency. But this is not done in the APC ‘cost-effectiveness’ literature. For any given budget this means less vaccines and treatments and lower ‘quality’ than would otherwise have been the case.

### **A dilemma**

We face a dilemma. We wish to give incentives for firms to cut costs – so, we face firms with legally binding 20-30 year contracts to supply long-term at low cost – but we want the flexibility to pay more if costs cannot be cut. The problem is that the incentive to cut costs embodied in the binding commitment may not work, and even backfire, while the ability to raise costs anyway undermines incentives to cut costs.

No really satisfactory story has come out of the APC literature as to how to tackle this dilemma, how incentives to cut costs and supply at long-term prices would be created, nor why sole supplier scenarios do not aggravate this. The most we get is Tremonti’s claim that “an alternative option could be to design a formula for the long-term price of the vaccine which guarantees the cost of production while creating an incentive to keep it as low as possible”.<sup>384</sup> But this is limp to say the least. There is no explanation as to how the incentive to keep costs low is created. Indeed, it seems to be clear that activities and incentive mechanisms at the R&D stage may aggravate activities and incentives at the manufacturing stage, and that (expected) activities and incentive mechanisms at the manufacturing stage would feed back to aggravate activities and incentives at the R&D stage, but it is not clear yet exactly how.

Kremer even argues that APCs “could move us beyond this counterproductive debate over access versus incentives,”<sup>385</sup> conveniently skirting around a huge range of practical issues. The above section suggests a range of extremely tough issues that still need to be thought through.

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<sup>383</sup> IAVI has made this suggestion.

<sup>384</sup> Tremonti, G. Background Papers, 2005, *ibid.* p18.

<sup>385</sup> Kremer, M., 19 November 2005, *ibid.*

Investors are hardly likely to be confident of the competences of those pushing policy when they see the misused notion of a \$1 manufacturing price for a malaria vaccine and all the gyrations needed to explain long-term supply. Instead of playing around with legal threats and trying to work out long-term pricing ‘rules’ from 20 plus years out, it might be better to encourage more competition? To this we now turn.

### **5.9. The need for more production capacity and competition**

Once, seven or eight leading industrial country manufacturers worked on five to six vaccine-related R&D projects each. Since 1988 the share of the four major developers has risen from 50% to about 80%.<sup>386</sup> Meanwhile, “R&D budgets have shrunk, and competition for capacity has become fierce”.<sup>387</sup> One corollary is a dramatically reduced number of vaccine R&D projects, especially for developing country markets: “*While new players are emerging to fill these voids, they have not replaced the multinational manufacturers, in some cases contributing to vaccine shortages.*”<sup>388</sup> In addition: “Smaller and emerging market manufacturers are less likely – *and financially less able* – to take on the risks of product development”<sup>389</sup> (emphasis added). Risks of bioterrorism and a range of other demands, such as bird flu, are also increasing pressure on systems capacity and political capital, and intensifying competition for funding.<sup>390</sup>

Would having more, and different, vaccine players be more valuable than having the same players – maybe even, it increasingly looks, just one big player – being enticed with ever-bigger payments (and having to compete against the increasing vaccine demands of bioterrorism, SARS, bird flu, etc.)?

How will capacity be created? The possibilities would seem to be:

- 1) Increased use of facilities by one or more of the four majors;
- 2) Partnerships between regional and major manufacturers;
- 3) Growth of biotechnology companies into major vaccine manufacturers;
- 4) Growth of regional small manufacturers in countries such as Brazil, Cuba, India, Korea, and Japan;
- 5) Development of new institutions to make vaccines;
- 6) ‘Global Vaccine Enterprises’ to include production facilities for trial vaccines;

For vaccines such as malaria, HIV, and TB, the order of impact of funding schemes that save all R&D payment to the end is approximately as listed above, mainly because of the bias of APC schemes towards those with access to long-term equity finance. Is this the

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<sup>386</sup> Aventis, GSK, Wyeth, and Merck, with the rest made up of Chiron (7%) Serum Institute (about 1%), Bio Farma (<0.5%) and the remaining 10% made up of all the rest. Based on 2000 market data. This might under-exaggerate the impact of domestic production in China, Brazil and India on account of government suppression of prices.

<sup>387</sup> Glass, S.N., Batson, A, and Levine, R., “Issues Paper: Accelerating new Vaccines.” Global Alliance for Vaccines and Immunization: Financing Task Force, 2001, p10.

<sup>388</sup> Glass et al. 2001, *ibid.* p5.

<sup>389</sup> Glass et al. 2001, *ibid.* p9.

<sup>390</sup> VMSR p6.

most appropriate response to expanding capacity for complicated vaccines? As purchase commitments become more late-stage, and other instruments are used to support research, the order of impact on manufacturing capacity is increasingly reversed. Current purchases bolster emerging manufacturers; a side-benefit of expanding current vaccines programs.

In the past, competition and the ability of emerging firms to take part in the manufacturing part of the process (for example because of improvements in regulation, etc.) has proved important in driving costs lower. Hepatitis B is a useful case study.

### **5.10. Hepatitis B: A case study**

In practical cases, Hepatitis B for example (see Farlow 2005, Section 3, and Mahoney, Lee and Yun 2005<sup>391</sup>), the real life-saving breakthroughs enabling access to vaccines for the poor came through lowering production costs. A range of measures were important for this, including:

- 1) Competition between firms at the manufacturing stage, strengthened production systems in emerging economies, and plenty of pressure to lower production costs;
- 2) Technological ‘shifts’ dependent on access to technology, IP, know-how, especially at manufacture and distribution stages;
- 3) Volume of production based on large procurement funds, and early and accurate demand forecasts, enabled scale economies;
- 4) Major improvements in regulatory systems in emerging economies;
- 5) Genuine price signals (compared to the lack of price signals of ex post subsidy schemes along the lines of preset APCs).

The original Hepatitis B vaccine developers were not the ones who developed and maintained the lower price market. In the successful delivery of long-term sustainable low prices and supply of Hepatitis B, there was much more emphasis on competition and genuine market forces, compared to the lack of such devices at a similar stage in the product life cycle in some of the current malaria vaccine APC proposals. Work on some recent ‘pull’ mechanisms (for pneumococcal and rotavirus) is all about getting the costs of an expensive product lower, and show just how challenging and problematic this can be. The case of Hepatitis B appeared in draft versions of the recent CGD report right till the very end, but was dropped from inclusion in the final report. Certainly, it would have reflected poorly on the report’s underlying hypotheses for malaria, HIV, and TB.<sup>392</sup>

This might dictate more emerging market incentives, more information and know-how dissemination, less reliance on precommitted APC subsidy schemes, and the avoidance of measures that lead to too few firms at the later stages of the production process. But this might require costs reimbursed at the end to be more related to production and less to

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<sup>391</sup> Mahoney, R., Lee, K. and Yun, M., “Intellectual Property, Drug Regulation, and Building Product Innovation Capability in Biotechnology: The Case of Hepatitis B Vaccine in Korea.” *Innovation Strategy Today*, 2005, Vol. 1, No. 2.

<sup>392</sup> At the time, several of the Farlow et al. group pointed out to CGD the contradictions in the Hepatitis B case when using it to support APCs.

R&D (the implication for IP is that less would be held in a set of ‘sole’ supplier hands),<sup>393</sup> and no need to fix prices 20 or more years out. Similarly, it is important to enhance scientific capacity within countries with clinical trial capacity. Since many of the very poorest countries that would be targets for building and sustaining clinical trial capacity are not in what might be called the Innovative Developing Country (IDC) group (Brazil, China, India, South Africa, and maybe South Korea for vaccines, etc.), one practical act would be to explore technology transfer and the distribution of regulatory capacity, and similar linkages, between IDCs, and clinical trials sites. Observe how potentially damaging to this are the current Kerry-Lugar proposals, as discussed in Chapter 10 below, because of the way these proposals bias incentives away from these sorts of developers.

### **5.11. Is it better to go with the ultimate ‘best’ malaria vaccine(s)?**

To avoid the above gyrations and the use of non-credible threats, it may be altogether easier to operate with what are believed to be ultimate ‘best vaccine(s)’ than with what might be believed to be highly intermediate short-lived vaccines. Given that it might not be optimal to roll out early low-efficacy vaccines en masse it might not be optimal to tie firms in to high capacity to keep supplying ‘the market’ with these vaccines.

But this all suggests a much more open democratic mechanism to judge what are ‘good vaccines’ en route, and not to leave this ‘decision’ to a ‘winning’ firm reacting to an imperfect scheme, and a committee running things ex post, after the huge build up of private sunk costs, through subsidy payments at the end, via countries that do not face a proper price signal anyway.

### **5.12. ‘Manufacturability’ is hard to judge**

Depending on technology “products [are] more or less manufacturable”<sup>394</sup> and there is some sense in avoiding testing vaccines that may never be made commercially. The Roadmap suggests that “manufacturability” should be weighted in decisions as to which vaccine candidates should be followed through.<sup>395</sup>

On the one hand it must be possible to spot inherently non-manufacturable features, but in other ways it is notoriously difficult to predict the development of future technology that might make something previously non-manufacturable into something manufacturable. Any mechanism that ranks “manufacturability” as a variable has to make some assumptions about future technological advances (10-20 years hence).

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<sup>393</sup> If, in spite of the logic in this report, an APC is nevertheless pushed through for malaria, this suggests that the terms of the APC might need to incorporate ways to ‘share’ technology to spread the burden of having to supply large capacity; would this be easier if the vaccine is less likely to be in need of follow-on (lower risk of obsolete capacity, and less risk that sharing valuable information might undermine the original vaccine, etc.)?

<sup>394</sup> RMSR p6.

<sup>395</sup> MVTR p20.

If an ultimately good but expensive-to-produce vaccine turns out best for protection (say, as part of a composite vaccine), but is deprioritized, what are the economic costs if the alternatives take much longer and are slower to develop? How much weight is taken off ‘protection’ to make a vaccine ‘manufacturable’? What are the ethical issues? Does it depend on treatment program issues too? What are the potentially perverse incentives created when the higher costs of manufacturability that might increase the efficacy of a vaccine, simply eat in to any ex post subsidy going to firms who could have made more money with the lower efficacy but more ‘manufacturable’ vaccine? If the firm was going to get, say, \$3bn anyway with the lower efficacy product, and purchasers pay only \$200m, why, in effect, spend the firm’s own resources to increase efficacy?<sup>396</sup> Again, this arises because there is no price signal and there is a fixed time-limited subsidy pool.

We need some better metrics to work out the value of deprioritizing research, even as we recognize the extreme difficulty of working out the counterfactual. And we need to be mindful of these perverse incentives and ethical issues.

### **5.13. The need for innovative vaccine delivery mechanisms**

The Malaria Vaccine Technology Roadmap urges “Early attention to downstream production, delivery, regulatory, and financing issues” to avoid delays in access.<sup>397</sup> One of the greatest concerns amongst many working on neglected disease is that countries simply do not use products when they are available and indeed are very cheap. Only half the children in sub-Saharan Africa get basic vaccination for diphtheria, tetanus, pertussis, and measles; indeed, rates in some countries have dropped below 25 percent:

*“A large proportion of the disease burden in such countries is unnecessary, since it could be reduced by the effective distribution of medicines that are currently available and inexpensive.”*<sup>398</sup>

Against this background, it is not really clear why one would not want to emphasize much more strongly ‘delivery’ and health-infrastructure issues. The argument seems to be that delivery and ‘R&D’ can be separated. For example, much of the APC literature has emphasized a malaria vaccine as replacing treatment/prevention, and claimed that one of the values of such a financing scheme is the ability to temporally separate flows of resources to pay for R&D from flows to pay for treatment.<sup>399</sup> But, because an imperfect vaccine has to be coordinated with treatment/prevention as part of a package, the value of the package is harmed if delivery fails. R&D and production costs simply cannot be treated independent of delivery issues, as CGD presupposes.

The Roadmap literature discusses the many practical implications of this:

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<sup>396</sup> It is naïve to presume that the solution of greater competition will hold.

<sup>397</sup> MVTR p7.

<sup>398</sup> International Policy Network, 2005, *ibid.* p17.

<sup>399</sup> Though the Tremonti Report, as we will see below, seems to indicate less confidence in this with its recent suggestion of alternative finance proposals, most of which accept that finance may have to be paid in advance.

- 1) How do we “create vaccine delivery systems that induce optimal immunity to multiple targets”?<sup>400</sup> This implies the delivery system is part of the optimal immunity calculation. But this feeds into the equation for working out the goals and production costs;
- 2) “How do we develop vaccine systems for multi-component malaria vaccines?”<sup>401</sup> Can we combine different stage vaccines with limited efficacy to get higher overall protection (i.e. are their synergies)? This depends on delivery issues.
- 3) “The need for periodic boosting requires strong health systems in malaria-endemic countries”<sup>402</sup> Another delivery issue;
- 4) And it is not just vaccines. Mention is made of “insecticide-treated bed nets, which continue to be underutilized despite their effectiveness, due in part to lack of planning for delivery.” Yes, another delivery issue.

Stakeholder responses to the Malaria Vaccine Roadmap also argued that delivery issues needed to be considered far more. Feedback from the Durban stakeholder meeting argued in favor of a “health systems roadmap to parallel the malaria vaccine roadmap”. Farlow (2005) argues the need for “vaccine/health infrastructure commitments”, “distribution commitments” and commitments to tackle market risk at many levels. Roadmap participants also argued that the role of industry in long-term supply was being treated in an unrealistic fashion. The findings of this report back this up, and blame it largely on the current obsession with APCs. The solution in the APC literature is to legalistically tie industry in even before performing R&D. We saw that this is problematic, and the only real result is a false sense of security, and the overlooking of financing for longer-term delivery.

We should not be surprised at the removal of long-term supply and delivery problems from debate. Large pre-set industrial subsidies invariably take attention away from efficiency issues. Too much attention to delivery issues would have taken luster off the APC subsidy schemes given that such schemes rely for their efficiency on there being no delivery issues, and it no doubt seemed better to ignore the problem by separating the delivery issues from the subsidy scheme.

#### **5.14. Capacity: Firms are willing if the terms are right, but what are the right terms?**

One of the underlying tones of the recent APC subsidy literature is that firms have to face ex post restrictions and ‘market’ risk to drive ‘quality’ even if this means that their products do not get mass use. Yet we also hear that “industrial capacities can be increasingly engaged under the right circumstances.”<sup>403</sup> One of the revelations that comes out of Moran et al.<sup>404</sup> is that firms are far more interested, perhaps for reputational value

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<sup>400</sup> MVTR p22.

<sup>401</sup> VMSR p23.

<sup>402</sup> MVTR p35.

<sup>403</sup> VMSR p4.

<sup>404</sup> Moran, M., Ropars, A-L., Guzman, J., Diaz, J., and Garrison, C., “The New landscape of Neglected Disease Drug Development.” London School of Economics, September 2005,

and to justify their involvement in neglected disease work, in seeing their neglected disease products (that are *never* going to be hugely profitable anyway) actually getting used than they are in facing mechanisms that deliberately restrict their use. Moran et al. comments that if companies are seeking APCs as insurance that their products will be used in developing countries, then a simple purchase fund will more likely deliver this goal on a sustainable level. Are these ‘right terms’ better created through these APC subsidy schemes and their rules and pre-set prices, associated institutions, and commensurate restricted up-front funding, or better created through PPPs, more up-front funding, and decent-sized procurement funds with more competition in the end market?

There is almost a “dammed if you do, dammed if you don’t” attitude in the APC proposals being put to ‘big pharma’ at the moment. If they do not react they look bad; if they do react they still look bad, both in the short-term and in the long-term. In the short-term it looks as if they will not do anything for malaria unless there is a multi-billion pile of cash (that in most cases they will not get, but the public do not tend to see this). In the long-term, they know they might have to push for the cash pile to be bigger and still have to publicly haggle over it or engage in damaging rent-seeking to get a fair deal when they find themselves as last firm in the chain. Making the cash pile bigger from the start to try to overcome these reputational risks is not the obvious way to make lots of firms want to go near the problem. If ‘right partnership arrangements’ are the way to get lots of firms involved, the APC and similar initiatives are barking up completely the wrong tree.

### **5.15. More competition to avoid R&D failure: The value – as well as the problems – of procurement**

Observe how a competitive procurement system allows firms to extract payments that are more commensurate with their production costs whilst also giving more incentive/ability to lower those costs and develop newer technology, and is thereby likely to avoid some of the backwards induction failures discussed above from the manufacturing end of the process back onto the R&D part of the process. Also, the cheaper (and more efficacious) a product is, the greater the cost savings on other parts of the package of measures too. In the case of the Hepatitis B vaccine the presence of this sort of competition has encouraged three generations of products, from the first high-cost plasma design to a recombinant design to better and cheaper ways of producing a recombinant vaccine. We also find, later, that procurement helps handle R&D ‘crowding out’ problems; there is less need for elaborate monitoring and mechanisms for separating payment from those who do not need it (who otherwise would harm those who do ‘need it’).

However, procurement may fly in the face of the need to repay sunk R&D costs (including finance costs), with this harming R&D incentives from that direction. This latter problem underlies the push for commitment devices such as APCs.

There is an unavoidable dilemma and a tradeoff.

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[www.lse.ac.uk/collections/LSEHealthAndSocialCare/documents/PRPP/TheNewLandscapeOfNeglectedDiseaseDrugDevelopment.pdf](http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/documents/PRPP/TheNewLandscapeOfNeglectedDiseaseDrugDevelopment.pdf)

One solution might be:

- 1) To have less of the sunk R&D costs to be repaid at the end by purchasers through subsidies – quite the opposite of current proposals;
- 2) For what R&D costs are left (and some *should* be left as we will see below when we discuss financial risk and the importance of incentivizing firms) to enter procurement style mechanisms with the use of financial instruments to insure companies against those risks that are not under their control, in exchange for which they are prepared to take less payment in the end market. In exchange, IP is more widely owned, via PPPs, to help remove the sole (or too few) supplier problem at the last stage;
- 3) Wider finance in place for a wider set of players, and not just those able to draw off ‘deep pocket’ equity-based finance for longer periods, under CGD-style APCs.

It is not obvious that the answer to the above manufacturing problem is an ever-bigger end subsidy, less end-market competition, and no ‘insurance’ of firms. This also suggests separating the R&D part of the problem more from purchases, and not using purchases to drive ‘quality’ decisions, given all the inefficient consequences. Instead purchases would principally be set the role of driving manufacturing costs.

Instead of more of the same, but bigger, there is need for what the Roadmap calls “a paradigm shift.” Indeed, if Moran et al. find that firms working on neglected products want to see their products being used, what better way to encourage firms that this will be so, if they know competition will drive prices down to enable them to be used in poor markets?

### ***5.16. Some conclusions and a summary on production costs and supply issues***

The most distinguishing features of past successful vaccines have been that they have been highly effective and affordable. Given that lowering costs was absolutely essential to success, it is puzzling why, for very much more complicated vaccines such as those for malaria, HIV, and TB, there is not a great deal more concern to create incentives to achieve affordable manufacturing prices and access at affordable prices during *and after* the subsidy allocation has gone, to both countries inside and *outside* of the APC scheme, instead of the easy acceptance of silly contract terms and verbal gyrations to wriggle out of every new logical and practical flaw in the APC proposal for these vaccines.

The Roadmap recognizes the need for strong pressures to create cheaper end products. However, it is less clear-cut about the inherent conflict between the need to create greater competition to drive cheaper end products, and the need for incentives to invest in R&D in the first place but which may create ‘sole’ (or too few) suppliers. This is reflected too in the conflict between the value of competitive ex post procurement mechanisms – that allow firms to fairly extract the costs of production, whilst competing to drive production

costs lower – and the problems of doing such procurement once firms have already sunk R&D costs.

### **A conundrum**

There is a further conundrum here. If price is set in advance (and hence a fixed size commitment) and firms do not believe that they can cover costs enough to make the overall investment profitable, they may be disincentivized from investing in the first place. But, to allow the price to be variable would mean that the overall commitment would become non-fixed.<sup>405</sup> Either firms face the risk of time-inconsistency from sponsors who are unprepared – after production costs have emerged and after firms have invested – to let prices rise higher to cover *all* R&D (one only needs to remember the AIDS drug debacles of the past to realize that a sponsor may find it politically difficult to raise prices later, and to wonder if the World Bank, the Gates Foundation, the British Government and other sponsors would want to be similarly tarnished). Or the sponsors have to agree to set the price and size later, and face budgetary uncertainty and an open-ended financial commitment, that may fail at the first political hurdle and will not be credible anyway and thus not encourage investors to invest in malaria vaccine R&D. There does not seem to be an easy way out of this open-ended risk to sponsors. And, as always, either risk feeds back to harm R&D incentives.

### **Long-term access and prices are a mess in the APC literature**

Thinking about long-term malaria vaccine supply and price issues is a complete mess in the APC literature at the moment – made worse by worries that the goal-2 vaccine has no long-term commitment. If nothing, this starts to indicate that the Malaria Vaccine Technology Roadmap also needs to spell out much more clearly what *it* means by “advance commitments to purchase”. Is it referring to large procurement funds, access to technology and know-how, competition at the manufacturing stage and maybe novel financial instruments? Or is it referring to large subsidies set in advance to be paid on the tranche of early vaccines and, perhaps, even a sole supplier, and legal contracts tying firms in – especially to long-term low prices – and all the new institutions and committees needed to achieve this?

More thought is needed regarding new financial instruments and production competition, and less thought to ‘price’/subsidy schemes on early purchased products. Price is best left till much later when it can be *one of the instruments* used, via competition, to help make sure that products are ‘manufacturable’ and affordable. Killing the role of prices turns out not good for either the long-term or the short-term goals. Replacing the role of price with non-credible contractual threats is, unfortunately, not going to overcome this fault.

The literature of Kremer, CGD, Tremonti, etc. does not even look into manufacturing cost and product price problems, and in the next chapter we will see how the cost-effectiveness evidence used to favor APCs similarly ignores all these problems too. The reason is relatively straightforward. To have explored cost and price issues would have

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<sup>405</sup> Even this is presuming that the subsidy pool is growing at the rate of discount required by pharmaceutical players, something that we really should not take for granted. More on this below.

raised the centrality of them as practical challenges in determining the overall solution to the malaria vaccine problem, and particularly for those solutions which are all-or-nothing blue-sky revenue-only mechanisms. Cost issues have to be overlooked in order to get simple solutions to present to politicians, and to avoid drawing attention to alternative solutions that might handle the problems better, but that might take away the simplistic attractiveness of the solution being offered.

## 6. Recent Malaria APC Cost-Effectiveness Evidence

This section covers, in particular, the malaria vaccine APC cost-effectiveness work of Kremer,<sup>406</sup> Kremer and Glennerster,<sup>407</sup> Berndt et al.,<sup>408</sup> Levine et al.<sup>409</sup> that has then been fed through the CGD, Tremonti, and G8 thinking. It is worth bearing in mind that the same small group have been recycling the same material based on the same methodology through all recent policy proposals. This chapter will especially concentrate on the analysis of Berndt et al. – the source, for example, of Tremonti’s claim that a malaria vaccine APC would cost \$15 per DALY (Disability Adjusted Life Year) saved – since Berndt et al. encapsulates many of the chief weaknesses of the methodology.

This chapter finds that the methodology is set up from the start to put higher weight on lower vaccine efficacy than a more complete cost-effectiveness analysis would conclude was optimal, and that this will distort goal-setting under any budget constraint. Furthermore, it concludes that the evidence is used to greatly exaggerate the case for APC schemes. This has not been a comfortable chapter to write and the author rather hoped he would not have to write it. Hopefully it is explained carefully enough and checked enough that the reader does not have to just take the author’s word for it (the papers and underlying methodology that are reviewed here are freely available on the web). A careful reading of the methodology shows what is going on. The author will happily amend it if he has misunderstood something.

### **The high cost impact of malaria**

Before looking at the Berndt et al. methodology, let us first recognize that, even if we desensitize ourselves from the human suffering of malaria for a moment, the deleterious economic consequences of malaria are very high, and that tackling malaria should be a very high priority.

It has been calculated that the annual drain on the economies of Africa alone from malaria is in the region of \$12bn.<sup>410</sup> Adding South East Asia and Latin America would raise this even further. This is an extremely difficult figure to calculate because of the challenge of working out chains of causation, especially at the macroeconomic level, and because of data limitations. It should, therefore, be taken as a useful ball park figure with suitable margins of error.

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<sup>406</sup> For example: [www.pm.gov.uk/files/pdf/Appendix%203.pdf](http://www.pm.gov.uk/files/pdf/Appendix%203.pdf), and <http://post.economics.harvard.edu/faculty/kremer/vaccine.html>.

<sup>407</sup> Kremer, M., and Glennerster, R., “Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases.” 2004, Princeton University Press.

<sup>408</sup> Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., Williams, H., “Advanced Purchase Commitments for a Malaria Vaccine: Estimating Costs and Effectiveness.” *NBER Working Paper Series*, April 2005, Paper 11288, [www.nber.org/papers/w11288](http://www.nber.org/papers/w11288).

<sup>409</sup> CGD, 2005, *ibid.* which draws on the work of the others.

<sup>410</sup> MVTR piii, perhaps drawing from Breman, J.G., Alilio, M.S., Mills, A., “Conquering the intolerable burden of malaria: what’s new, what’s needed: a summary.” *Am J Trop Med Hyg*, 2004, Vol. 71 (2 suppl.), pp. 1-15.

The macroeconomic impact of malaria is especially illusive but very high – including economic losses due to lack of foreign investment into malaria endemic countries, impact on trade, the drain on human capital and demographic effects including the reduced opportunities for specialization both within the household and for the economy as a whole, the discouragement of tourism, and slowed overall economic development. Indeed there is a vicious cycle of high disease prevalence and low economic growth, with slow economic growth in turn preventing improvements in living standards and creating serious constraints on countries' abilities to maintain malaria-control efforts. It is recognized that this impact is greater than the currently measured aggregate of microeconomic effects that include the direct expense of preventing and treating the disease incurred by both government and individuals, and the indirect costs of being sick with malaria.

Sachs and Malaney<sup>411</sup> calculate (after controlling for the other standard growth determinants) that annual economic growth in malaria endemic countries between 1965 and 1990 averaged 0.4% of per-capita GDP, as against 2.3% for the rest of the world, suggesting that over the long-run, malaria could reduce GDP by nearly one-half in highly endemic countries: "These analyses do not constitute proof that malaria is a cause of low incomes and poor economic growth, but that the disease must be considered at least a legitimate contributor, and possibly the major contributor."<sup>412</sup> See Arrow et al. Chapter 7 for analysis of the human and economic burden of malaria, and also Chima et al.<sup>413</sup>

*"The 'true' economic costs of malaria are undeniably large, but just how large is not known. Admittedly, the information base is small, which accounts for part of the problem, but the methods themselves are not as well developed as needed. Adding up all of the effects from the best microeconomic studies using the human capital method, the totals do not begin to approach the magnitude of effect seen with top-down macroeconomic approaches... Understanding both the magnitude of malaria's economic effects as well as its operative pathways will accomplish two goals. It will better place malaria in its appropriate economic context and it will improve strategies by which to combat it."*<sup>414</sup>

### **Tiny levels of funding on malaria vaccines**

It is clear from all the evidence that there is great economic, social, and humanitarian value in spending more on alleviating the deleterious impacts of malaria, and indeed of the value of vaccines in general.<sup>415 416</sup> However, the global community spends only about

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<sup>411</sup> Sachs, J., and Malaney, P., "The economic and social burden of malaria." *Nature*, 2002, Vol. 415, pp. 680-685.

<sup>412</sup> Arrow et al. 2004, *ibid.* p180.

<sup>413</sup> Chima, R.I., Goodman, C.A., Mills, A., "The economic impact of malaria in Africa: A critical review of the evidence." *Health Policy*, 2003, Vol. 63, No. 1, pp. 17-36.

<sup>414</sup> Arrow et al. 2004, *ibid.* p194.

<sup>415</sup> Bloom, D.E., Canning, D., Weston, M., "The Value of Vaccination." *World Economics*, July-September 2005, Vol. 6, No. 3. Also see: "Vaccines are cost-effective: a summary of recent research." *GAVI Research Briefing*,

[www.vaccinealliance.org/General\\_Information/Immunization\\_informa/Economic\\_Impact/vacc\\_cost.php](http://www.vaccinealliance.org/General_Information/Immunization_informa/Economic_Impact/vacc_cost.php).

\$65m annually on malaria vaccine R&D – and this is after a recent build-up to this level – and way too little on malaria control (including R&D to improve control), though big strides are being made just recently on treatment and prevention.<sup>417</sup> However, using the fact of high impact of malaria alone to back up one particular R&D funding scheme over any and all other approaches, or one particular efficacy vaccine over another efficacy vaccine is erroneous, even if it is a good advocacy tool.

Cost-effectiveness has to be determined at many levels. There is the choice between the various malaria options (including over ‘quality’ of product, quality over time, speed of product development), and the choice between malaria and other health options, and the choice between health options and all other options (education, housing, infrastructure, clean water, etc.<sup>418</sup>). The issue is the efficient use of resources in response to the – always binding – budget constraint (and the issue of shifting the budget constraint if at all possible). The opportunity cost of resources devoted to R&D for a malaria vaccine of a particular efficacy is always the alternatives foregone – including higher efficacy vaccines – and the marginal return on some of these alternatives is high.

Now, let us look into the specifics of the Berndt et al. methodology.

### **6.1. Ignoring technological complexity and true underlying development costs**

In working out how much total R&D subsidy to pay at the end for ‘a’ malaria vaccine (follow-on vaccines are seemingly not handled in Berndt et al), via an APC, Berndt et al. state: “We did not use those cost of development estimates nor any other cost of development estimates in our analysis.” CGD, similarly, highlights at the start of a chapter titled “\$3bn per disease”, as a key selling point, that: “Our recommendation [of \$3bn per disease for HIV, malaria, and TB vaccines] is not based on any estimated cost of vaccine R&D.” It is claimed that by basing the size of the total available R&D subsidy pool on what would be needed to “make the *revenues* from R&D investments on a malaria vaccine similar to *revenues* realized from investments in typical existing commercial pharmaceutical products,”<sup>419</sup> this avoids having to consider the *costs* of developing such complicated vaccines, including all needed generations of vaccines.

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<sup>416</sup> For reasons why *P. falciparum* has attracted particular attention, given its especially deleterious consequences, see Miller, L.H., Baruch, D.I., Marsh, K., Doumbo, O. K., “The pathogenic basis of Malaria.” *Nature* 2002, Vol. 415, pp. 673-9.

<sup>417</sup> [www.reliefweb.int/rw/RWB.NSF/db900SID/HMYT-6G2JQ4](http://www.reliefweb.int/rw/RWB.NSF/db900SID/HMYT-6G2JQ4).

<sup>418</sup> According to the World Bank’s annual publication, “Environment Matters,” October 2005, close to one-fifth of the burden of disease in developing countries can be attributed to environmental risks – with unsafe water, poor sanitation, and poor hygiene as leading risk factors, causing 1.7 million premature deaths per year; and urban air pollution estimated to cause about 800,000 premature deaths annually: <http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/ENVIRONMENT/0,contentMDK:20671693~pagePK:148956~piPK:216618~theSitePK:244381,00.html>. DFID points out that half the annual deaths from communicable diseases in developing countries “are associated with malnutrition. Vaccines do not provide the total answer.” DFID, June 2005, *ibid*.

<sup>419</sup> Berndt et al. 2005, *ibid*. p1.

**Everything based on realized revenues only, of the wrong sort of products**

Barder et al. also claim, as part of “plenty of evidence” of the power of their APC subsidy scheme proposal, that the size of the total available subsidy is “based on realized revenues which have in practice spurred innovation by the pharmaceutical industry.”<sup>420</sup> Kremer et al. even argue that “Perhaps the most attractive approach is to look at concrete evidence on the revenue needed to induce research on pharmaceuticals in high-income countries.”<sup>421</sup> The word revenue(s) has been picked out and highlighted in each case.

As IAVI puts it, based, as IAVI explains, on CGD calculations and methodology: “One of the *toughest challenges* in developing an AMC is determining the market size needed to stimulate vaccine R&D. Rather than use estimates of actual R&D costs, *which could be far off the mark* [emphasis added, on words written in all seriousness it would seem], economists<sup>422</sup> calculate the market size based on sales revenues of existing commercial products, reasoning that *comparable revenue levels* will be attractive enough markets for [HIV] vaccines.”<sup>423</sup> The next line of the quote is: “IAVI, working with a model developed by the Center for Global Development, estimates that *an AIDS vaccine AMC would require total lifetime sales revenues of about \$4 billion*” (again, the emphasized words would seem to have been written in all seriousness). This is not just the wrong way to do things; it is dangerous.

**Implicit presumption about costs**

IAVI explains that the idea is to create for firms “*financial returns* comparable to those they could expect from spending their resources developing a successful *drug* for the Western market,”<sup>424</sup> but then completely misses the fundamental financial principle that *financial returns* to any investment are based on both the *revenues* generated and the *costs* needed to generate those revenues. This is such a simple and basic principle of financial economics that one wonders how anyone could ever be taken seriously suggesting otherwise, and how such an erroneous notion could persist in a correctly-functioning consultation process. Since when has the structure of costs of development of HIV vaccines been the same as that of drugs for a Western market, such that those designing an APC for a HIV vaccine only need look at *revenue* flows for such drugs?

Basing the size of the total subsidy pool fixed at the start – to be repaid across *all* malaria<sup>425</sup> vaccine developers after the development of initial and follow-on vaccines – on (a measure of) the typical *revenue* deemed necessary to stimulate the discovery of a developed-economy drug, *implicitly* means that the size of the total subsidy for the malaria vaccine(s) is based on the typical *costs* of developing such a drug. In equilibrium, investment in drug development should be driven to the point where this is so. It is

<sup>420</sup> Barder et al. 2005, *ibid.* p10.

<sup>421</sup> Kremer, M., Glennerster, R., Wezsacker, G., Podolsky, R., Lee, J., “A Technical Guide to using the Malaria Vaccine Spreadsheet.” April 2005, p37, [http://post.economics.harvard.edu/faculty/kremer/webpapers/Vaccine\\_spreadsheet\\_documentation05.pdf](http://post.economics.harvard.edu/faculty/kremer/webpapers/Vaccine_spreadsheet_documentation05.pdf).

<sup>422</sup> Please do not lump *all* economists together.

<sup>423</sup> [www.iavireport.org/Issues/Issue9-3/iavireport\\_aug\\_final.pdf](http://www.iavireport.org/Issues/Issue9-3/iavireport_aug_final.pdf), emphases added.

<sup>424</sup> Zandonella, C., 2005, *ibid.*

<sup>425</sup> Or HIV, or TB, or any other vaccine, since the methodology treats them all as requiring the *same* revenue stream (“\$3bn per disease”); this alone should have given a clue to the vacuity of the methodology.

elementary economics: If the average cost of developing drugs is low, and if investment in drug development is driven to the point where the marginal private cost of generating a new drug is equal to the marginal private benefit of a new drug to its developer, in equilibrium more drugs are developed with each having a smaller market size and smaller required revenue stream. Needed market size is driven by underlying costs of development.<sup>426</sup>

Fixing the size of a malaria subsidy pool, makes a presumption about the expected costs of developing malaria vaccine(s) including all needed follow-on vaccines, and the costs of all the risks (including all those risks that we later discuss that are themselves created by the APC subsidy scheme). In Berndt et al. the presumption is that these R&D costs for malaria (and HIV, and TB and all vaccines) match those of previously developed drugs used in this calculation.

Yet we know that “the parasites that cause malaria are much more complex than the viruses and bacteria that heretofore have been controlled by vaccination,”<sup>427</sup> and that “stage-specific expressions of proteins, the presence of multiple antigenically distinct strains in nature, and within-strain antigenic variation are critical to the parasite’s survival, are unfavorable to the host, and greatly complicate the challenge for vaccine developers,”<sup>428</sup> and hence, one would naturally presume, the costs of coming up with a solution.

#### **Compounded by complexity**

This is all compounded too by the complexity of the human immune response. In the case of HIV “natural immunity does not appear to have a strong impact on the final outcome of HIV infection,”<sup>429</sup> but this is not the case for malaria. The human immune response in the case of malaria is a function of the human host genetics, transmission dynamics of the parasite, and even the age of the host. For example, in areas where transmission is most intense, infants are the most at risk of developing severe and fatal malaria. In areas of less intense transmission, it is older children who are most at risk. Similarly, the age of first exposure to parasites (or a vaccine when available) plays a heavy role in the subsequent immune response. Non-immune adults are more susceptible to developing severe disease after a first infection than non-immune children, yet adults acquire immunity faster than children: “For a vaccine to be optimally effective, it must elicit the appropriate protective responses and sustain those immune responses over time, either due to vaccine administration or due to boosting by exposure to parasite... Much progress has been made, but no vaccine delivery system has been shown to be optimal or adequate.”<sup>430</sup>

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<sup>426</sup> Which might also include marketing and rent-seeking costs.

<sup>427</sup> Hoffman, S.L., and Richie, T.L., *The Vaccine Book*, Academic Press, 2003., Ed. Bloom, B.R., and Lambert, P-H., Chapter 6, “Malaria”, p294.

<sup>428</sup> Hoffman, S.L., and Richie, T.L., 2003, *ibid.* p295.

<sup>429</sup> Lee, T-H., and Novitsky, V., “HIV Vaccines: Design and Development.” In *AIDS in Africa*, 2nd ed. Ed. Essex, M., Mboup S., Kanki P.J., Marlink R.J., and Tlou, S.D., Klumer Academic / Plenum Publishers, New York, 2002, p596.

<sup>430</sup> Hoffman, S.L., and Richie, T.L., *ibid.* p298.

### **Optimal incentives need cost information**

This suggests that the optimal vaccine will vary over time as the rate of transmission changes (e.g. as malaria is eradicated from a given population and the levels of natural immunity vary across the age profile) and that different vaccines will be needed. If incentives are not to be distorted, this will require the complicated disbursement of any available APC funds across vaccines over time, *based also on* expected underlying costs, even as the rules governing this disbursement must be credibly fixed in advance based on knowledge of the future science, vaccine needs, and these costs.

Berndt et al. even recognize this: “The scientific challenges [and hence costs] of developing a malaria [and HIV, and TB] vaccine are formidable.”<sup>431</sup> So why is knowledge of this then thrown out by the same set of authors when setting terms, and why is only revenue considered? As Tremonti explains: “Berndt et al. conclude that the mean market size for new drugs developed during the 1990s was around \$3.1 billion in NPV (US\$, 2004 prices). That analysis shows that, with a donor commitment of \$2.3 billion for a malaria vaccine, enough to provide an overall market size around the average for new medicines, the donor commitment would cost \$15 per life-year saved – a *very cost-effective result* in comparison with other international development interventions” (emphasis added).<sup>432</sup> We will later see how even this \$2.3bn has been formulated by Tremonti on the basis of erroneously discounting the value of the APC at only 6%, and a range of other highly-favorable assumptions.

It says something about the laxity of the current policy-making process, and the resistance of policymakers towards critical analysis, that such despairingly bad reasoning can get fed to G8 finance ministers by a European Minister of Economy and Finance. Incidentally, weeks before Tremonti submitted his report to the G8 ministers, one of the world’s leading industrial economists had warned the UK’s Department for International Development, during its APC consultation meeting, that the data being put together by Tremonti were inappropriate. F.M. Scherer expressed “Concerns that the Grabowski data set which was used was for a different type of product - e.g. small molecules in the 90s, development costs for a single drug - whereas AMC are targeting large molecules (which are more expensive to develop).”<sup>433</sup>

What is the point in basing all proposed figures on inappropriate data, ignoring the need for multiple follow-on products, and trivializing a hugely complex (and costly) scientific problem? Such a fundamental, almost trivial, flaw at the heart of extremely heavily promoted literature is hardly reassuring to industry that policymakers have a clue about what they are doing. CGD titled many of their press releases as “\$3bn per disease” and even had an entire chapter titled with the \$3bn figure. If there is anything more guaranteed to scare firms and professional investors off it is this sort behavior. But let us proceed.

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<sup>431</sup> Berndt et al. 2005, *ibid.* p5.

<sup>432</sup> Tremonti, G., Background Papers p9. Notice how, even if it fails it is still able to be labeled cost-effective.

<sup>433</sup> <http://www.dfid.gov.uk/consultations/amc-consultation-note.pdf>, p3.

**From the top of the ivory tower down<sup>434</sup>**

One of the more surprising aspects of the APC literature is to not base the APC size on a ‘bottom-up’ notion of expected costs of development, based on the complexity of the underlying scientific problem. This requires some notion of expected trial attrition rates, trial sizes, appropriate risk-adjusted rates of return (to also include the risks of the APC subsidy payment scheme itself, which this author finds to be high), and a pile of assumptions about needed follow-on vaccines and the scientific problem. The science for all this is so sparse that the obvious thing to conclude is that it cannot be done and that any methodology that depends on it being done should not be absorbing valuable institutional and political capacity at this stage of the policy process. But advocates of APC schemes, including politicians, seem unable to accept this, given that it would undermine the idea being promoted. So, they embark on an essentially random exercise, calling it ‘top-down’, as if, somehow, that made it more scientific,<sup>435</sup> and suggesting that this still justifies giving the ‘winning’ developer all the IP even if much of the costs are borne elsewhere.

We are even told (as if it meant something about malaria, HIV, or TB) that because of the typically skewed nature of the data, “the sales revenues of the *median* NCE [New Chemical Entity] are insufficient to break even,<sup>436</sup> implying the *mean* sales revenue may provide a more reliable estimate of what level of expected revenues may be effective in spurring industry investment [for malaria, HIV or TB vaccines?]”<sup>437</sup> (emphasis in original). If you are out by a factor of five or ten, or whatever it turns out to be, this is a bit like sitting around on the deck of the Titanic<sup>438</sup> trying to work out the value of slightly thicker steel on the hull.

Remarkably, it has even been argued by IAVI, that this methodology *avoids* having to discuss the ‘contentious’ issue of an appropriate rate of return (as complained about previously by Farlow<sup>439</sup>).<sup>440</sup> Instead of criticizing those who fail to do things properly, not doing things properly is instead extolled as a virtue.<sup>441</sup> Again, we see the lack of financial market thinking behind APC promotional efforts. Advocates seem to believe that

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<sup>434</sup> See Zandonella, C., 2005, *ibid.* p20, who intimated that this is from where the critics pitched their arguments, before going on to describe in detail the way all the figures have been worked out in just such an ‘ivory tower’ fashion.

<sup>435</sup> Remember the perverse incentives of trying to adjust back up later if the subsidy pool is set too low at the start.

<sup>436</sup> Calculating the break even point requires *cost* data!

<sup>437</sup> Berndt et al. 2005, *ibid.* p7.

<sup>438</sup> [http://en.wikipedia.org/wiki/RMS\\_Titanic](http://en.wikipedia.org/wiki/RMS_Titanic). The wikipedia entry is quite instructive about the impact of overconfidence when designing and sailing a new (policy) vessel.

<sup>439</sup> Farlow, A.W.K., “Capital Costs, Cost-Effectiveness of HIV APC, and Speed of Vaccine Development.” Comment to the WHO Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 10 December 2004.

[www.economics.ox.ac.uk/members/andrew.farlow/CIPIH10December2004.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/CIPIH10December2004.pdf)

<sup>440</sup> Though the subsidy pool has to grow at an appropriate rate to maintain equal commercial value between goals over time.

<sup>441</sup> Reading these arguments, one realizes just how little this literature is driven by a desire to get a result that actually works, and how much more it is driven by a desire to get a ‘policy success’, even if the policy does not work.

convincing politicians is all that matters, and that financial markets and investors will not see through what is being promoted.

### **Subsidies based on industry ‘opinion’?**

Berndt et al. even suggest that “An alternative method of estimating the necessary purchase commitment size [for malaria, HIV, and TB vaccines] would be to ask individuals outside of but familiar with the industry their opinion on what level of expected revenues is needed to spur substantial R&D investments [for malaria or HIV or TB vaccines<sup>442</sup>]; these opinions can arguably serve as a rough check on our estimates as derived above.”<sup>443</sup> When those asked for their opinions do not have a clue as to the costs of developing malaria, HIV, or TB vaccines, what articles do they go to to help them think of a number? And why not ask the correct (and therefore tough) question: “their opinion on what level of expected revenues is needed to spur R&D investments to generate a malaria or HIV or TB vaccine and all needed follow-on vaccines”?

### **A problem that has proved intractable**

The problem of knowing how big to set the overall subsidy pool has a long history. Realizing that setting this size could not be done without scientific and R&D information, the original methodology suggested by Kremer<sup>444</sup> was an auction, that would supposedly ‘reveal’ this information. Farlow 2004 section 11 (and elsewhere in that paper) showed that an auction would not work in this case for a host of practical reasons. The auction idea has been abandoned. But something had to be found to replace it. Hence the top-down approach based on revenues based on entirely unrelated R&D projects. Tremonti now argues that the subsidy size can all be adjusted later by some all-seeing, all-wise committee (and in spite of the perverse incentives created by doing so).

### **Huge scientific challenges**

It is dangerous to compare the problems and costs of generating malaria, HIV, TB and other vaccines to those of ‘typical developed economy drugs markets’. The cost structures and challenges of developing malaria, HIV, and TB are totally unlike developed economy drugs and previous vaccines too. These are some of the greatest scientific challenges ever known to mankind. Comparing in this way, will only ever lead to a chasm between the understanding of the scientists of the challenge they face and an extreme overconfidence of politicians in schemes to tackle it, even if such schemes are not based at all on the scientific difficulty and therefore likely to waste a lot of time while they distort and delay more appropriate approaches: “Developing a vaccine against HIV is one of the greatest scientific challenges of all time. The science is really hard. [Yet] Advance market mechanisms provide incentive for the required long-term commitment and significant investment.”<sup>445</sup>

When the original draft CGD report came out, it happily talked about a range of costs for developing a malaria vaccine, repeatedly referring to a \$6.25bn figure. A few months

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<sup>442</sup> Or, at least, one presumes that this questioning would all be with respect to malaria, HIV, and TB vaccines. Unfortunately, it does not sound like that was the intent.

<sup>443</sup> Berndt et al. 2005, *ibid.* p10.

<sup>444</sup> Kremer, M., No 10 Policy Unit Appendix 7.

<sup>445</sup> Kate Taylor, IAVI’s senior director of policy and advocacy, quoted in Zandonella, C., 2005, *ibid.*

later the cost had dropped to \$4bn, and then \$3bn.<sup>446</sup> By the time the report of the Commission for Africa came out in February 2005, the \$3bn figure had taken on an air of authority and accepted wisdom: “Advanced purchasing agreements guarantee the size of the market,<sup>447</sup> providing an incentive to pharmaceutical companies to produce drugs.<sup>448</sup> For Malaria, *the market size needed to deliver the malaria vaccine* [observe the notion of there being ‘the vaccine’, (emphasis added)] is \$3 billion (CGD, 2004).”<sup>449</sup>

What happened to so drastically alter our understanding of the science of malaria vaccines in just three months? Given the dangers of pitching an APC too low – with unnecessarily delayed investment at first, followed by a perverse incentive to delay vaccine R&D *even further* when the APC size has to be raised – this is all rather astonishing. The Commission for Africa can only report what it is told. Such statements ultimately simply reflect the state of lobbying efforts, rather than any rigorous analysis of the R&D issues.

What does all this say about the veracity of the original figures? Of the current figures? Of *any* figures? Are advocates – because they are not concerned to set terms correct, or high enough, at the start, simply happy to see no response at all, or massively delayed response, or very low quality vaccines, or even eventual collapse of the APC? What does this say to investors and developers thinking of investing in ‘better’ vaccines? If those promoting the approach do not trust the approach, why should developers? Or *is* the idea to see all of the subsidy go on one low-value product, that is so heavily subsidized to the purchasers that they will use it anyway, even if it was the least appropriate result *ex ante* and other developers are disincentivized (and even if most pharmaceutical firms balk at the idea)?

### **Looks better the more wrong it is**

In consequence, all CGD cost-effectiveness figures (and those who use their figures and methodology, such as IAVI) are worked out on the basis of an essentially randomly chosen figure. This creates the perverse result that the lower and more ‘wrong’ the figure is, the more cost-effective the proposal becomes. A \$100m APC for malaria might have absolutely no impact, be a complete waste of time and energy and a huge distraction to policy makers, and a drain on the systems capacity of malaria PPPs and political capital, but it would still be astronomic “value for money” according to this methodology.

This is nicely illustrated by a small comment made by Berndt et al. at the start of their paper. They suggest that “the promising results of the recent GSK trials suggest that developing a malaria vaccine may not be as technically difficult [and hence as costly] as many had previously thought.”<sup>450</sup> This is a surreal assertion in a paper where *any*

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<sup>446</sup> In the space of the same meeting according to one of those present at the time.

<sup>447</sup> As we have shown, this is not the case and drastically simplifies a highly difficult set of issues. Such agreements supposedly guarantee *additional* market – the whole point of such instruments. The commission statement is therefore another hypothesis, and *not* a fact.

<sup>448</sup> Of course they produce *some* effect. That they provide the required incentive to get early-stage vaccines developed is another issue altogether. Yet another hypothesis, and, again, not a fact.

<sup>449</sup> [www.commissionforafrica.org/english/report/introduction.html](http://www.commissionforafrica.org/english/report/introduction.html), Chapter 6, Footnote 92, p409.

<sup>450</sup> Berndt et al. 2005, *ibid.* p9. A few pages later there is another surreal assertion. Berndt et al. suggest that a pessimistic interpretation of recent low productivity in the industry is that “Developing a vaccine for

technological improvement reducing the costs of development would perversely have absolutely no impact whatsoever on the size of incentive the paper's methodology would deem was 'necessary' to stimulate development of the vaccine (and needed follow-on vaccines). Perhaps, after reading the relevant sections in this report pertaining to the GSK candidate vaccine, if Berndt et al. conclude that the costs of developing a malaria vaccine (and follow-on vaccines) are just as high as ever, they will raise the size of the APC they advise?<sup>451</sup>

### **Lack of cost knowledge harms other things too**

On a very practical level, the reader might like to consider how the following claim can be made to work with a complete lack of knowledge of the science and costs of developing malaria vaccines, and how this would harm the cost-effectiveness of a mechanism supposedly spreading subsidies over products and creating valuable follow-on activity: "By selecting *carefully* [meaning?] the combination of price and quantity (which make up the market revenue guaranteed by the commitment), the sponsors can decide the extent to which they wish to focus the incentives on early discovery of a new vaccine, and the extent to which they want to use the commitment to reward the developers of subsequent improvements."<sup>452</sup>

But it is the difference between revenue and costs that matter – so just manipulating the revenue makes no sense. The 'right' combination of price and quality cannot be known without knowledge of the (expected) technology and likely costs. A few minutes thinking of how this could possibly be done leaves one numb. And all this, while recognizing, as CGD do, that "*it is difficult to predict which technologies will succeed and hence hard to anticipate costs.*"<sup>453</sup>

At least the cost-effectiveness methodology is being consistent with the spirit of the APC literature. The top-down methodology on revenues, reflects much of the approach to malaria, HIV, and TB vaccine problems in general: That a model can be imposed on a problem even if the problem does not match the model, and that instead of working from the science up to the financial and economic incentives needed to tackle it, a simplistic economic model can be imposed from above with the science forced to fit the model. And if it is "hard to anticipate costs," just ignore them.

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malaria will be very, very costly." But then they argue that the lack of success in the future to bring 'blockbusters' to market means the industry will focus on smaller targeted therapies and that this is good news for malaria APCs. How does this latter reasoning offset the "very, very costly" nature of the R&D problem, let alone help to set APC terms? This shows how little R&D *cost* thinking is going on in the Berndt et al. methodology, given its obsession with revenues alone.

<sup>451</sup> Remember this is a mechanism where if the price starts wrong it is hard to adjust it (increasing the size 'too quickly' creates an incentive to delay R&D).

<sup>452</sup> Barder et al. 2005, *ibid.* p9, (emphasis added).

<sup>453</sup> CGD, Feb 2005, p57 (comment removed from final report).

## **6.2. Ignoring other components of cost of development**

The overall cost of vaccine development, and therefore overall measured cost-effectiveness, should also include *all* funding needed outside of the scheme being proposed. When working out the cost-effectiveness of an APC, this should include all non-APC subsidies, tax-breaks, and other benefits granted for research, the spending of national governments and foundations, and any costs of ‘vaccine enterprises’ outside of the purchase of the vaccine via the APC subsidy scheme.

APC subsidies for malaria, HIV, or TB vaccines are likely to cover only a very small portion of the overall costs of vaccine development. Indeed, if they collapse down just to paying the high costs of one developer of a low ‘quality’ vaccine, they will have hardly done anything to incentivize R&D. Yet the cost-effectiveness figures for such subsidies have been deliberately generated, quite remarkably, by assuming that the impact of the vaccine is *all* down to the APC.<sup>454</sup> That is *all* DALYs saved are apportioned to the APC even if the APC may represent only a tiny portion of the total cost of development of a vaccine. All the Kremer, Berndt et al. and CGD figures are based on doing this. This is clearly going to create a more favorable result for lower-quality vaccines compared to higher-quality vaccines than is truly justified.

It generates some pretty absurd claims too, such as: “For products at relatively early stages in their development, a commitment of \$3 billion for each priority disease – an amount that would be comparable with sales of medicines in rich countries – would be a very good deal for the sponsors: a bargain compared with other development interventions, each life-year saved would cost less than \$15.”<sup>455</sup> This completely meaningless figure was even repeated by Tremonti to back up his Report: “As we shall see, vaccines bought under an AMC for a malaria vaccine are estimated to cost just \$15 per life-year saved – well within the range of highly cost-effective interventions.”<sup>456</sup>

This is the same methodology as a plumber would use to justify a huge fee for his or her workmanship plumbing in a few sinks and making a home ‘habitable’ – a million dollars’ worth of value divided by the hours spent putting the pipes in. The quality of workmanship could hardly make a dent in such a notion of cost-effectiveness. As Berndt et al. indeed put it: “Sensitivity analyses suggest most characteristics of a hypothetical malaria vaccine would have *little effect* on the cost-effectiveness,”<sup>457</sup> (emphasis added). This should have alerted policymakers, but should not have surprised them; it is built into the methodology from the start.

Incidentally, since we do not really know how much such vaccines will cost to develop – across all R&D funding, it is actually quite difficult to work this out and do any reliable cost-effectiveness of potential vaccines – these figures are unusually deceptive anyway.

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<sup>454</sup> This way of doing things seems to have entered with the Kremer No 10 papers which presume no role for any other players except those private firms being paid via the APC subsidy scheme.

<sup>455</sup> [www.cgdev.org/doc/books/vaccine/MakingMarkets-policyhighlights.pdf](http://www.cgdev.org/doc/books/vaccine/MakingMarkets-policyhighlights.pdf) px.

<sup>456</sup> Tremonti, G., Background Papers, 2005, *ibid.* p3.

<sup>457</sup> Berndt et al. 2005, *ibid.* p1.

They simply assert that if policymakers spend some measure<sup>458</sup> of the costs of developing a ‘typical’ drug, and *if* the APC works, then \$15 per DALY saved is the figure that comes out of the calculation. But this is meaningless.

### **6.3. Ignoring delay and the ‘mechanism risk’ of an APC**

Cost-effectiveness – viewed from the perspective of the global budget constraint and all malaria options – is heavily harmed by delay and by any inefficiency generated by the tradeoff between goal-1 and goal-2 (see more below). For example, if a mechanism for repaying vaccine R&D involves holding off payments to check if a vaccine is working (as suggested for malaria, HIV, and TB by Kremer and Glennerster<sup>459</sup>) this will wrack up capital costs, more costs imposed on alternative parts of the package of measures, costs of monitoring, and welfare losses of patients, and so forth.

However, by the methodology of these studies, unsurprisingly – but still rather alarmingly – “cost-effectiveness [of a malaria vaccine] is robust to vaccine efficacy, slow or low adoption...”<sup>460</sup> and “relatively insensitive to changes in assumptions about efficacy [and] take-up rates.”<sup>461</sup> If a better 80% vaccine meant “fast and high adoption” and a “high take-up rate”, this methodology would hardly pick this benefit up. But this should not surprise us; it is built into the methodology from the start. The ceiling value of a vaccine is so high (i.e. malaria so harmful), that hardly any of these things make any difference to the value of having ‘a’ malaria vaccine, indeed *any* malaria vaccine: “Even if adoption of the vaccine is very slow, the program would still remain very cost-effective from a public health perspective and would provide a considerable amount of revenue to the vaccine developer.”<sup>462</sup> The plumber analogy would be that – on the basis of a million dollars’ worth of value divided by the hours spent putting the pipes in, it wouldn’t matter how long the plumber took or how many the leaks – it is still highly cost-effective.

#### **Standardising to the moment of discovery**

The Berndt et al. methodology is particularly deceptive at this point. It states that: “Since the values of revenues and cost per DALY saved are expressed in real terms *at the time a vaccine is developed*, even though altering the years until a vaccine is developed will change the nominal price paid, it will not alter the results of the calculations presented here,”<sup>463</sup> and that “A vaccine commitment would also be cost-effective *at the time of vaccine development* under a wide range of contract provisions,”<sup>464</sup> and that “*once a vaccine is developed*, purchasing vaccine at the pre-specified price would be a very cost-effective expenditure. There is little reason to fear, therefore, that a vaccine commitment would tie donors to future purchases that would not be worthwhile, *if a vaccine were developed*,” (italics added in all quotes, and, perhaps the reader should pause and fully

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<sup>458</sup> Revenues do not have to be for average drugs, but picked off the distribution for average drugs.

<sup>459</sup> Kremer, M., and Glennerster, R., 2004, *ibid*.

<sup>460</sup> Berndt et al. 2005, *ibid*. p13.

<sup>461</sup> Berndt et al. 2005, *ibid*. p21.

<sup>462</sup> Berndt et al. 2005, *ibid*. p21.

<sup>463</sup> Berndt et al. 2005, *ibid*. p12.

<sup>464</sup> Berndt et al. 2005, *ibid*. p22.

take in exactly what is being said by Berndt et al. in all the italicised portions before proceeding).

This standardises all calculations of cost-effectiveness to the moment of discovery, and therefore cannot tell us much about how the timing of that moment of discovery impacts cost-effectiveness. Nor, indeed, could this methodology ever generate any negative cost-effectiveness impact should that moment never arise in the first place or be massively delayed because of bad policy advice. Even if encouraging politicians to pursue an APC will delay an outcome, this is still highly cost effective. Even if a malaria APC is set up to fail, this methodology says that it is still great value for money.

We are even told by the same authors that “it is difficult to know how much a vaccine [APC] commitment would speed up vaccine development,”<sup>465</sup> which is an extraordinary remark to make after just telling the reader that the cost-effectiveness evidence for a malaria vaccine APC has all been worked out standardised to the moment of vaccine development.

#### **Timing and delay does not matter in these studies**

In the methodology too, the present discounted value of the firms’ revenues is found by discounting at firm cost of capital of 8% real (11% nominal),<sup>466</sup> and the value and cost per DALY and all future expenses to the program sponsor at 3% real. So timing does matter. To keep the Malaria Vaccine Technology Roadmap malaria goal-1 and goal-2 equally valuable, and if Berndt et al. are using the correct discount rates, then the commitment needs to grow at real 8% per year. At the *moment of vaccine discovery* it might be reasonable to discount from that moment forward all flows at real 8% and 3% respectively, but it is not correct to ignore the trajectory that gets us (or fails to get us) to that ‘moment’. *Should we get* to such a moment, the vaccine is indeed ‘valuable’ in the sense of malaria being ‘very bad’. But it is not right to then use this fact to make APC schemes have value without having to talk about the efficiency of the APC scheme itself in getting us to that ‘moment’ and creating that value, or whether such schemes will even work.

We are told, in reference to malaria vaccines, that the “historical record suggests adoption of new vaccines in developing countries could be delayed ten to 15 years in the absence of a purchase commitment,”<sup>467</sup> even as a malaria vaccine APC is then justified without at any point having to prove anything about its effectiveness (dollar for dollar against alternatives) in overcoming such delay. Having read the chapter above on long-term supply obligations, the reader should anyway have immediately spotted the vacuity in this last claim. We saw how it rests on an unrealistic contractual threat, and presumes that the money will not be spent to bring about the goal in any other way.

In fact, the most we get from Berndt et al. on the efficiency argument is that “under a large range of values, a vaccine commitment *may be sufficient* to stimulate substantial

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<sup>465</sup> Berndt et al. 2005, *ibid.* pp. 23-24.

<sup>466</sup> C.f. Tremonti’s use of 6%.

<sup>467</sup> Berndt et al. 2005, *ibid.* p24. Observe how this is confusing issues.

research *towards* a malaria vaccine”.<sup>468</sup> Even if the instrument is set far too low to bring about discovery quickly (or ever), it will still be deemed highly cost-effective by this methodology. Worse, if the APC subsidy scheme is likely to simply fail, this still says it is highly cost-effective.

#### **6.4. Treating the usefulness of a malaria vaccine as being for ever**

The Berndt et al. methodology also ignores the fact that an imperfect vaccine will lead to more new vaccines being needed later – indeed a hugely difficult follow-on problem that may lead to more funds being needed and much higher costs than originally suggested. But such cost-effectiveness studies never presume anything less than a vaccine that maintains its original effectiveness with no need for fresh funds, even if it is a low ‘quality’ vaccine.<sup>469</sup> Berndt et al., being based on typical cost of developing drugs, has nothing to hint at what would happen to cost-effectiveness if we needed a stream of follow-on vaccines over several generations, say 20 years, and whether some trajectories for this are better than others (e.g. higher efficacy first vaccine, requiring fewer follow-on vaccines, with higher treatment regimes, versus lower efficacy first vaccine, more follow-on vaccines, still high treatment regimes, etc.). Incidentally, who will do all the financial topping-up if needed?

Furthermore, by ignoring the manufacturing cost issues (discussed in the previous chapter) this approach is incapable of exploring the different costs generated by goal-1 or goal-2 options once issues like polymorphism and antigenic variation intervene, and their impact on cost-effectiveness. For any given budget constraint, this approach always justifies heading off in the direction of a lower efficacy less efficient goal. In addition, revaccination costs would add dramatically to costs, but this is also ignored.<sup>470</sup>

It should strike the reader a little odd that, in such studies, a high-efficacy vaccine that lasts for ever, does not much more dramatically improve in its relative cost-effectiveness compared to a low-efficacy vaccine that loses its usefulness, uses up all the subsidy funds, and then requires a longer stream of vaccines and even a major APC funding top-up. We are told that “even a 30 percent effective vaccine would be highly cost-effective,”<sup>471</sup> as if that was it. Even this presumes that a 30% vaccine gets wide use and stays efficacious for ever (in Berndt et al., the cost-effectiveness of even the 30% efficacious vaccine is calculated on the basis that it takes all the subsidy pool and is used

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<sup>468</sup> Berndt et al. 2005, *ibid.* p25, with emphases added.

<sup>469</sup> There is also a tendency when applying the methodology to HIV to concentrate attention on preventative vaccines, though therapeutic vaccines may create a range of follow-on problems and may also aggravate production costs if firms hold off scaling up.

<sup>470</sup> The HIV cost-effectiveness studies are also a bit ambiguous about what happens if a set of vaccines is needed to protect against a range of the most important strains or a single vaccine to protect against all. For HIV there is also a distinction between vaccines that prevent and those that postpone development of serious disease. The IAVI studies that this author has seen pertain to the first sort, which are by default lower cost per DALY.

<sup>471</sup> Berndt et al. 2005, *ibid.* p21.

for ever). If several multiples of funding are needed, and if the vaccine needs re-engineering at regular intervals (increasing average production costs) and roll-out is well short of 100%, then this should enter the cost-effectiveness calculations, but it does not. If ‘blowing’ all available funds on the 30% vaccine means that a better vaccine never sees the light of day, the impact of this has no impact on cost-effectiveness.

Incidentally, 30% efficacy still leaves 70% suffering due to the lack of efficacy of the vaccine, with the cost of this both in the short- and long-term impacting cost-effectiveness. And if it is really short-duration (one year), it is not clear to this author what the consequences are for the long term impact and longer-term cost-effectiveness. In short, the 30% cost-effectiveness calculations are extremely dubious to say the very least.

### **6.5. Presuming low production costs and very low long-term vaccine prices**

We previously explored a range of short- and long-term price problems, and found that there are many ways in which targeting a low and then a high efficacy goal may feed higher product costs. Yet, Berndt et al. maintain that their APC cost-effectiveness calculations are defined only for the “first 200 million people immunized, after which the price would drop to \$1 per person immunized.”<sup>472</sup> They also presume that adding a three-dose vaccine to the EPI package “would be no more than \$0.75.”<sup>473</sup>

Supposedly, via the APC route, most of the incremental cost of a malaria component to EPI for the first 200 million courses is ‘windfall’ subsidy to the ‘winning developer’. But let us think of the most extreme case, where developers expect that production costs are \$15 or more per course for the first 200 million doses of a malaria vaccine, absorbing all the available APC subsidy on manufacturing costs alone. According to Berndt et al, this would still generate “less than \$15 per DALY saved, including purchase and delivery costs,”<sup>474</sup> even if no firms responded to the APC, and the vaccine did not get developed in the first place (think through the underlying R&D problem). How can a scheme that leads to a vaccine not being developed, still be deemed cost-effective?

Indeed, if production costs did *not* come in at a dollar or so as hoped, but varied up to the full \$15 (or beyond) this should show up in the cost-effectiveness of the APC subsidy scheme, since expectation of this (as we saw above) feeds slower product development and lower average quality; but it does not under the Berndt et al. methodology. In particular, if manufacturing costs are coming in at an expected \$15 or more per course of treatment and therefore a great deal of R&D has to be covered by non-APC funding, and many private players come to conclude that only the product with, for example, foundation-sponsored R&D costs will cover its costs, and they do not develop products, then this should show up in the cost-effectiveness methodology. Again, it does not. If low

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<sup>472</sup> Berndt et al. 2005, *ibid.* p14.

<sup>473</sup> Berndt et al. 2005, *ibid.* p14.

<sup>474</sup> Berndt et al. 2005, *ibid.* p13.

‘quality’ products get to ‘unfairly’ compete against treatments, because of the pre-sunk subsidies, at a fraction of the production cost of the vaccine, this also should show up in the cost-effectiveness methodology. It also does not.

**We cannot just presume low long-term prices**

Given that the challenge with recently-developed vaccines such as those for pneumococcal (*streptococcus pneumoniae*) or rotavirus, and for previously developed vaccines such as Hepatitis B and *Haemophilus influenzae* serotype b (Hib), has been all about getting production prices lower, we cannot simply presume low prices and then feed them into cost-effectiveness calculations. Recent news articles show the very real struggles to get the costs of these vaccines down to acceptable levels for poor countries.<sup>475</sup> It leads to the perversity of justifying the choice of a funding scheme for malaria vaccine development that has nothing to say about how it will achieve low vaccine prices – and may even delay getting low long-term prices – on the basis of the low prices supposedly produced by that scheme!

The issues of long-term price and supply we already saw were completely unresolved in the APC literature, and hence should leave cost-effectiveness issues also unresolved. Yet the cost-effectiveness evidence of Berndt et al. supporting a low efficacy (goal-1) vaccine, and, indeed, heavily used to favor the APC approach, presumes low manufacturing prices in both the short-run and long-run, as if this highly practical problem has somehow mysteriously been resolved from the start of an APC.

In Berndt et al. all long-run purchases made after the subsidized purchases are used up, are ignored in working out the cost-effectiveness of the APC scheme, on the assumption that either these purchases continue to be produced by the original developer and are very low priced, or “because for later sales it is increasingly less likely that the supplier would remain the same,”<sup>476</sup> on the notion that this means the problem drops out of the equation. However, since the whole point is to work out the cost-effectiveness of the subsidy scheme – *whoever* provides the long-term supply (even if different from the original recipient of the subsidy) – this either means that high-cost long-term supply would be tolerated but be ignored for cost-effectiveness calculations (clearly the wrong way to do things) or it is being presumed that the long-term supplier has very low prices (\$1 per course), which is equally dubious. In a previous chapter, we found that the long-term price supposedly produced by an APC scheme is presumed achieved by legal ‘threat’; hardly a reasonable assumption on which to base cost-effectiveness evidence to favor such a scheme.

**6.6. Treating a malaria vaccine as outside of a package of treatment and prevention**

Unfortunately, there has been a tendency in some policy circles to separate the vaccine R&D issue excessively, and sometimes entirely, from all other aspects of the problem.

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<sup>475</sup> [www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069\\_pf.html](http://www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069_pf.html).

<sup>476</sup> Berndt et al. 2005, *ibid.* p19.

It is often argued that once a vaccine is rolled out, the other components can be cut. We find repeatedly that though this may hold for some previously developed vaccines, such as smallpox, this convenient distinction does not work so neatly in the case of malaria, HIV and TB – especially for lower efficacy and shorter lived vaccines. Kaper et al. explain: “The circumstances surrounding this [smallpox] disease and the vaccine were unique, and it should not be taken for granted that future vaccination programs will be able to duplicate this success. The smallpox virus was an uncomplicated agent to manage with vaccines. It was represented by only a single strain, it lacked an environmental reservoir, and the symptoms of disease were easy to identify. Moreover, the smallpox vaccine was inexpensive, it was easy to administer, it could be manufactured in the field, and post-exposure prophylaxis was possible.”<sup>477</sup> All *cost-effectiveness* thinking – and hence any new R&D mechanisms/incentives for vaccines such as malaria – should be in terms of a package of malaria interventions evolving together over time, and not on the assumption that the vaccine simply replaces everything else. This is clearly so for a 50% efficacious vaccine, but applies also to an 80% efficacious vaccine.

By ruling out any budget constraint, and by ignoring the reality of a malaria vaccine nesting within a complicated package of measures, and a choice over vaccine ‘quality’ given this budget constraint, methodologies such as that used by Berndt et al. carry the danger of always suggesting that even a very poor vaccine is cost-effective. Indeed it is impossible for such studies to find otherwise, even if – once the correct full budget constraint and full range of options are considered – it may actually turn out to be a very poor outcome, and even damage overall efforts. Doing cost-effectiveness in this more robust way would actually be quite a challenge, but if a vaccine is just one tool in a toolbox of measures, its exact relationship with the other tools needs to be more clearly worked out and worked into policy formulation and cost-effectiveness.

### **6.7. Assuming masses of failure elsewhere but not of the APC itself**

Farlow 2004 Section 8 reviews the multiple layers (about 10) of distortion of evidence in previous APC cost-effectiveness analysis<sup>478</sup> used to generate a case heavily biased in favor of APC subsidy schemes for HIV, malaria, and TB, and used to disparage the value of all other approaches. The basic underlying principle then, and now, was that APCs are perfect instruments applied perfectly, and all other approaches are not. Meanwhile, those promoting APC subsidy schemes for malaria, HIV, and TB vaccines have assiduously avoided cost-effectiveness calculations of the *true* marginal impact of a dollar spent on the APC scheme versus the marginal impact of a dollar spent on any other approach.

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<sup>477</sup> Kaper, J., Rappouli, R., and Buckle, M., “Vaccine Development: Current Status and Future Needs.” *American Academy of Microbiology*, 2005, <http://asm.org/ASM/files/ccLibraryFiles/Filename/000000001841/VaccineDev-TextOnly.pdf> p3.

<sup>478</sup> Kremer, M., No 10 Policy Unit submission. To read about the ten distortions see Farlow 2004, *ibid*. Section 8.

We also find that such cost-effectiveness studies never say anything about what happens if there is any ‘crowding out’ of subsidies.<sup>479</sup> We will discuss this in much more detail in a later section, but a standard issue when handing out subsidies is to make sure that they go only to those purchasers who really need them and to those firms who are incentivized by them. Otherwise, the power of such subsidies is ‘crowded out’. This is something that any study of a system based on subsidies would regard as completely rudimentary. Why is it not done in this case? Perhaps it is because the underlying models used to justify these subsidy schemes (such as Kremer Appendix 3) face no targeting issues or ‘crowding out’ problems themselves, and hence neither does the cost-effectiveness evidence based on this view of the world?<sup>480</sup>

### **6.8. Hiding behind the value of a malaria vaccine even if not achieved via an APC**

This cost-effectiveness methodology has *nothing* to say about the cost-effectiveness of any particular mechanism for achieving the development of a vaccine, since alternative mechanisms are never compared in this literature.<sup>481</sup> Instead, a chosen approach (an APC in this case, though those promoting other approaches could theoretically have used the same methodology) hides behind the value of removing malaria itself, and hence the value of a vaccine per se.

Of course, it is not the effectiveness of a malaria vaccine *itself* that should be used to justify putting in place a particular financial and institutional R&D mechanism, but the effectiveness of the mechanism in bringing about the creation of that vaccine. These studies never have anything to say about the actual response of firms and hence speed to vaccine development, and nothing on the creation of capacity and long-term supply or long-term price, or of how any of the problems generated by APC subsidy schemes themselves might be tackled.

#### **Using the value of a vaccine to avoid having to prove effectiveness of R&D**

Instead, those who use this work to lobby for a malaria APC, use the potential value of a malaria vaccine itself to avoid ever having to prove the effectiveness of the particular funding mechanism they propose. G8 leaders were even persuaded of the effectiveness of the APC approach to malaria, HIV, and TB vaccines, on the basis of the value of the malaria, HIV, and TB vaccine(s) themselves.

Appendix E of the CGD Report even totally conflates the two, titling itself: “A tool to estimate cost-effectiveness of an advance market commitment,” when it does nothing of

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<sup>479</sup> Both across countries in purchases of vaccines and in the use of vaccine technology, but also across types of financial instrument used, especially if monitoring is done very poorly such that payments are not properly handled to remove payments from those not being incentivized by them.

<sup>480</sup> Kremer and Glennerster claim “sponsors should decide” how this problem is handled to avoid windfalls (Kremer, M., and Glennerster, R., 2004, *ibid.* p106). Farlow 2004 and 2005, and below, explains why this cannot be so (mainly because of coordination failure, risk to private investors, and lack of clarity of what is going on both to those running the scheme but also to investors).

<sup>481</sup> See Farlow, A.W.K., 2004, *ibid.* Section 3 for more on this.

the sort. Similarly, several of the same authors repeat the claim in the Tremonti Report that “reviews the rationale of the AMC approach and shows that *it* [the AMC] is *cost-effective*, it has a high social rate of return and it is *complementary to other interventions...*”<sup>482</sup> (emphasis in original) when it does none of these things. The Tremonti background papers even claim that analysis suggests that “purchases under” APCs “would be cost-effective at a wide range of commitment sizes,”<sup>483</sup> and that “the range for a cost-effective AMC is large,”<sup>484</sup> and that even at twice the level being proposed “this would be one of the most effective development interventions in the world.”<sup>485</sup> Observe the use of the phrase “purchases under”, since it is the purchases that are driving the cost-effectiveness claims, and not a careful analysis of the proposed mechanism itself. IAVI has now also adopted this habit of interchangeably equating “cost-effectiveness of an AIDS vaccine” with “cost-effectiveness of an AIDS vaccine AMC”.

What is even the point of a statement like: “there is no single ‘correct’ value for the market size, but rather a range of values within which an advance market commitment would be likely to accelerate the development of new vaccines,”<sup>486</sup> if that means that \$3bn of APC subsidies could be too low to do much of any use at all (given all the risks that firm’s face, both from the science and from the APC scheme), and yet would *still* pass the test of being “outstanding value for money”? What is the sense in claiming that at “the illustrative figure of £3 billion...The estimate of cost-effectiveness shows that *a commitment of this size would be outstanding value for money,*” (emphasis added)?<sup>487</sup> This is about as meaningful as claiming that going to Mars and back for a few billion dollars would be “outstanding value for money”, even if nobody takes up the offer of trying to do. These statements mean essentially nothing of any practical worth.

Tremonti makes the even more stunning observation that such a wide range of cost-effectiveness should “assuage the possible concern that because of uncertainties, it is difficult to be sure that an AMC is set at the best possible size,” politely expressing the notion that such instruments can be set extremely badly (even so badly as to fail) but still be deemed highly cost-effective. Thus, those proposing the APC scheme are relieved of any responsibility to prove efficacy before claiming multiple billions of dollars of public funding, given that even an atrocious application would be within the range of acceptable cost-effectiveness. No other proposed R&D mechanism has ever been able to come up with such an excuse, or to get away with it. Perhaps this is because only this mechanism has been able to use the ‘market’ card quite so ruthlessly, even if it is meaningless? Rather than be deemed a virtue, that an instrument can be ‘cost-effective’ at a wide range of applications, even truly bad applications, should immediately raise suspicions.

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<sup>482</sup> Tremonti, G., pii and repeated in the background papers to the Tremonti Report, p1.

<sup>483</sup> Tremonti, G., Background Papers, 2005, *ibid.* p9.

<sup>484</sup> Tremonti, G., Background Papers, 2005, *ibid.* p9.

<sup>485</sup> Tremonti, G., Background papers, 2005, *ibid.* p9.

<sup>486</sup> Barder et al. 2005, *ibid.* p8.

<sup>487</sup> Barder et al. 2005, *ibid.* p8.

### **We haven't a clue**

Bluntly, all these descriptions of the virtues of a very wide range of cost-effectiveness, are really just the practical manifestation of the fact that for diseases like malaria, HIV, and TB we simply do not know enough about the science and costs of development to even begin to fix the relevant terms so far in advance. As Tremonti observes: "Determining the appropriate size of an AMC is a difficult exercise because R&D on vaccines is an uncertain investment, particularly when scientific challenges are still very hard, and donors imperfectly observe the costs and risks faced by industry."<sup>488</sup> Tremonti's solution, in the footsteps of CGD, is to ignore the challenges.

The sensible route – and the only route open to us – should be to invest in approaches that are more efficient in light of the scientific result sought, in the full knowledge that these approaches will therefore be the most cost-effective. Instead, APC advocates promote on the hypothesis that the scheme will work (in spite of concerns expressed by many in industry that it would not have the impact suggested), ignore a huge range of issues such as those of delay and failure, and then justify the scheme on the basis of cost-effectiveness of a vaccine however generated. If these mechanisms were as powerful as suggested, there would be more evidence of this fact and great incentive to present it. The reader might well dwell on why it is that proponents of APCs for malaria, HIV, and TB vaccines in particular end up making such heavy use of evidence about *only* the effectiveness of a vaccine itself and never about the effectiveness of the APC mechanism.

### **The cost-effectiveness challenge**

Why have vaccine efficacy figures and APC cost-effectiveness figures recently been treated on their own, separated away from an approach containing all malaria options and a global budget constraint and all of the above issues? Is it because looked at on its own, a 50% vaccine target might look good, but in the context of this greater package – with all of the other costs of vaccine development (direct or consequential) properly accounting for, and the budget constraint imposed on other parts of a more global solution – it might look much less good? Might encouraging the overuse of low-value vaccines look bad compared to some of the alternatives?

The challenge is to create a cost-effectiveness framework to help trade off near-term and far-term mortality given a realistic assessment of a budget constraint and other non-vaccine elements present. For example, what if a vaccine based on RTS,S can save lives, but the investment to make it happen could delay development of a vaccine that could save more lives later? The same problem arises in working out how to balance the fielding of available interventions now versus investing in R&D for better interventions in the future. What is the formula that will save the most lives cumulatively? The Berndt et al. cost-effectiveness methodology is incapable of telling us.

We need a methodology which judges the marginal cost-effectiveness impact of R&D towards vaccines with 50% or 80% (or any other) efficacy, 1, 2, 3 (or any other) number of years of duration, any degree of potential polymorphisms and antigenic variation, etc.

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<sup>488</sup> Tremonti, G., 2005, *ibid.* p8.

instead we get a methodology based on only the total value of an any-efficacy/any-duration vaccine. Maybe it is the risk of looking bad that stops this sort of analysis from entering the cost-effectiveness domain from the start? After years of under-spend on all malaria-fighting initiatives, policy has recently taken a turn for arguing in favor of vaccine R&D measures based on cost-effectiveness evidence that presumes there is, essentially, no financial constraint, even if ultimately this attitude risks harming all malaria activities and many other neglected disease and vaccine initiatives.

The Berndt et al. methodology means that there is always a ‘cost-effectiveness’ justification for a vaccine that comes out of the two goal process, even if it uses up all of the subsidy pool, is a low efficacy goal-1 vaccine, and better vaccines are lost forever. As Kremer is quoted as putting it: “Such a purchase commitment would be highly cost-effective even if it covered vaccines that departed significantly from the ideal.”<sup>489</sup> Even if the APC is likely to fail – and firms realizing this, will not invest – the Berndt et al. methodology says that it is still highly cost-effective. Are advocates of malaria APCs interested in a policy that will succeed, or only in achieving a ‘policy success’ regardless of the likely end result?

### **6.9. Bold claims based on this methodology**

On the basis of this sort of methodology, a myriad of references are made to the cost-effectiveness of a malaria vaccine APC. What do we make of these claims in light of the above analysis, and in light of the previous work of Kremer that employed multiple levels of deliberate distortions to push out a result favorable to APCs over all other approaches?

Here are a few of these claims (though all source from the same very few individuals):

Asked “Is there any evidence that your system would be cost-effective?” Kremer argued in November 2005<sup>490</sup> that: “Yes. The sales revenue of a typical, new rich-country drug is about \$3 billion. To create this sort of market in the developing world, you might have a donor commit to spending \$15 per person for the first 200 million people vaccinated. By comparison, it costs \$500 per person per year to purchase and deliver HIV medications.”

“A commitment of this size would create a market comparable to a developed country pharmaceutical, while providing a very cost-effective investment for donors.”<sup>491</sup> Indeed, Kremer claims that an APC is up to four and a half times more cost-effective for donors than publicly funded research and joint ventures into HIV, malaria, and TB vaccines.<sup>492</sup>

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<sup>489</sup> The Guardian, Comment, “Not just for profit, or not just?” Friday November 4, 2005, [www.guardian.co.uk/birdflu/story/0,,1627785,00.html](http://www.guardian.co.uk/birdflu/story/0,,1627785,00.html). See also “Even a 30 percent effective vaccine would be highly cost-effective,” Berndt et al. 2005, *ibid.* p21.

<sup>490</sup> <http://msnbc.msn.com/id/10206224/site/newsweek>. Newsweek, 19 November 2005. It is quite shocking to see this sort of argument still being made in late 2005, even after all we have learnt about the problems with the \$3bn figure.

<sup>491</sup> CGD, March 2005, *ibid.* p87.

<sup>492</sup> See Kremer, M., No. 10 Policy Unit Summary p2 and tables on p4.

“Our quantitative analysis suggests that an APC is *the most cost-effective means* of encouraging the development of new health products.”<sup>493</sup>

“It is thus clear that purchases under a vaccine commitment would save more lives than almost any alternative use of funds.”<sup>494</sup>

“Once a vaccine meeting appropriate technical requirements is developed, purchasing it at the agreed price will be one of the most cost-effective health interventions conceivable.”<sup>495</sup>

“This would be among the most cost-effective public health interventions imaginable.” A line from “UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria”<sup>496</sup>

“A guaranteed market enhancement like advance contracting could unlock innovation today, speed the development of a vaccine tomorrow, and assure rapid access – and lives saved – for many years to come. It is one of the most cost-effective development interventions available to us.”<sup>497</sup>

As this report was going to press, economists worldwide were being told that an APC is “a way to cheaply change”<sup>498</sup> the lack of malaria, HIV, and TB vaccines, and to save millions of lives from these diseases, before yet again homing in on the \$3bn figure for malaria, HIV, and TB.

“Ultimately, if no vaccines were developed, such a commitment would cost nothing. But if vaccines were developed, the program would save millions of lives and would be among the world’s most cost-effective health interventions.”<sup>499</sup>

Of course the claim that it would cost nothing is not true. Clearly, if things were not working out, there would be a very strong incentive to spend the subsidy pool on *any* result that came out – even a low-quality result, rather than risk the political embarrassment of complete and utter failure. Success is tautological: Whatever the funds got spent on is by definition a ‘success’. And ‘we’ still pay, whatever the outcome. All the real resource costs of vaccine R&D, including all ‘failed’ R&D, has to be paid by

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<sup>493</sup> [www.number-10.gov.uk/su/health/06/default.htm](http://www.number-10.gov.uk/su/health/06/default.htm). See also the risk section below for the case of multiple uses of APCs.

<sup>494</sup> Kremer, M., and Glennerster, R., 2004, *ibid.* p93.

<sup>495</sup> Kremer, M., and Glennerster, R., 2004, *ibid.* p94.

<sup>496</sup> [www.cid.harvard.edu/books/kremer04\\_strongmedicine.html](http://www.cid.harvard.edu/books/kremer04_strongmedicine.html).

<sup>497</sup> CGD, March 2005, p94. See also sections below on ‘crowding out’ and long-term supply issues. And observe that we have never used such an instrument ever before; the present tense ‘is’ is therefore somewhat disturbing.

<sup>498</sup> This really was the blurb sent in the email accompanying the release of Barder, O, Kremer, M, and Williams, H, “Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases.” *The Economists’ Voice*, 2006, Vol. 3, No. 3, Article 1. [www.bepress.com/ev/vol3/iss3/art1](http://www.bepress.com/ev/vol3/iss3/art1).

<sup>499</sup> The Princeton University Press promotional material for Kremer, M., and Glennerster, R., 2004, *ibid.*, [www.pupress.princeton.edu/titles/7830.html](http://www.pupress.princeton.edu/titles/7830.html).

someone – whether it be taxpayers or through pension holdings in pharmaceutical firms. As an economist would put it, there is no such thing as a ‘free lunch’.

**Did Tremonti swallow or was he fed?**

The Tremonti Report swallowed the notion of conflating immunization cost-effectiveness with that of an APC/AMC in its entirety: “Immunization is a very cost-effective form of public health intervention...As shown by the estimates [in the Tremonti background papers, based on the analysis of Berndt et al. and CGD] AMCs for vaccines stand out as a particularly cost-effective instrument to fight disease and poverty.”<sup>500</sup> But then again, one or two of the key advisors to the Tremonti Report were behind much of this APC cost-effectiveness literature (and the CGD Report, and the No. 10 Policy Unit files) and perhaps we could hardly have expected Tremonti to have therefore concluded otherwise.

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<sup>500</sup> Tremonti, G., 2005, *ibid.* pp. 2-3.

## **7. First and Second Malaria Vaccine Goals: Tradeoffs and Risks**

This section is especially ‘exploratory’ – a contribution, perhaps, to an ongoing dialogue. The author would be only too happy to amend it after feedback, and indeed, would strongly value feedback.

### **7.1. There is no ‘pull’ for the goal-2 vaccine: All emphasis is on the goal-1 vaccine**

The present discounted value of any new commercial malaria vaccine incentive is very low indeed at the horizon of the 2025 goal described in the Malaria Vaccine Technology Roadmap.<sup>501</sup> 20 years of discounting at rates typical of large pharmaceutical firms, of 11%-14%,<sup>502</sup> makes \$1bn of *nominal* payment at such horizons practically worthless to private investors.<sup>503</sup> Thought of another way, so as not to distort commercial activity away from the second goal, a \$1bn promise made today<sup>504</sup> would have to grow at a minimum rate of 11-14% per year to keep constant the net present value, NPV, of payment for achieving the second goal compared to the first goal – at least in the eyes of very large pharmaceutical players relying on an APC for repayment.

On the Berndt et al. discount rate of 11% nominal or 8% real, each \$1bn today would have to grow to just over \$8bn in nominal terms by 2025, or about \$4.7bn in real terms<sup>505</sup> (i.e. the latter figure is the cost *in today’s prices* of each \$1bn if it is, efficiently, allowed to grow and is claimed in 2025). A \$3bn/\$6bn payment made today would have to translate as a commitment to pay, *in today’s prices*, \$14bn/\$28bn<sup>506</sup> when claimed in 2025. This would have to be written in to all legislation offering payment for the second goal, and indeed would have to grow beyond 2025 so as not to harm the 2025 goal.<sup>507</sup>

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<sup>501</sup> The logic in this section equally applies to HIV. IAVI have been doing recent ‘cost-effectiveness’ analysis based on a 2025 baseline. Or, perhaps more specifically, they have been using CGD analysis to do ‘cost-effectiveness’ analysis based on a 2025 baseline.

<sup>502</sup> Figures vary. Berndt et al. *ibid.* use real 8% (nominal 11%). Di Masi et al. suggest approx real 11%-12%, or nominal of about 15% (DiMasi, J.A., Hansen, R.W., Grabowski, H.G., “New estimates of drug development costs.” *J Health Econ*, 2003, Vol. 22, No. 2, pp. 151-85). Tremonti, for some inexplicable reason, uses nominal 6%. This is already too low, but once option-price thinking is also incorporated, it is even more off-track.

<sup>503</sup> To simplify, this chapter ignores various issues related to *flows* of R&D expenditure. The point is to demonstrate how weak the pull power of APCs is in these cases and at this moment in time for these cases, and hence why it is not going to be a good use of limited systems capacity and political capital trying to force them being set up any day soon.

<sup>504</sup> Or any part of such a sum that is not used up on an early goal-1 vaccine.

<sup>505</sup> Assuming 3% inflation (and hence 8% real growth).

<sup>506</sup> \$24bn/\$48bn nominal payment.

<sup>507</sup> From the moment of vaccine discovery, Berndt et al. index only to the rate of inflation, not to the rate of the cost of capital, immediately biasing everything to the first goal (after the first goal, firms in practice need cost of capital, whereas they only get cost of inflation, unless I have misunderstood Berndt et al.).

Tremonti uses a nominal discount rate of 6% to discount future APC payments under an APC even when discounting for the cases of HIV, malaria, and TB. This report will treat this 6% as no more than just a political gimmick.

### **Sensitivity to required rates of return**

The figures are very sensitive to even small differences in required rates of return.<sup>508</sup> If we take the higher figure, of Di Masi et al, of 14% nominal required rate of return for a typical large pharmaceutical firm, the 2025 goal would require the nominal pool of subsidy be allowed to grow to just under \$14bn for each current nominal \$1bn. That translates in real terms (a real rate of 11%), to just over \$8bn *in today's prices* for each currently promised \$1bn. Even just another 1% higher required nominal rate of return, (taking it to 15%) takes the figure to just over \$16bn, and just under \$10bn in real terms, i.e. \$2bn more in real terms. A \$3bn/\$6bn commitment made today would translate as a real commitment to pay, *in today's prices*, of about \$25bn/\$50bn<sup>509</sup> (\$30bn/\$60bn at 15%), if claimed in 2025, if politicians really do allow the subsidy pool to grow at a real rate of 11% to keep both goals equally valuable to the sort of players that they are seeking to attract. This would have to be written in to all legislation offering payment for the second goal. Some care has to be taken with these figures; an earlier footnote pointed out that all R&D expenditure flow issues are being ignored in these calculations. So, these should not be quoted as in some way alternative estimates of costs of development. The key message to pick up is that these figures suggest that early malaria vaccine R&D expenditure is not very valuable, at realistic costs of capital, to those being expected to do it under a malaria vaccine APC.

The above suggests that there is very little value in any R&D made today towards the second goal instead of the first goal, unless the pool of subsidy is allowed to grow at quite high rates. Alternatively, these discount rates can be thought of as entering the 'rule' used by the committee distributing a fixed pool of funds such that the payments to early sellers of qualifying vaccines have to be heavily reduced to leave funds in the APC pool for later developers. It also suggests some problems in trying to work out what the appropriate subsidy pool should be, since an opinion would have to be made about the appropriate rate at which the pool should grow to keep commercial balance between the two goals. If the discount rate is set too low, and the original size of the subsidy pool is set too low, no firms will respond to the incentive for the second goal, and the real value of the subsidy

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Also see Tremonti, G., 2005, *ibid.* p11: "Because the starting year of the purchases under the program is highly uncertain, the commitment should be indexed to account for inflation."

<sup>508</sup> In Berndt et al. when the choice between using 8% or 11% is discussed, the fact that using 11% instead of 8% knocks \$600m off the net present value (NPV) of the incentive (from \$3.44 billion to £2.81 billion) is relegated to a footnote. The footnote further explains that 8% is chosen because, apart from being close to the average stock market return, it "allows for consistency in our analysis between estimating the NPV of revenues of existing products and estimating the NPV of revenues under a vaccine purchase commitment" (Berndt et al. 2005, *ibid.* p8). Nothing is said about the extra non-diversifiable risk of the APC itself and the extra discount rate it would necessitate, even though it is recognised that it might fail to work (c.f. "If thirty years pass and no substantial progress has been made on the product of interest, a vaccine commitment may not be the most useful approach, and the policy would be worth reevaluating." Kremer, M., and Glennerster, R., 2004, *ibid.* p84 and CGD, 2005, *ibid.* p46).

<sup>509</sup> \$24bn/\$48bn nominal payment.

pool falls ever behind. If the discount rate is set too high, and the pool is set just correctly at the start, the pool grows ‘too rapidly’, and the marginal benefit of delaying is positive.<sup>510</sup>

Observe how sensitive goal-2 reaction is to getting right the size of the subsidy pool and the rate of growth/discount (including if interpreted as a rate of growth/discount in a rule about early and late distribution of funds). It can take many years for a subsidy pool that is set too small to grow big enough to draw forth a positive reaction. This is why it is not possible to claim, as IAVI does, that we can naïvely ignore the ‘contentious’ issue of an appropriate rate of return.<sup>511</sup>

**It does nothing if set too low, but is difficult to adjust upwards**

Maurer,<sup>512</sup> for the time being taking the CGD range of \$15-\$25 per course at face value (hence with the upper bound 167% of the lower bound), and presuming the players are large pharmaceutical firms using equity finance for their activities, observes that if the size of the total subsidy pool starts, optimistically, at the bottom of the range when actual costs are at the top of the range, and the interest rate is 10%, it will take 8 years for the incentive to have any effect.<sup>513</sup> If real R&D costs also grow at 5% per year (starting at the optimistic end of the range), it takes 15 years to have any effect. The consequence is delay, and strong pressures towards ‘poorer quality’ (broadly defined) outcomes at any given size of the subsidy fund, in order ‘to get a result’.

This suggests that a ‘pay-as-you-go’ system for funding vaccine R&D may be more capable of adapting to a changing environment and less likely to fail to get a result (if set too low) or to overpay (if set too high). This perverse incentive also bites if the total pool of subsidy is allowed to be raised but not enough firms sign on to the contract in the first place.<sup>514</sup> Holding off signing (and, indeed, therefore delaying vaccine work) or signing on to the scheme but refraining from investing too hard, is privately profitable if it leads to a higher eventual payment. Though, as with all schemes built on the notion that size can be increased later, how many politicians or officials will agree in advance (the US Treasury?) to funding such an open-ended liability?

The rate of discounting/compounding would be even higher for venture capital, VC, funding of biotech, and to compensate for the perceived ‘mechanism risks’ of mechanisms relying on these complex subsidy schemes, a risk that this author finds to be high (see below). Throw in an option-priced component to investments, and the required rates of return to early malaria and HIV research are almost certainly huge, but also very difficult to work out if such a discount rate must enter a rule about the subsidy

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<sup>510</sup> The reader can fill in the range of other scenarios.

<sup>511</sup> Zandonella, C., 2005, *ibid*.

<sup>512</sup> Maurer, S., “The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research” Goldman School of Public Policy, University of California at Berkeley, March 2005. See p75.

<sup>513</sup> Or it collapses first, since all the institutions are in place doing nothing and getting increasingly despondent.

<sup>514</sup> This is on top of the original need for the APC subsidy scheme to grow to keep the present discounted value of goal-1 and goal-2 equal over time.

distribution. We observe too that it would be difficult to set up a growing pool of subsidy with a cut-off date to stop growing, given that knowledge of such a cut-off date would feed back to numb R&D incentives.

### **Political naïvety**

Surely, it is politically naïve to believe that 11%-14% growth of the subsidy pool would be tolerated in effect for 20 or 30 years, or even for ever? And given the political pressures to spend allotted monies ‘to get a result’ – even ‘any result’ however poor – also naïve to believe that a cent of the subsidy pool would go on anything other than the first goal and the first player to position itself to take it. When one adds in the high expected costs of goal-2 vaccines and the chance that these costs eat in to the early purchase subsidies of such vaccines, there is no way at all that a \$3bn or \$6bn nominal APC directed at large pharmaceutical firms could have an iota of impact on the 2025 malaria (or HIV or TB) goal.

With this fact alone pushing even further off the date of the second goal, one cannot escape the likelihood that most of a malaria APC goes on a less challenging vaccine (if a vaccine comes out of this process) and leaves the much more difficult task for others to deal with, and that the second goal is almost entirely dependent on basic research and PPP activity, with very limited, if not non-existent, fresh commercial incentive. This is why it becomes imperative to understand better the motivations behind the first goal and how to set it efficiently.

The issue is, will there be diversion of resources towards the first goal and away from the second goal? And if so, what is the impact on the second goal. The question then is how the first and second goals are connected. We will turn to that in a moment.

## **7.2. More on rates of compounding/discounting**

Before moving on, perhaps we should say a little bit more about the above rates of discounting/compounding? We need to consider these since an APC is a distant payment and therefore can only go to those who can attract the private finance to invest in R&D in the hope of getting it. This targets APCs primarily at developed-economy equity-financed large pharma companies and VC financed biotechs who feed products into ‘large pharma’ companies’ development programs. These rates are high for various reasons:

- 1) The private sources of capital are expensive. This is not a critique. It is part of the capital cost puzzle. The author has elsewhere<sup>515</sup> (and a little bit below) discussed the important role of private capital in pharmaceutical R&D.<sup>516</sup> The issue here is

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<sup>515</sup> Farlow 2004, *ibid.* Chapter 12.

<sup>516</sup> Unfortunately Kremer, M., Towse, A., and Williams, H., 2005, *ibid.* took this observation to mean favoritism to ‘publicly funding projects’ on the basis that publicly-required rates of return are lower, even though Chapter 12 of Farlow, A.W.K., 2004, *ibid.* and Section 3 of Farlow, A.W.K., July 2005, *ibid.* (and many other places) make it abundantly clear that this is not the argument being made. Indeed, if Kremer, Towse, and Williams saw their observation fully through, they would come up with some of their own capital cost figures, or support some of the figures discussed in this Chapter.

- that this cost needs to be *fully* factored into any (growing) pool of APC R&D subsidy if the subsidy scheme is not to lead to perverse incentives;
- 2) For pull subsidy schemes *to actually work* – *all* capital cost needs to be *fully* repaid by sponsors through the APC subsidies;
  - 3) To get the size of the APC subsidy pool set efficiently, all capital costs need to be worked out *in advance* if the overall payment is not to be set too low. It is difficult to imagine this being done well. This is key because ‘winning’ firms get more than just subsidies; they get important IP rights, control over prices in markets outside the subsidy scheme, and control over key technology;
  - 4) APCs are risky themselves. How might ‘risk creation’ of such schemes, and consequentially high capital costs, offset any improvement in choice of research leads and trial attrition rates, which is the whole point of such schemes?

To the extent that such schemes would incentivize lots of players to take part (this author is not convinced by this claim one bit), a sizeable chunk of APC subsidies for vaccines such as malaria will be taken up in the cost of finance. But exactly how much? Would a required nominal rate of return to financial capital invested in current malaria (or HIV or TB?) vaccine R&D of 20-25% be outrageous? The author was taken to task by a prominent civil society leader for even suggesting this, arguing that the issue was clinical trial sizes. 20-25% *would* be way beyond anything in the Berndt et al. cost-effectiveness methodology used for setting the size of a malaria APC and used to justify an APC in the first place. However, the issue *is* also the risk of vaccine R&D for complicated vaccines at long horizons, since this is likely to be the biggest chunk of financial disincentive in these cases. The rates may be lower for neglected drugs late in the development chain, or where the science is much simpler, or where ‘sharing’ is less critical (and hence imposes less risk and a lower required rate of return to investment).

### **High required rates of return of biotechs**

Many biotechs work on the basis of higher required rates of return, and biotechs are argued by many as key players in keeping multiple malaria (and HIV and TB) vaccine routes open. 20%-25% is not outrageously high compared to speculative investments that VC firms normally make, but is it too high for this case? Or too low? The author would gladly amend this if the appropriate evidence were provided.<sup>517</sup> Again, APCs are not supposed to be schemes to repay the high manufacturing costs of low-quality vaccines of sole-suppliers, but rather to incentivize multiple parallel developers.

Indeed, this author argues that current levels of private funding for malaria, HIV, and TB vaccine R&D are low for many reasons, and not just the ‘lack of a market’, with one of them being the very high rates of risk and consequent high rates of discounting of the value of way-off markets. One only has to look at the rise in global spending on HIV vaccine research, and yet the way that very little privately *financed* research has been motivated – contrary to expectations. This should be a warning sign.

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<sup>517</sup> A request was put out, but to no avail: Farlow, A.W.K., “Capital Costs, Cost-Effectiveness of HIV APC, and Speed of Vaccine Development.” WHO Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 10 December 2004, [www.economics.ox.ac.uk/members/andrew.farlow/CIPIH10December2004.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/CIPIH10December2004.pdf).

Add a bit (or a lot) of ‘crowding out’<sup>518</sup> caused by other research support incentives (that are not properly extracted from APC payments), and allow for a few non-eligible countries (South East Asia and Papua New Guinea in the case of malaria, Russia, India, China and South East Asia in the case of HIV) that it is difficult to bar from later ‘spoiling’ markets for vaccine products,<sup>519</sup> and suddenly the pull subsidy scheme becomes even less powerful. For an untried scheme with no track record or evidence, the advocates presume a huge and rapid response that we have never seen in the past. And they deliberately ignore all these capital costs issues, a key component of trying to work out the power of such instruments,<sup>520</sup> as if there is some sort of virtue in doing so.<sup>521</sup> They even manage to get G8 finance ministers to insert claims about the ‘potential power’ of such APC subsidy schemes into their announcements with no evidence at all for any power.

The obvious alternative to responding to a mechanism that gives such low expected payoff, once all the risks are taken into account, is to just not bother responding. Some suggest that this is no problem; we should just try the APC scheme anyway, regardless. The problem, however, is that we would still be left with all the consequences of the scheme including potential problems with key IP, the need for committees to run it, liability consequences, irreversibility of badly-set terms (due to worries about litigation by those who *did* respond and the disastrous consequences of even hinting at renegeing on the scheme, etc.), and huge alienation of pharmaceutical companies whipped by the stick of a non-working ACP that was supposed to be a carrot, harmed by the reputational disaster inflicted upon them. Alternatively, most firms would not respond and the ‘reward’ would go to the limited respondent(s) who *would* respond (maybe after huge public and foundation funding) for a product of an altogether lower average quality.

### **7.3. Tradeoffs between vaccine goals given the financing constraint**

Let us return to the tradeoff between goal-1 and goal-2 vaccines given a tightly binding budget constraint. A binding budget constraint never gets mentioned in the APC literature. Such constraints only seem ever to be apply to other instruments. The limited nature of resources, financial and otherwise, is a common refrain in other literature. The Roadmap mentions it many times:

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<sup>518</sup> See Farlow, A.W.K. *Innovation Strategy Today*, 2005, pp. 92-97, for a range of crowding out issues.

<sup>519</sup> Farlow, A.W.K., 2004, *ibid.* Sections 2.3 and 2.4,

[www.economics.ox.ac.uk/members/andrew.farlow/GlobalHIVVaccine.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/GlobalHIVVaccine.pdf).

<sup>520</sup> Just as a thought experiment, the author has previously played around with such large finance costs and crowding out, coming up with \$60bn to \$135bn for a HIV vaccine if all activity had to go via an imperfectly functioning APC with size set to reflect the risk. Even if these are orders of magnitude too high, we can still confidently conclude that current lobbying for a HIV APC as a “very high priority” completely misses the point and is likely to be counterproductive.

<sup>521</sup> Zandonella, C., 2005, *ibid.*

“Current funding for malaria vaccine research and development falls short of what is needed.”<sup>522</sup>

“The number of possible combinations of antigens, adjuvants, and other platform components is staggering; all possible vaccine concepts cannot be evaluated.”<sup>523</sup>

There is a “large number of potential vaccine candidates and limited ability to test concepts in clinical trials.”<sup>524</sup>

“The community increasingly acknowledges the need to coordinate limited resources and maximize the scientific value of all efforts.”<sup>525</sup>

There are “capacity limitations for attenuated parasite vaccine approach.”<sup>526</sup>

For all our desires that it was not so, this constraint is a reality that we have to work within, even as efforts are made to expand funding.

Given a claimed \$12bn economic loss due to malaria in Africa alone per year<sup>527</sup> (i.e. even if we ignore the huge level of human suffering), it may seem obvious to the reader that it is worth spending to prevent this. However, so long as there are limited resources available relative to the size of the problem, then there *will* be true opportunity costs of investments towards the goal-1 vaccine, in terms of delay or even loss of the goal-2 vaccine. These resources include not just financial resources but also vaccine trial capacity, institutional capacity, health systems capacity, and other ‘real’ resource constraints.

Once the budget constraint is binding, the first goal, however loosely worded, would have to become genuinely and, according to APC advocates, legally, operational and will *have to* bind on policy-makers and sponsors (especially if they are legally bound to pre-agreed product subsidy contracts, as currently proposed).

Amongst other things, the interplay of minimal efficacy, scientific issues such as polymorphism and antigenic variation and the degree of knock-on costs, the level and interplay of control interventions, the size of R&D going into non-vaccine alternatives, the level of capital costs, and early versus later (potential) vaccines will all have to be tackled. The author is not aware of any analysis of these tradeoffs even roughly made.

Nobody has worked out if it is better, given the budget constraint and all these tradeoffs and costs, to have high early control with vaccine R&D targeting a later highly efficacious vaccine, or to have vaccine R&D targeting an early low efficacious vaccine,

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<sup>522</sup> MVTR p36.

<sup>523</sup> MVTR p18.

<sup>524</sup> MVTR p18.

<sup>525</sup> MVTR p3.

<sup>526</sup> MVTR p18.

<sup>527</sup> See caveats and discussion about this figure above.

still high control, and a delayed (even deterred) more efficacious vaccine. It has simply not suited policy advocates to explore these issues.

Under the assumption that there *is* a binding budget constraint – such that if all the available resources go on one outcome, nothing is left for the other – let us now explore the potential tradeoffs between goal-1 and goal-2. All of the following should be converted into lives saved or lives lost due to policy success or failure.

#### **7.4. Dangers to the second goal from the first goal**

The first goal, once operationalized via an APC, has a paradoxical affect on the second goal. On the one hand, the incentive towards the second goal may be weakened if the first goal is met (including if the required package of non-vaccine measures is achieved), since the second goal is made less valuable to investors at the margin. As the Roadmap puts it: “One semi-successful product can inhibit development of other products.”<sup>528</sup> This could be because a semi-successful vaccine has used up all of the allotted vaccine subsidies in the APC pool. Or it could be that, to the extent that a 50% vaccine combined with a large package of control measures actually works, the lower will be the marginal benefit to a firm investing towards an 80% vaccine. It is already the case that the “jump to 80% efficacy is huge – how will this be done?”<sup>529</sup> without the marginal private cost of the jump now being even greater. Having deliberately operationalized the first goal – given all the R&D and production capacity sunk in achieving it – the second goal is made less likely.

On the other hand, if the first goal proves unachievable, it will have seen a wasteful diversion of resources even while the second goal is disincentivized (or it becomes prohibitively expensive to achieve the second goal, given the tightening of IP costs, etc... see below). If fresh funding for the second goal hangs on the success of the first goal, funding may even be harmed. We need to explore the potential impact on public and private incentives of failure of the first goal and lives lost, or of being forced to accept a bad result just to have ‘a result’.

#### **How useful is goal-1 to goal-2?**

The Roadmap points out that “regardless of the ultimate success or failure of specific candidates, the efforts that go into their development and clinical evaluation will bear fruit in the form of improved understanding and more advanced vaccine concepts,”<sup>530</sup> and it is argued that the ultimate hope is to combine components with partial efficacy.

If the 80% can usefully be build off the 50% vaccine and if *all* developers *have access* to the technology of partially-effective vaccines to do this, then the exact ability to do so should be spelled out, to help evaluate the tradeoff with goal-2. To the extent that the goal-2 vaccine feeds off the same investments that lead into the goal-1 vaccine, and goal-

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<sup>528</sup> VMSR p5.

<sup>529</sup> RMSR p2.

<sup>530</sup> MVTR p7.

2 developers have access to the results of those investments, the tradeoff is weaker. The question then is to what degree are the investments towards the goal-1 vaccine more *specific* to it, and to what degree do goal-2 developers have access to goal-1 technology?

### **RTS,S**

Many argue that RTS,S vaccines have high specific costs, such that a large diversion of resources to them, while having some positive benefit in scientific lessons learned, will take resources away from other vaccines. It would be good to get details on this, but, again, it is yet another area where details have been avoided by the sort of cost-effective analysis above that essentially assumes that there is no budget constraint and no tradeoffs across vaccine goals and packages of measures.

When we hear that “the number of candidates remaining in the pipeline exceeds the available resources and capacity to thoroughly investigate them,”<sup>531</sup> and that there is “limited ability to test concepts in clinical trials,”<sup>532</sup> this indicates that the first goal is to some extent at the expense of the second goal. Later, in the chapter on finance, we explore how the commercial incentives of the first goal combined with the lack of any incentive for the second goal may also aggravate work on the second goal. We also remind ourselves, that the second goal was pushed off to 2025 (and not the original 2020) as the first goal was introduced, suggesting yet more real costs to goal-2 vaccines.

With reference to recent malaria funding announcements, one correspondent (a universally respected leading malaria vaccine expert) commented: “There is a substantial danger that application of an advanced payment scheme will favor the first, imperfect vaccine (almost certainly RTS,S) at the expense of better, second generation vaccines and it would be very unfortunate if this happened. However, these are not mutually exclusive goals...there may be better ways of encouraging big pharma to embark on production of the first generation of malaria vaccines whilst also providing support for those coming behind and I think it is the responsibility of economists to work out how to do this! Ultimately the money to achieve each of these goals will have to come from the rich countries but this may best be directed through different routes.” Another correspondent observed that: “The difference with Hib is that alternatives to RTS,S can be conceived, i.e. they are also in clinical development, though not in industrial development. In other words, Hib polysaccharides did not cause relative harm, but a premature RTS,S might well. This harm can be estimated globally in terms of excess mortality/year; at worst it might reach several hundred thousands.”

### **7.5. Dangers to the first goal from the second goal**

At the same time, the second goal may also pose a risk to investors, both public and private, working towards the first goal. We remember that, for investors, it is expectations that matter and not what actually transpires, so it is perfectly possible to have expected failure on one goal but with so much risk attached to the other goal that the

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<sup>531</sup> MVTR p11.

<sup>532</sup> MVTR p18.

expected failure on the one goal does not automatically incentivize the other goal. Both goals can fail even if there was a high suspicion that one goal would fail and the other might *otherwise* have been achievable. Are we really presuming that firms do not face risk if they target, at great private costs to themselves, a goal-1 vaccine even as there is the second goal and the possibility of renegeing on the first goal?

### **The 2025 date and the 80% target**

The danger to the first goal is greater the *nearer* the second goal is to the first goal. Imagine the impact of risk on investment decisions of a firm investing in the first goal (both R&D and manufacturing costs and investment to get long-term price lower) if policymakers are targeting to replace them in 5 years or less. Indeed, according to the CGD report, firms will be forced to invest to supply a goal-1 vaccine at a very low long-term price whether or not goal-2 is achieved, but with an obligation to supply if goal-2 *is not* achieved but therefore facing excess capacity if goal-2 *is* achieved. Clearly this is a further disincentive to do malaria vaccine R&D in the first place.

Under APC schemes for the goal-1 vaccine, firms *need* the second goal to be delayed to 2025 – and indeed, they may need the use of all the subsidy pool on the first goal and consequent uncertainty about funding for the second goal – to increase their chances of extracting costs sunk towards the first goal. A 2020 goal would play havoc with private investments directed towards a 2015 goal; some sizeable ‘space’ between goals is needed for the two-goal approach in an APC framework.<sup>533</sup>

### **Will goal 1 never be abandoned? Is 50% ever subordinate?**

It might be claimed that the development of an 80% efficacious goal-2 vaccine does not suffer because the goal-1 50% vaccine is ‘subordinate’. But how is this actually operationalized? Given that the NPV of subunit vaccines, for example, is hugely higher than combination and whole-parasite vaccines, how does the overall goal not become a de facto goal of an expected 50% vaccine,<sup>534</sup> with the 80% a heavily subordinated, and even non-existent, target?

If committed devices, such as APC subsidy schemes, are in place, how could any goal be subordinate if that would require the *possibility* of renegeing on it, the loss of credibility, the undermining of investment incentive towards even that goal, and the possibility of litigation? But what if the ‘improved scientific understanding’, at some point, dictates that the first goal *should* be abandoned? How can firms be encouraged to invest in the first goal if it (and their rewards) could be abandoned? Or is renegeing on the first goal ruled out however inefficient it may turn out to be, or even if *not* renegeing will thereby destroy the chances of a better second goal outcome?

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<sup>533</sup> Even the wording now sounds a bit of an ‘add-on’: “Beyond 2015... the goal of ... 2025 has been adopted.” MVTR p5.

<sup>534</sup> We do not ‘know’ that subunit vaccines cannot be developed to hit a higher efficacy target, given that we have only tried a small subclass of all potential subunit candidates. The observation here is all about probabilities over ‘quality’.

### **Goal 1 risks from lack of other supporting measures**

Similarly, private R&D incentives will be weaker for goal-1 vaccines if there is perceived high risk that the required supporting non-vaccine mechanisms will not be put in place, thus weakening the payoff to the goal-1 vaccine. But those non-vaccine mechanisms depend on the attitude of purchasing nations to the likelihood of goal-1 vaccines. Repayment of sunk R&D costs via APCs forces investors to face the risk of malaria control measures failing. The Roadmap points out that, on top of this, “Some countries may just wait until 2020 [now put back to 2025] for the 80% vaccines.”<sup>535</sup> After all “50% is about what current interventions achieve.”<sup>536</sup> Certainly, one can see the uncertainty being created for investors if it turns out that the goal-1 terms are not credible, or if it is confusing to investors working out how countries, other companies, and funders will respond.

### **Make 50% truly subordinate**

Once the 80% efficacy goal is taken seriously, it may be less risky, for firms and public funders, to seek to incentivize the 80% efficacious vaccine and truly make the 50% one-year vaccine subordinate – and put in financial contracts to enable this to become subordinate – rather than emphasize the 50% efficacious vaccine and hope it does not disincentivize activity, including private investment, that might lead to the 80% target. Perhaps, it might help to view the Roadmap document with only the 80% efficacy goal – pushed back to 2025 – to give a feeling for the sad state of affairs.

## **7.6. Dangers to the first goal from the first goal**

The last possibility (already covered elsewhere) is that if a vaccine ever meets the standards required of the first goal, it has little value or becomes useless after some time, yet has consumed all the subsidy pool. Where will funds come from for more and different vaccines later? The literature on ‘holding back’ subsidy to see what happens, and subsidy ‘bonus schemes’<sup>537</sup> ties itself in knots.<sup>538</sup> If a low-efficacy target has been set, the follow-on fight against long-term viral insurgency is mirrored in the struggles to get the bonus scheme to work, with the subsidy fund being depleted all the time. The bonus subsidy scheme becomes just as complicated as the original follow-on subsidy scheme, has to be set in advance, and is riddled with risks to developers, with ‘rent-seeking’ and corruption and dangers of data distortion. Indeed, it is hard to imagine that such schemes could ever be made to work or ever be believed. No wonder this was removed in the original key models.<sup>539</sup> We won’t even go near the layers of liability and safety issues impacting on all of this.

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<sup>535</sup> MVTR p3.

<sup>536</sup> RMSR p3.

<sup>537</sup> “The Bank may want to commit itself to make additional resources available and pay a higher price for vaccines which outperform the minimum standard.” Line taken from “A World Bank Vaccine Commitment.” Glennerster, R., and Kremer, M., April 2000, [www.iaen.org/files.cgi/80\\_kremerglenn.pdf](http://www.iaen.org/files.cgi/80_kremerglenn.pdf).

<sup>538</sup> See Farlow, A.W.K., 2004, *ibid.* Section 7.6.

<sup>539</sup> Kremer Appendix 3.

### **7.7. Will the APC subsidy pool need heavy ‘topping up’ later?**

Remember that we are not discussing the notion of a, possibly very large, purchase fund to procure products based on information available much later in the R&D process, with competition at the manufacturing stage. Neither are we referring to contracts to pay for production capacity (which are a sort of ‘pull’ instrument). Instead, the APC subsidy scheme – supposing it is not just a Rube Goldberg machine to pay a large sum of money to one large developer – refers to a ‘legally binding’ set of contracts, with discretion to lower terms, to determine how a *fixed* sum of *R&D subsidy* gets distributed over different generations of vaccines according to a set of terms fixed in advance – both those vaccines that are a partial improvement and those that are a large improvement – so as to incentivize follow-on developers and to encourage the development of higher quality vaccines.

#### **A fixed fund**

Even sticking to the presumption of a fixed-size subsidy pool for a moment, somehow the APC scheme would have to ‘know’ how much to ‘hold back’ subsidy payments to early vaccines. Observe how very different this is from how a standard market, with active price signals, would work. With no price signals and a ceiling on subsidy funds, the APC requires terms to be set correctly at the start so as not to have too much of the fund used up ‘too early’, and for *purchasers* to be well informed about all potential future vaccines. Otherwise, those investors into ‘better’ vaccines may come to believe that their products will arrive *after the subsidies are all gone*. This is difficult to achieve under ‘normal’ circumstances, never mind for imperfect vaccines that somehow have to integrate with a package of measures, in often highly dysfunctional settings, interacting with other funding mechanisms and a limited-size subsidy pool, over time.

#### **Purchasers do not ‘decide’**

That this ‘hold-back’ could be achieved is undermined by purchasers anyway. We already found, in Section 4.2 above that if purchasers face a flat \$1 price (as claimed), this will not work. Contrary to a normal market, all price signals have gone (including the connection of price to quality). Purchasers could not *themselves* ‘drive’ the *efficiency* of subsidy (re)allocation, even if they drive the sales. They can only make their decisions relative to the rules set up at the start of the scheme and by the bounds of discretion of the committee running the scheme, a committee that has to somehow know how much to ‘hold back’ on early subsidies, based on their knowledge of the scientific possibilities, the underlying R&D costs, and the benefits of vaccines of different efficacy and duration.

That countries themselves have information to make ‘globally efficient’ choices is stretching things a bit too. How, for example, do such countries ‘know’ about future potential vaccines so that their behavior incentivizes the creation of these ‘future’ vaccines as APC advocates claim it would? This issue never arises in a normal market. Advance subsidy schemes with a limited pot of funds driven by ‘country-level decision making processes’ presume countries know all this information.

Yet again, we find advocates of malaria APC subsidy schemes hiding behind the purchasers: “The power to distribute the funds would not lie in the hands of the

adjudication committee. No funds would be distributed unless and until developing countries decide that they want to use the vaccine...In particular, it would not be responsible for allocating funds for R&D, or for deciding which company received the return.”<sup>540</sup> The motto that “purchasers decide” is designed to absorb some of the sting of those who argue that the subsidy scheme would struggle to achieve an efficient (re) allocation of the subsidy pool, and not just collapse down to be spent on the ‘first’ vaccine even if very low value.<sup>541</sup>

### **Will the subsidy pool need to be even bigger?**

On the one hand it is claimed that “The funding now available for public-private partnerships is not sufficient to create a pipeline of second-generation products,” and that “even if this additional funding were available, it would not be enough to generate the amount of investment needed to produce an adequate pipeline of vaccine candidates to produce a reasonable chance of second generation products and a vibrant market.”

On the other hand, we are told that an APC subsidy scheme “can be designed [but it is not explained how] to create incentives for new products and competition,”<sup>542</sup> and efficient follow-on “can be achieved [again, it is not explained how] by providing for competition (encouraging innovation for more efficacies products after the discovery of vaccines that meet the AMC standards),”<sup>543</sup> by somehow designing the subsidy rules ten or twenty years out to leave just enough in the subsidy pool for follow-on developers.

There is, after all, a need to “continue to introduce better vaccines after 2015,”<sup>544</sup> and this has to be incorporated in the rules *now*, in order to get investments *now*. “Design” includes the *size* of the funds made available. CGD, for example, claims that though APCs will “require the sponsors to enter into an agreement, enforceable by law, to make multiyear payments of uncertain size and duration... to an unknown recipient at some unknown time in the future,” nevertheless the commitment has “a known upper limit.”<sup>545</sup> To cover this limit, a claim is then put in for 6 diseases for \$20bn (see the Tremonti Report, and contrast it with the remarks that APC advocates make about unrealistic expectations regarding PPP funding levels).

However, it is also claimed that the subsidy pool could not be fixed in size and yet still achieve this result:

*"It is difficult to get the right quality, in particular to reward follow-on products that offer higher quality. Our view is that it should be possible to set an effective quality threshold, and that the terms of the APC must allow for superior quality follow-on products to be used...(However) there may not be enough money left in the initial APC to*

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<sup>540</sup> Barder et al. 2005, *ibid.* p7.

<sup>541</sup> Farlow, A.W.K., 2004 showed many ways for such schemes to collapse in self-fulfilling fashion down to just one seller.

<sup>542</sup> Barder et al. 2005, *ibid.* pp. 2-3.

<sup>543</sup> Tremonti, G., 2005, *ibid.* p.ii.

<sup>544</sup> VMSR Group C p21.

<sup>545</sup> CGD, April 2005, *ibid.* p59.

*reward the R&D involved in developing some of the superior follow-on products. This is quite possible, as the commitment is only designed to generate at least one product that meets the quality threshold. Clearly a view would have to be taken by the donors as to whether they wished to finance follow-on products with **additional money**. This would be a separate investment decision from the original APC.*<sup>546</sup> (emphasis added)

#### **APCs are supposed to be R&D devices**

The problem is that APCs are not procurement devices; they are R&D repayment devices. The whole point of such devices is to take away the risk that funds will not be there to repay firms their *expected* R&D costs. Efficient incentives require each generation of products to cover their *expected* R&D costs; later products will not be incentivized if this expectation does not hold *from the start*. It follows that, so as not to harm investor confidence via time-inconsistency problems, any ‘additional money’ for follow-on vaccines should be credibly promised in advance if it is not part of the original APC subsidy pool. But this makes the ‘additional money’, by default, part of an even larger original subsidy pool. The Tremonti Report argues that “AMCs should be tailored to establish appropriate incentives for stimulating investment in the research and development of the relevant vaccines (including continuing research into new and improved vaccines after discovery of the first generation of effective products)”, but time and time again Tremonti offers no indication as to how this would be done in practice.

#### **All potential monies need spelling out at the start**

If the notion is that the original pool of funding would pay for a 50% efficacious malaria vaccine and leave little or nothing for the 80% efficacious vaccine, and that more funding will somehow have to be made available for the 80% vaccine, then this needs to be explicitly spelled out from the start. It clearly intensifies the risks of time-inconsistency to follow-on and goal-2 investors and harms the second goal.

It has even been argued (by IAVI) that an APC could be increased by the back door. If late arrivals to the APC do not recoup all their development costs, they can charge a higher long-term price until they recoup their development costs (an effective extension to the original APC). However, firms would be well to doubt such notions, since if an APC is being used as an R&D instrument, statistically, ‘winners’ would be expecting to cover – via their APC payments – many times their actual out-of-pocket R&D costs. Hagglng to get a higher long-term price *ex post* on top of what already looks an extremely profitable deal already would appear profiteering, even if it was only an attempt to achieve a fair *ex ante* return that takes account of attrition rates (i.e., all the failures) and capital costs.<sup>547</sup> Most large firms would wish to avoid such reputational damage. They would also find themselves competing against other firms supplying at very low long-term price (according to APC advocates). How could some eligible

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<sup>546</sup> Towse, A., and Kettler, H., “A Review of IP and Non-IP Incentives for R&D for Diseases of Poverty. What Type of Innovation is Required and How Can We Incentivise the Private Sector to Deliver It?” April 2005, p87.

<sup>547</sup> Spot how we are repeatedly basing arguments on the presumption that we are not simply facing a Rube Goldberg machine.

markets be forced to buy at their higher prices? This would further aggravate reputational damage to follow-on firms.

### **Cost-effectiveness**

This ‘additional money’ should be included in the overall budget constraint and worked into all cost-effectiveness figures too. This means an end to methodologies – such as Berndt et al. and Tremonti – that simply divide an essentially random figure, like \$3bn, by DALYs saved to give a ‘cost per DALY’ saved, and then use this completely meaningless figure to justify targeting a low efficacy vaccine even though additional money will be needed for a higher efficacy vaccine later, with all the cost-effectiveness implications of this ignored. If two or more lots of APC subsidy funds will be needed, before and after 2015, this needs to enter calculations *now*.

### **Risk of polymorphism and antigenic variation**

Clearly, we want to incentivize firms to invest in capacity to tackle problems such as polymorphism and antigenic variation, and we want them to have incentives not to waste resources. At the same time, however, it is difficult to imagine that an ex post committee-run subsidy scheme would not create a great deal of risk for firms from the way the committee would respond to these problems. These risks impact heavily on the value of investments, and are probably, already, a big factor in stopping firms from investing in such vaccine R&D.

Responding by making the APC subsidy pool even bigger to ‘cover’ all the risk – and in the process facing firms with a great deal of reputational risk – is not the most obvious first-line defense. We find, below, that a more appropriate response might be to think more about the underlying financial problem and the sort of instruments and institutions, such as PPPs, that might help to encourage such investments but also help to cope with the risks. This requires us to study much more the nature of the risks, how to ‘price’ risk, and to start developing such instruments for handling risk. An obsession with the sheer size of an APC has proved to be a hugely effective distraction from this.

### **Funds unbounded at top, yet still highly uncertain**

We hear that “there is need to balance the need to save lives as soon as possible with the need to continue to improve the efficacy of later-generation malaria vaccines.”<sup>548</sup> Yet, there is no model of this tradeoff under any relevant resource constraint (including tradeoffs between different efficacious vaccines, vaccine technologies, drugs, control, etc.). It is difficult to imagine resisting the political pressures to exhaust a fixed size subsidy pool on the early vaccine to make an APC ‘work.’ It is even more difficult to believe that politicians would agree to an APC growing at sufficient rate, and difficult also to imagine that the need for top-up ‘additional money’ will not undermine R&D incentives. This danger is even reflected in the wording of the recently proposed Kerry-Lugar Vaccines for the New Millennium Bill, which says that new funds will have to be created by the US Treasury *every time* a new vaccine is created.

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<sup>548</sup> MVTR p5.

The current thinking seems to be that a separate \$3billion (or over \$5bn if judging by recent G8 documents) will be created for each vaccine, so that even when one is on the market, there could be another APC for a vaccine that ‘jumps higher’. However, if the notion is to augment the market of a first generation product, the augmented sum will have created no incentive for other developers (it was not promised in advance), and we still face the sole supplier problem (the first generation product has the IP).

The danger is that the fund becomes unbounded at top, yet still highly uncertain to investors – killing dynamic R&D incentives. Given the constraints on malaria funding across the board, and the fact that only recently has the global community been investing more than \$60m per year in malaria vaccine research, it is rather amazing to see the casual assertion that several hundred times that amount will be created as and when APC advocates deem it will be needed and that investors can believe this.

### **7.8. The risks of using the 50% goal as a way to pull in more funding**

The Malaria Vaccine Technology Roadmap argues that the “The 2015 goal conveys the urgency of the need for a malaria vaccine as soon as possible”<sup>549</sup> and the Malaria Vaccine Vision Meeting argues that “a focus on achieving some early successes should be the logical starting point,” with this then interpreted in the Roadmap as a 50% efficacious vaccine (since ‘early success’ could have been interpreted in many other ways).

It may therefore be that the 50% goal could simply be used as a signaling or a policy advocacy device, in the hope that somehow ‘success’ on a potentially less efficacious early vaccine can be used to loosen later resource constraints for later ‘better’ vaccines. In certain respects, this may be a rational strategy. However, it also carries risks and costs if it is operationalized, that need to be spelled out:

- 1) The inferior goal has associated costs that a ‘better’ goal would not have and these costs are borne by other parts of an overall package of measures, even if it is not the most efficient goal from the perspective of these other parts of the overall package. Not only is there need to fund continuous treatment programs but the package of other control measures is potentially distorted;
- 2) It may be that it forces acceptance of too high a production cost;
- 3) Similarly, there are knock-on consequences if less efficacious vaccines have negative consequences too (such as for natural immunity in a population, etc.). These costs again fall outside of the subsidy mechanism, and on to funders outside of those funding the vaccine discovery effort;
- 4) It signals an intent to defy APC logic, by allowing APC funds to be ‘wasted’ on an early inefficient vaccine in the hope for more APC funding to be created later,

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<sup>549</sup> MVTR p4. Though this is not a particularly meaningful statement. Would one really pitch to the lowest common denominator for a vaccine that would then struggle to last and cost a great deal to integrate with other treatments and, by draining funding, harm better vaccine creation and overall malaria control? The “urgency of the need for a malaria vaccine as soon as possible” is taken as read by everybody whatever approach they support. The issue is whether the goal structure, including whether it is *fixed* or not, is as rational and efficient as it could be.

- but this creates negative sentiment to investors. The risk of first goal investors rises, since there are worries about credibility. The risks of second goal investors rises because of the waste of the first goal and the uncertain realization of the top-up subsidy funds for the second goal;
- 5) We may not get a 50% vaccine anyway (too many problems with parasite/human interaction, liability issues, ethical issues, insufficient candidate vaccines, etc.), and meanwhile, by the logic above, firms are disincentivized from the goal-2 vaccine activities, that is then put behind schedule. Failure to meet the first goal, or ‘success’ of a low-value vaccine that countries are then forced to use (or are distorted into using by subsidies) may undermine further funding for R&D on other parts of a ‘better’ package of measures;
  - 6) It ignores political constraints. The budget constraint is dependent on the interest of politicians, an interest that waxes and wanes. Their lack of understanding of the issues – reinforced by any policy ‘spin’ they are fed – can make them feel that a problem has been cracked when it has not and they lose interest. There seems to be a strong presumption that the budget can be ‘blown’ and that a new budget will be generated later through the political process. Yet, can it be presumed that a follow-on generation of politicians will put more money into the effort? As Barder, Kremer, and Levine put it “because of the risks of volatile political commitment” this is “making a strong assumption about the likelihood of continuing political commitment over the years ahead, and there would be no legally binding framework to lock in such commitments.”<sup>550</sup> As Moran et al. observe, APC subsidy mechanism “are no more sustainable than other publicly-funded approaches.”<sup>551</sup>
  - 7) If a lower-quality target is set that turns out wrong and needs revising, and, indeed, fails miserably, this sends out a bad signal. We have seen all too many cases of over-hyped claims harming later efforts when they turn out less rosy than originally spun;
  - 8) There are ethical issues of targeting an inferior vaccine route, both from the perspective of trials but also from the perspectives of end users of less efficacious products and of therapeutic products. In addition we have many cases of highly efficacious vaccines getting much less than complete coverage. Should the ethical emphasis instead be on getting good vaccine(s) that get higher levels of use?;
  - 9) It may not be the most efficient way to crack the budget constraint anyway. Treatment/prevention costs from the use of the low-efficacy vaccine are higher (ignoring the point about distortion towards the overuse of a low efficacy product), so overall costs are being pushed up in the hope of encouraging more funds later;
  - 10) If the first goal is non-optimal anyway, but being forced on investors, they will be weary of responding – the finance metrics will just not add up;
  - 11) If the first goal disincentivizes ‘collaboration’ (say in combination with an APC that strongly emphasizes non-collaboration) it will prove self-defeating;
  - 12) It is not clear what all the liability issues are from encouraging low efficacy goals;

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<sup>550</sup> Barder et al. 2005, *ibid.* p12. Though they were referring to the original APC on the presumption that the funding extension problem discussed here would never arise.

<sup>551</sup> Moran et al. 2005, *ibid.* p63.

- 13) On the assumption that all the subsidy pool is drained away by the first goal, leaving nothing for second goal, it will provide even less of an answer as to where funds for the second goal will come from.

Given the budget constraints and the needed interaction with other interventions, and the expected costs of a less efficacious vaccine, this simply ends up being a rather expensive, round about, and potentially more costly route for raising further funding for goal-2 vaccines. If malaria vaccine R&D has survived on paltry sums for years (only just breaching \$65m a year), and then \$6bn or so is blown on a poor outcome, is it realistic to expect to be able to ask for more later?

All of this simply points up yet again that we still have not done a hard-headed calculation of the costs of goals-1 and goal-2 under *any* global budget constraint, or articulated the assumptions being made about relaxation of funding constraints in the future. We are left with a whole range of long-run supply and cost issues unresolved, and funding for the 80% vaccine unexplained. Each of these feeds back to harm R&D incentives, and harms the speed of development and ultimate access to a vaccine.

### **7.9. Alternative 'goals' to remove inefficiencies and risks**

If goals are to be based on product characteristics, the above logic suggests that to avoid the dangers of goal-1 – *especially* if it is *operationalized* in a fixed commitment such as an APC – there should be only one ultimate goal with short-term deviation from that one ultimate goal democratically discussed at the time and treated as an 'option', a flexible choice based on cost-benefit analysis based on information and discoveries over time. If the first target is always logically subordinate to the second target, why have it? Why tie one's hands?

However, rather than goals based on the characteristics of a specific vaccine, it might even be best to have *other* goals instead to demonstrate progress.

For example, goals could be based on:

- 1) Process metrics, such as the number of candidates in the pipeline. Some voices in the Roadmap process suggest shifting the focus of the second goal to this, and others argue that we “Must focus on process rather than technical goals,”<sup>552</sup> (underline in original). Others comment “Establishing a firm date of 2015 places too much emphasis on candidates already in the pipeline such as RTS,S. Accelerating the number of candidates to choose from (more candidates in a shorter time period) should be a goal as well,” (brackets in original),<sup>553</sup>
- 2) Risk reduction metrics, such that demonstrated success at reducing risks, and the articulation of this as a 'major achievement' even if there seems no product to show for it. Of course this requires better modeling and measurement of risk. One

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<sup>552</sup> RMSR p1.

<sup>553</sup> MVTR p9.

- side-effect of preset APC subsidy ideas is a complete downplaying of a range of risk issues, with the solution proffered being to make the subsidy pool bigger;
- 3) The nature of candidates in the pipeline;
  - 4) The quality of vaccine trials;
  - 5) The number of developing country trial sites;
  - 6) The goal of having better tools available to select candidates (Roadmap feedback also suggests this);
  - 7) More metrics of sharing and coordination, for example, early successes such as the standardization of assays and reagents: “One approach is to establish a centralized, open center to generate and maintain a repository of reagents and assays. While this initiative will require resources and a collaborative community effort, it could yield some early, tangible successes and help to generate some momentum for increased collaboration.”<sup>554</sup> As the Malaria Vaccine Technology Vision Meeting puts it, we need “one small success to generate momentum. Simple standardization of assays may be a place to start to develop an example of how to coordinate activities.”<sup>555</sup> After all, inconsistent reagents, assays, formulations, and production techniques hinder comparison of vaccine candidates. We therefore know that standardization is very real progress and probabilistically increases the chances of getting a good vaccine. Why could it not make a suitable process goal?;<sup>556</sup>
  - 8) It is also not clear why there is no goal beyond severe disease and the under 5s (Another RMSR comment).

**Many scientists urge not concentrate on product-characteristic-specific goals**

Many involved in the Malaria Vaccine Technology Roadmap have urged policymakers not to fix goals based on specific product-characteristics, including excluding species other than *P. falciparum*, but especially *P. vivax*. As a thought experiment, imagine the extreme case of a world of deep scientific uncertainty relying solely on push devices for the time-being.<sup>557</sup> Given the current very low pull power of incentives (especially for an 80% efficacy goal at a 20 year horizon) and the very low logic of fixing product-specific goals for operational purposes now, product-specific goals at this moment in time would make little sense; outcomes would depend on what the push and unfolding knowledge (about many aspects of the problem and not just about the vaccines) showed was possible and needed.

Product-characteristic goals are non-judgeable anyway at time-frames of any interest (i.e. they only get judged at the end). Other goals make more sense once one realizes that the interest in product-characteristic targets only came about because of the desperate need *now* to permanently fix a ‘pull’ scheme *now* for a 20-30 year horizon. The whole policy-making process has gradually been turned on its head by this need to get a ‘result’ to feed the politicians, such that we now cannot tell whether the eventual goals and incentive

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<sup>554</sup> MVTR p10.

<sup>555</sup> VMSR p13.

<sup>556</sup> Though there is some difficulty in coming to a consensus on standardizing assays, when different people are looking at different alleles (see VMSR p10).

<sup>557</sup> Extreme to make a point, and not to suggest a personal position being taken.

mechanisms have any basis in the science or in the politics, with the malaria science made to fit the policy instrument, and not the other way around. Moving towards process and other-metric goals, and away from fixed product-specific and region-specific goals, may help put some balance back in to policy making.

## **8. Malaria Vaccine R&D: More ‘Risk’ Issues**

### **8.1. Good and bad private sector risks**

The section looks at a range of risk issues. To a specialist in risk, the language here will seem very rudimentary. In an area of genuine uncertainty, it may even be too reassuring to use the language of risk, since it may suggest something much more readily quantifiable than true ‘uncertainty’, in the Knightian sense,<sup>558</sup> would allow. It may also suggest too high an ability to hedge<sup>559</sup> risk than is actually the case. Unfortunately, the collapse of interest in risk issues has accompanied the rise of interest in a quick-fix APC solution – which masks all risk issues in a big payment. Too much attention to risk issues would have also caused awkward issues for a methodology that has based itself only on *revenues* from product development, ignoring all cost and finance issues.

#### **8.1.1. Risk versus incentive**

Stakeholder feedback to the Malaria Vaccine Roadmap says that there is a “Growing need among funders, governments, industry, and researchers to mitigate [the] high risk of malaria vaccine R&D.”<sup>560</sup> There is need to: “Create an incentive for small, medium and big pharma to buy in to malaria vaccines while minimizing their risk.”<sup>561</sup> But little is provided anywhere in the literature as to how this is to be done. This desire to remove risk recognizes that it is not just ‘price’ times quantity of sales, and overall size of ‘subsidy’, that feeds the economic return to developers. The quotes beg the question of what is a ‘good’ risk for the private sector to face and what is a ‘bad’ risk, and hence the ‘optimal’ *amount* and *nature* of risk? It is standard in economics for there to be a tradeoff between risk and incentive. Whilst there is clearly much risk that can be removed from malaria vaccine R&D, there is also other risk that plays a useful incentive purpose. For an economist, too, it is not risk from individual sources that matters per se, but how those risks co-vary with each other.

For efficiency, the general principle is that private firms should face those risks that they can be motivated by and/or that they are better able to hedge, but they should be shielded from those risks that will not motivate them and that they cannot hedge. Stripping all the interesting scientific complexity out of APC models, rules these issues out from the start and results in APC models (to the extent that they mean anything) being all about the first kind of risk only, even in cases in which this is far and away not the only kind of risk present.

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<sup>558</sup> Knight, F., *Risk, Uncertainty, and Profit*, 1921, Boston, MA: Hart, Schaffner & Marx; Houghton Mifflin Company.

<sup>559</sup> In finance, a hedge is an investment that is taken out specifically to reduce or cancel out the risk in another investment.

<sup>560</sup> MVTR p5.

<sup>561</sup> RMSR p26.

### **8.1.2. Optimal risk**

An economist would *not* interpret the phrase “minimizing their risk” as meaning to “get rid of all of their risk.” The word “minimize” can only ever be thought of relative to a purpose.

Solving how much risk private players should face (i.e. the “minimize their risk” bit), requires solving jointly the structure of finance, the type of R&D incentive instruments used including how much APCs should be relied upon (since the whole point of APC subsidy schemes is to face firms with risk), how much collaboration should be used (and the nature of financial instruments and combinations of institutions to achieve it), the use of PPPs, the distribution of IP over players and over time, and the allocation of ‘risk’ across players. Toying with the parts separately, or putting all emphasis on one in lobbying efforts, can only generate waste and inefficiency.

APC advocates have had to ignore the risk story entirely, since once such a story is allowed to surface, the APC becomes a much blunter instrument, and much more complicated to operationalize. If *all* risk is taken off firms, an APC will not be used. If a proportion of risk is left on firms, the whole APC will not be used. By greatly simplifying the scientific complexity of malaria vaccine R&D and the strategic set-up of the industry (Kremer Appendix 3) to cover only the sort of risk that firms can control and fully hedge, a solution was generated that is ‘totally APC’, and based on just ‘price’ times quantity of sales. Furthermore, we will also discover shortly that the risk of the APC *itself* cannot be hedged and that such models therefore presume that APCs work perfectly and are risk-free themselves every time. This report concludes that this is far from the reality.

Of course, if we knew more about risk, we could quantify it more. This would also help us to set up metrics to target useful risk-specific goals, and avoid the dangers and inefficiencies of concentrating on metrics defined only by end-product characteristics. Hopefully this section will also help the reader to think a bit more about these alternatives.

### **8.1.3. Interactions of risk**

Interactions of different risks complicate matters. It may be that there is a particular ‘risk’ that we would like firms to face. For example, we might like firms to face the cost of selecting inherently ‘bad’ vaccine candidates.<sup>562</sup> But it may be that because of risks that are still in the system – dysfunctional delivery systems, failure to coordinate on the right ‘package’ of measures, hopeless demand forecasts, scientific difficulties, lack of coordination across players, etc. – we are prevented from facing firms with all of this ‘good’ risk. Even after tackling these other risks, those risks still remaining that are outside of the control of firms and their ability to hedge risk away, will either have to be worked into the way firms are compensated (the size of APC subsidies they get will have to be adjusted), or will need to be shared with other players via non-equity forms of

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<sup>562</sup> Many candidates will not pan out. That does not make them ‘bad’ choices. The notion is that the quality of choice over research leads is a function of how much penalty the chooser suffers if they put little effort into the choice or are ‘careless’ in the choice of vaccine leads to follow.

finance. Indeed, the latter is at the heart of PPP models. It follows that decisions about the split over APC and PPP and control over IP can only be worked out in a framework analyzing the risks.

This possibility is hinted at in the Tremonti Report, where it is recognized that the value to investors of an APC/AMC is highly dependent on other parts of the package of support measures: “In the absence of complementary national investments and commitments and continued donor investments in research and system support, AMCs will not succeed in achieving their goal of providing sustainable access to vaccines.”<sup>563</sup> The Tremonti Report does not however explore the impact on investors of this risk, and hence the impact on the strength of any APCs set up to feed to investors.

## **8.2. ‘Blockbuster’ and reputational risk**

The chief point of mechanisms, such as APCs – and other ‘blockbuster’-based systems<sup>564</sup> – is to exploit the value of putting risk on to firms, on the understanding that firms are best positioned to deal with this risk and that it will incentivize them to choose vaccine leads wisely and generate incentives to put in ‘effort’. At one extreme, if firms are fully insured – they get a flat payment regardless – they face no risk, but their incentives are weaker. As risk increases, at some point the marginal incentive impact of extra risk is less than the marginal cost of imposing that risk, and there are potential gains to be shared between sponsors and firms by not imposing risk on firms beyond that point.

Facing the private sector with *all* the risk, ‘blockbuster’-style, may have negative consequences:

- 1) Incentives are less than optimal, rates of R&D are lower, and costs are higher (finance costs have to contain the cost of this risk). One reason private firms do not invest in malaria, HIV, and TB vaccine R&D is not because of low purchasing power of potential users, but because the risk set-up is totally wrong, and trying to use an ever-bigger APC is not the most efficient way to overcome these risk problems. Indeed, it would make many of them worse, especially that of reputational risks;
- 2) Lack of willingness to ‘share’ information if ‘sharing’ will risk undermining the value of investments, an affect that may be especially strong in a time- and fund-limited settings such as an APC;
- 3) Too much reputational risk. If (on the assumption an APC works as an R&D device, which this author no longer believes) 10-20 firms are each putting several hundred million dollars into the R&D process, building on top of an already huge collaborative process funded by taxpayers, charitable foundations and others, but

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<sup>563</sup> Tremonti, G. Backup Papers, 2005, *ibid.* p13.

<sup>564</sup> The term ‘Blockbuster’ is descriptive and not pejorative. If a CGD-style APC is *not* generating a blockbuster outcome, it is failing as an R&D instrument.

there is only one ‘winning’ firm, then that firm has to be paid all the out-of-pocket R&D costs of the 10-20 firms plus all capital costs, receiving a multibillion dollar payoff and taking the PR consequences. Given the small expected size<sup>565</sup> of a malaria, HIV or TB market, this may even be worse when viewed from an ex ante perspective when the expected PR damage across an entire portfolio of products, may heavily outweigh the expected profit. Firms may wonder whether they really do want to inflict the same sorts of problems on themselves as they faced with AIDS drugs – and this all for a low efficacy product that might lose its usefulness anyway;

- 4) There is a great need for clinical trial facilities for large-scale vaccine testing, especially in resource-poor settings where the disease of interest is endemic. How does this fit alongside ‘blockbuster’ incentives that require ‘winning’ firms to get back many times their outlays? How is trust not harmed? Is this problem not already harming the involvement of large pharmaceutical firms? How is corruption in the ‘windfall’ part of the process to be avoided?;
- 5) Once other methods are being used,<sup>566</sup> it becomes less apparent what risk is being borne by firms. Neither is it clear what they are getting as reward (e.g. IP) for the risk they do shoulder. One correspondent complained that the whole point of an APC is to force entrepreneurial risk onto firms, yet that GSK had hardly borne any of this risk in the case of its candidate malaria vaccine and would still expect a big pay-out: “For RTS,S most of the costs have already been engaged and to a large extent by public funds (US DOD, WHO, NIH, EC, etc.). Only a few companies will ever have the sufficient S&T assets on their own to come into the process and that is the reason why they [Tremonti and GSK] claim so big. On the other hand, a consortium of companies and public sector bodies can work better and cheaper.”

### **8.3. The risk of production plant that is never used**

One risk that has not really been tackled in any of this literature, is caused by the high probability that expensive manufacturing capacity for highly imperfect vaccines is replaced, and the risk attached to capacity put in place for vaccines that ultimately fail. This has been undermining R&D incentives for malaria, HIV, and TB vaccines for years (the author can think of HIV vaccine cases) but hardly ever gets mentioned. It is probably fair to say that this has not really arisen before in the context of previous vaccines to anywhere near the same extent. In the case of meningitis conjugate C in the UK in the 1990s, often used by APC advocates to justify support for an APC, this was not a problem, since *all* developers made sales, and covered *all* their costs. No firm put in capacity that it did not use.

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<sup>565</sup> I.e. it may be large, but the probability of getting it is small.

<sup>566</sup> Maybe through necessity, if the science is complicated and it is difficult to get equity markets to handle the information in the ways implied by the APC literature.

This is, in a sense, an extreme case of follow-on, when a product jumps all previous products. What are the incentives to expediently create new capacity when vaccines are replaced? Since replacement is only statistical, how is this handled in the size of, and the rules for distributing, any available APC subsidy? Meanwhile, this need takes place against the background of needing to maintain the trust of developing countries in vaccine products and in the underlying ethical basis of trials. This makes it less tenable to keep 'replaced' vaccine capacity going.

#### **8.4. Risk, sharing the value of IP, and the role of PPPs**

This raises the issue of how much IP and monopoly pricing power 'winner(s)' should be rewarded for the amount of risk they take on and given the amount of scientific risk shouldered by other players. The thoughts above about the optimal sharing of risk suggest also an optimal share of IP – and certainly not that the 'winning' firm(s) get all IP as currently suggested in the GSK-APC case. Setting up a mechanism that allows all of the IP-bargaining power to winner(s) even though this builds on a hugely collaborative effort, runs the risk of facing winner(s) with a huge reputational backlash and future market battles reminiscent of those with AIDS drugs. This feeds back to reduce their R&D incentive in the first place.

One of the reasons private firms might value PPP-style arrangements, instead of APC-type arrangements, is to avoid some of this risk. Ex ante, when no firm knows if *it* will be the winner, and all firms have 'equal' likelihood of 'winning', the present discounted value of a highly risky 'blockbuster' reward (including all the risk of the dysfunctional markets) may be comparable to a much smaller but more certain payoff via mechanisms, such as a PPPs, that share risk with other players (including governments and other funders). Once reputational risk is included, the 'blockbuster route' will have even less expected value from an ex ante perspective.

A 'blockbuster' APC route may only appeal to a firm that is much further in the process and regards itself as already having a large first-mover advantage. That is, a firm's response to a question about what it prefers – APC or PPP – suffers from time-inconsistency:<sup>567</sup> Ex ante, before knowing its drawing from all the potential vaccine leads, the firm may prefer the PPP route, but ex post, when it perceives the 'upper hand' and a first-mover advantage on a particular vaccine lead, it claims an interest in an APC. This seems to have recently happened with GSK with its candidate RTS,S malaria vaccine.

#### **8.5. The time-inconsistency of APCs: A risk that cannot be hedged**

'Time-inconsistency' refers to what happens when firms have sunk heavy R&D costs, and buyers subsequently have the power to bid prices down to levels that do not cover –

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<sup>567</sup> Even if the question means anything, which usually it does not (see below).

through the product prices of the winning firms – the *collective R&D* costs of all firms. Knowing this *ex ante*, no firm invests.

APCs are supposed to tackle this time-inconsistency problem through a commitment to purchase at a fixed set of terms (though we have repeatedly found that, because of all the unknowns, this is not true). CGD proposes an APC with a two-stage pricing structure to ensure that the “*producer received a fair return on their investment*” but that “*once this return had been achieved*” prices, it claims, would fall. A committee we are told will determine at a later date any adjustments needed to achieve this.

Unfortunately, given the potentially huge levels of already (and sometimes long ago) sunk investment, time-inconsistency does not disappear under an APC. It simply changes form and shifts on to the shoulders of the APC committee, political processes,<sup>568</sup> faulty allocations across developers, and quality issues.<sup>569</sup> Indeed, just making an APC subsidy scheme even bigger to try to compensate for the risks of this, might simply aggravate the risks.

We remember that getting back development costs in the *ex post* sense is insufficient in the *ex ante* sense. The relevant required return to investors is *before* firms invest and is based on:

- 1) Expected trial attrition rates;
- 2) Expected capital costs, including any necessitated by the risk of the R&D repayment mechanism itself;
- 3) Expected portion of the market allowed to each firm by the committee(s);
- 4) Expected pricing structure allowed by the committee(s).

This *never ‘looks fair’ ex post*. It must be fully understood by all firms, buyers, political commentators, and the general public that ‘*fair return*’ is *ex ante* return. APCs are attempts to legally fix this return in advance of R&D investments. But it is very difficult to make this credible, and for this not to cause problems for firms later, reflected then in poor response of firms to APCs.

### **A simple example**

Let us run a simple example. Once again, such examples only make sense if we presume many parallel R&D efforts and that only one or two winners get paid actuarially fair rewards – i.e. that firms treat investments as high-risk gambles with a large, but ultimately only just profitable<sup>570</sup> payoff given all the failures, with most firms getting

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<sup>568</sup> Before discounting the notion of time-inconsistency of political processes, think what would happen if, after ten years, nothing had come out of the APC. See also Farlow 2004, *ibid.* Chapter 7 for the political side of this in recipient countries under an APC funding scheme where political time-inconsistency leads to the self-fulfilling over-use of ‘poorer-quality’ vaccines. All of these make it often time-inconsistent to encourage investors to invest in more difficult and/or higher-quality outcomes in the first place.

<sup>569</sup> In particular the time-inconsistency of promising payments for investors into follow-on vaccines, only then to renege when all of the subsidy funds have gone (or to have to rely on new pull funds and fresh terms set after the investments have been sunk) will feed back to weaken incentives to engage in follow-on innovation.

<sup>570</sup> Driven to this by entry to the industry.

nothing. This reasoning would not make sense if one developer is being lined up to take all the subsidy pool, or if self-fulfilling pressures generate this outcome.

Imagine if, instead of the ‘fair’ return of \$6.25billion for a couple of hundred million dollars’ worth of out-of-pocket research costs, a firm expects, say, 75% chance of purchases at the agreed fair \$6.25bn, and 25% chance of the committee renegeing and paying only half. Even in the bad state, this still ‘looks’ a ‘very good’ deal from the public’s ex post perspective. The problem is that this is not a ‘fair’ return judged ex ante. The ex ante expected value of investment has fallen from \$6.25bn to \$5.47billion.

If \$6.25bn *was* the risk-adjusted figure required to generate optimal research intensity, and if we wish for vaccine development to not be slowed by this risk of renegeing, the promised payment by the sponsor has to *rise* to at least \$7.14bn<sup>571</sup> (assuming firms are risk neutral), generating a premium of \$890m to compensate for the risk of renegeing.<sup>572</sup> If vaccine developers are risk-averse, the figure must be even higher.<sup>573</sup> Sponsors pay more for the same level of research intensity.

The problem is that fighting ex post for the ex ante ‘fair’ return looks ‘greedy’. After all, the general public knows about the firm’s out-of-pocket R&D costs – supposedly firms have fed information to those running the APC scheme to help make the scheme work<sup>574</sup> – and about the very ‘generous’ payment the firm is getting relative to those out-of-pocket R&D costs. Clearly there are heavy reputation risks/costs to large pharmaceutical firms from the ex post fight to get the ex ante fair deal.<sup>575</sup> Imagine what would happen to all the figures above if the complexity of generating, say, malaria or HIV vaccines (the first vaccine and the required follow-on vaccines) was calculated to need \$10 billion or \$15 billion if using an APC (in order to have enough vaccines in trial with most developers getting nothing)? Would firms be so sure of not suffering time-inconsistency at the hands of the committee running everything when the scheme pays out at the end? Is this why CGD fixed the notion that payment should be based on typical drug market revenues and not on the expected costs of developing HIV and malaria vaccines?

### **A risk that cannot be hedged**

Crucially, it would be impossible to hedge this risk, since, unlike scientific risk, it is less obviously statistically random. This risk is only ever likely to be asymmetric and against a firm each time. No financial market would arise to hedge this risk since actuarially fair terms could *not* be set on any hedging instrument. Besides, the APC committee, if it

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<sup>571</sup>  $x$  such that  $0.75*x + .025*0.5x = \$6.25bn$ , if vaccine developers are risk-neutral.

<sup>572</sup> The calculation also presumes that the probabilities are not altered in the process of adjusting up to \$7.14bn. This is unlikely to hold. If the probability of renegeing rises with the APC size, the APC size will have to rise *even further* to compensate. Size settles at the stationary point (if there is one) in this process.

<sup>573</sup> Vaccine developers have different required risk premia, with some – biotech and emerging developers – especially badly hit. It depends on ability to hedge risk.

<sup>574</sup> We repeatedly see that the scheme relies on truth revelation, only to discover strong incentives to not tell the truth.

<sup>575</sup> The limit case of this risk happens when the sponsor reserves the right to abandon the scheme if it is not working.

knew a hedge was in place anyway, would have an incentive to abuse the hedge, and those providing the hedge would not profit from creating the hedge.

We remember yet again the way the key Kremer Appendix 3 model, underlying all APC thinking, not only ruled out most scientific risk but implicitly ruled out any risk of the APC *itself*, especially of the APC committee. APC committee risk, unlike scientific risk, is *not* hedgeable.

One way, possibly, to view PPPs is as a method to hedge this sort of risk, since such PPP institutions, unlike financial markets, hedge across generations and enable firms to avoid this sort of risk (though, of course, replacing it with other forms of risk that we also need to analyze), because firms will not have had to sink the huge costs presumed in the APC schemes before the committee gets to act.

### **Controlling this risk**

In normal market circumstance, not involving an APC and an APC committee, at least a firm would have some control over these probabilities via marketing and price. There are only two ways to control risk in the case here however.

The first way is to capture the scheme early and reduce the number of players (and this may involve strategically holding on to information advantages and not ‘collaborating’) and to ‘rent-seek’. Intuitively, rent-seeking is a way to overcome the lack of hedging instruments. Observe, however, that it is not open to all players equally. Some players have higher ‘hedging’ (i.e. rent-seeking) powers and are more able to hedge the risk away by rent-seeking. This particularly disfavors smaller, less powerful, players, and players further away from the committee and power base.

The second way is to permanently fix the subsidy terms in every detail. Outside of completely fixed terms, firms (especially those lacking power) worry that ex post returns will be bid down to *look* more ‘fair’ ex post or to leave funds for later developers, and they do not invest ex ante. But, in a world of great scientific uncertainty and unknowns, the cost of creating fixed contract terms at 20 year horizons is that those terms are very inefficient.<sup>576</sup> There is a tradeoff between the inefficiency of the permanently fixed terms, that are highly likely to be wrong (and to feed reputational risk) but that at least pose no risk of renegeing, versus the efficiency of having flexibility over terms, but the high risk of renegeing. Both create extra costs and risks to developers.

This problem is especially problematic for:

- 1) Mechanisms concentrating R&D repayment in the ‘end period’;
- 2) Long investment horizons (even tiny amounts of uncertainty about whether the program will be fair or work as promised will compound very heavily);
- 3) The more complex the science. It is inefficient to permanently fix terms but impossible to determine terms after firms have sunk R&D costs without creating

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<sup>576</sup> I.e. there is an option cost/penalty to fixing early.

- risk to firms. Observe how this intensifies problems with HIV, malaria, and TB vaccine R&D;
- 4) The less easy it is to determine ‘rules’ ex ante if rules are not fully fixed;
  - 5) The greater the required ex post discretion and the difficulty of ‘repairing’ bad rules ex post;
  - 6) The harder it is to judge ‘results’ (including the case where judging results is one-off, at the end, and when population level results only show after a delay);
  - 7) Situations where ‘quality’ matters, since time-inconsistency shows up in ‘quality’ as much as in price (see Farlow 2004 Section 7). Indeed, once price is fixed, ‘quality’ and rent-seeking take the strain instead;
  - 8) Situations where reputational damage can be high, for example when companies have portfolios of products, and PR damage harms the value of the portfolio. There may be reputational problems to the ‘winner’ if discretionary elements in the ‘end-game’ have to be fought over, And there may be further reputational damage (and aggravations from non-eligible countries who had contributed greatly to the overall effort) if the program covers only the very small last portion of the overall costs of creating a vaccine, and/or the firm gets all the IP to the vaccine. From the firm’s perspective, the chance of reputational damage will weaken the firm’s ex post bargaining position and increase their chances of facing time-inconsistency. Is it conceivable that a firm that had spent ‘only’ a few hundred million dollars on vaccine research would not face severe bargaining problems in the ‘end game’ trying to extract the ex ante fair \$6bn payment? Firms may simply prefer not to open themselves to such situations in the first place and simply not invest (or they capture the mechanism as early as possible).<sup>577</sup>

Again, it is *expectations* of all this that matter for investors, since we are viewing the APC as an R&D device and not as a device to cover just manufacturing costs.

Can alternative funding mechanisms protect firms from these problems while still giving all players good incentives? For example, an alternative way to reduce the chances of these high-stakes ‘two-stage’ games, rent-seeking and ‘capture’ is to give payment towards R&D costs *before* reaching the purchase stage and, in exchange, remove some of the R&D payment at the end and IP from purchases (i.e. some PPP-type control of IP).

### **8.6. ‘Rent-seeking’, corruption, and reputation risks**

We have already thought a lot about ‘rent-seeking’ behavior, and corruption. Here we are interested in the risk that this creates for players and the direction from which it may come. The intuition here is that although firms might engage in rent-seeking if finding themselves facing the incentive to do so, they might actually rather avoid it in the first place, and choose an alternative R&D funding mechanism: Rent-seeking eats into the collective payoff to be shared; it creates risk that has to be priced in to payments; and it reduces the average quality of outcome and is bad for reputation. The problem is that

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<sup>577</sup> Remember that firms do their reasoning in the ex ante sense, and it is these probabilities that matter.

rent-seeking may be self-fulfilling: If others are doing it, it may be at a firm's disadvantage not to do it, and hence all end up doing it.

We have already seen that the per-purchase R&D subsidy to winning firms, supposedly, is fixed (at, say \$14, or \$24, regardless<sup>578</sup>). Hence the portion of the subsidy pool that a firm gets is driven by the decision of a committee, according to a set of rules (but with discretion). Instead of competing on price and quality, the danger is that firms are incentivized to rent-seek the subsidy pool instead, either through the countries concerned, through international institutions helping with purchase decisions, or via the committee running the scheme. Incentives for this come from two directions:

**From the direction of purchasers:**

There are no 'eligible' country signatories to the original APC subsidy contracts. They 'commit,' via their purchases, after a committee has cleared a vaccine. Purchasers pay 'only', say, 10% of the initial procurement price per course, and yet their small, marginal, contributions are essential to success of the whole program - involving billions of dollars. They therefore have a veto over success of the program, and compared to the value of rent-seeking them, they can cheaply be 'rent-sought'. The tranche of vaccines using up the subsidy is, after all, only a very small part of the overall potential number of treatments. See Farlow 2004, Section 7, for several ways for firms to rent-seek the scheme through the purchasers.

**From the direction of the firm:**

At the margin, the manufacturing cost per vaccine is supposedly a tiny proportion of the ex ante required payments to the firm. The purchaser only pays \$1, say, for a vaccine costing, supposedly, \$1 to manufacture,<sup>579</sup> leveraging \$14 or \$24 or whatever the scheme has determined<sup>580</sup> from the fixed subsidy pool. It is worth the firm to spend up to the expected value of this 'windfall' to get it, though in general the firm would not need to invest anywhere near this windfall in rent-seeking costs to leverage it.

For example, firms may use deals on non-vaccine products linked to decision-making on vaccines products (say, purchases of antibiotics from the same firm that also potentially supplies vaccines – this clearly favors larger firms with multiple product lines), or firms may engage in political lobbying, or insider 'deals' with influential political figures, better still if this influence is signaled early on. Clearly, there are reputational damages to consider – another reason firms may prefer to avoid such situations ex ante even if they go along with rent-seeking ex post – though some rent-seeking acts are less obviously damaging to reputation.

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<sup>578</sup> Though, we also saw above that the price any firm gets ought to account for differential costs of development; this has not been addressed by APC advocates yet, who, after all, just ignore R&D cost issues.

<sup>579</sup> The logic goes through whatever the level, since the rent-seeking is about the portion of the subsidy pool that pays for the R&D, and this may be constant even as the average manufacturing cost varies.

<sup>580</sup> One sees that as this gets higher, the problems just get worse.

Another form of rent-seeking might be when a large developer of a first product has large marketing and sales budgets enabling it to hold off follow-on vaccines. The high per-unit product subsidies generate high rent-seeking value. This is a run-of-the-mill economic phenomenon. If firms expect in advance to have to face such a scenario, and believe that policymakers might be incapable of the level of monitoring required to prevent it, this feeds back to weaken R&D incentives in the first place and slows vaccine development. Observe that this may even happen in very resource poor settings if economic rent has been created to drive this behavior. Again, it is the *expectations* of this that risk destroying incentives to invest in a range of products and follow-on innovators.

**Risk to those with less ‘deep pockets’ financial**

This creates a great deal of risk to smaller less ‘influential firms’ or firms with less ‘deep pockets’ financially. The standard argument is that firms with ‘deep pockets’ do not even need to rent-seek; they use their ‘deep pockets’ financially to signal their rent-seeking ability. Since in the rent-seeking game, they are able to survive longer and spend more to get the subsidy than smaller players, smaller players come to recognize this and, by backwards induction, conclude that there is no point competing in the first place. For example, how many millions of dollars, and what locational advantage, does an Indian/Korean/Chinese firm have to lobby the US Congress (or the US Secretary to the Treasury according to the Kerry-Lugar Bill) and the committee distributing the pool of subsidy, compared to a major US pharmaceutical corporation?

**Narrowing down the number of firms**

One way for a firm to reduce the risk and cost of rent-seeking is to narrow down the number of firms finding themselves at the rent-seeking stage. Indeed, a firm may find it useful strategically to deter others from competing against it (the threat that the firms will end up *ex post* engaging in rent-seeking being used to deter other firms *ex ante*). Indeed, the best strategy of all may be to signal the ‘take over’ of the subsidy-distribution process. This carries reputational risks however.

The rent-seeking advantage of larger firms is reinforced if large developed economy developers are (perceived) more generously subsidized, and those subsidies are not sufficiently removed from their pull rewards. Preventing this removal is a privately very valuable form of rent-seeking in its own right. Biotechs and others find such subsidies much more difficult to hide.

Larger firms are also able to use patents, know-how, and other strategic assets more effectively than developing country competitors, and may be (perceived) more able to influence decisions of the APC committee and purchase committees after research costs have been sunk. This influence is hugely valuable; it can add literally hundreds of millions or even billions to the value of a research project and force similar-sized losses onto competitors. Given the huge sunk costs of vaccine research, firms ‘would be fools’ not to invest in influencing decisions.

So, both the risk of time-inconsistency and the risk of rent-seeking narrow down the number of potential players, and disfavor smaller less influential less financially endowed players

**The key point – firms may want to avoid rent-seeking incentives**

The key observation is not that this behavior takes place but that certain market structures and payment systems encourage it more than others. If big pharmaceutical firms do not wish to be in situations involving this sort of behavior being forced onto them, they will either prefer alternative payment systems (e.g. PPPs), or will see to it to control the amount of rent-seeking they are forced into.

It may be that firms may be already trying to avoid this, including ‘big pharma’ firms, and that things like APCs would force into existence a situation with too much rent-seeking risk given the reputational damage it might cause. Furthermore, if the incentive structure is set up to encourage lower quality outcomes, and goals are perceived as ‘bad’, most firms will simply not respond anyway.

**Rent-seeking, non-vaccine interventions, and variable efficacy**

If a package of measures, including treatment, vector control, etc., requires coordination, investments, planning, and individual production capacities to achieve overall optimal impact, this suggests avoiding components that encourage rent-seeking behavior since it will distort the overall package.

These are not like standard US drug markets, or indeed, previous vaccine markets. There is much more possibility that the vaccines developed will not be 100% efficacious. Variable efficacy/duration make these settings much more open to rent-seeking, since quality is one of the variables to be rent sought. Without credible control, there are dangers of self-fulfilling collapse of R&D projects for ‘higher quality’ vaccines, because of risk that ‘too much’ of the subsidy will inefficiently go to early developers. Rent-seeking aggravates an already difficult ‘quality’ problem.

Furthermore, the marginal loss to a firm of *not* pushing through with the use of a product is high, and the marginal return of rent-seeking on the last purchase is very high (indeed it is pure profit) given low marginal cost of its production (supposedly). So, on the one hand the high marginal cost of lost sales may deter investments *ex ante*.<sup>581</sup> On the other hand, firms can mitigate this loss through rent-seeking. If we throw in that the funds likely available for better later products are now going to be lower or gone, then lower quality overall becomes much more self-fulfilling.<sup>582</sup>

**Monitoring and policing**

To protect their investments and to ensure that those with longer, more expensive, higher ‘quality’ R&D projects get repaid on average, vaccine developers need to trust that monitoring and policing of this rent-seeking behavior takes place, though the long-term

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<sup>581</sup> We always have to remember that this is *ex ante* thinking. The *ex post* covering of out-of-pocket R&D and interest costs is not enough. *Ex ante* reasoning requires the covering of *many times* these costs.

<sup>582</sup> See Farlow 2004 *ibid.* Section 7, which spells out the logic more clearly.

multi-institution and multi-country monitoring and policing of such behavior would be difficult.

If payment is linked to demonstration of ‘reduced disease progression’ and topping-up of funding is done retrospectively (as some APC advocates suggest), rent-seeking is even encouraged after the event. For example, when facing unclear long-term results (polymorphism for malaria, or highly uncertain time from infection to first onset of symptoms in case of HIV) a biological marker may be used instead to work out how much to pay in subsidies after the APC has started to pay out,<sup>583</sup> but this just becomes another thing to rent-see.<sup>584</sup> This suggests the possibility that if quality can be determined more en route, with lower pressure to rent-see, average ‘quality’ of outcome could be higher.

### **Problem much less severe for once-and-for-all products**

Rent-seeking and time-inconsistency are less of a problem for once-and-for-all products. Intuitively, the first, best, and once-and-for-all product gets the entire subsidy available in the subsidy pool, but that is a fair return. Key underlying APC models (Kremer Appendix 3, and Berndt et al.) were set up on the notion that there was a once-and-for-all ‘vaccine’ and no particularly strong need for a stream of follow-on vaccines. Once we move away from once-and-for-all products, the pool has to be split. The Kremer model was a poor reflection of reality, and we have ended up with qualitative issues, rent-seeking and time-inconsistency playing much bigger roles than ever considered in that model. However, the policy agenda built on those original models has maintained momentum without going back to question the missing complications in the underlying model. Indeed, politicians still often talk as if there is ‘a vaccine’.<sup>585</sup>

### **General principals – the importance of competition**

Into an already challenging scientific problem, why throw in an incentive scheme that creates all these rent-seeking incentives and risks (on top of time-inconsistency risk)? In truth, a committee would fall massively short in monitoring and preventing such behavior. At best they would simply force firms to use less efficient rent-seeking approaches. Investor and researcher expectations would respond accordingly.

Multiple competing projects are more likely to lead to a vaccine. A way therefore has to be found to incentivize this competition without relying on R&D payment schemes that introduce rent-see of the decision process and reduce competition, even as we are also trying to track down and eliminate as much other risk as possible. The reader can make up his or her mind, but this author argues that this strongly suggests that a purchase fund

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<sup>583</sup> It being too expensive to have claw-back provisions of subsidies that have already been paid.

<sup>584</sup> Incidentally, rent-seeking does not necessarily ‘disappear’ under other systems. The issues are who faces it, how to remove it as a risk to firms, and whether some mechanisms are more or less prone to creating it than others. Any mechanism that builds up large sunk costs running up to a committee decision will be more prone than one where such costs are ‘neutralized’ over time. Shortly we see the problems that milestone payments have working under an APC, suggesting great difficulties also in removing rent-seeking.

<sup>585</sup> “...a vaccination to prevent malaria that could be ready in three to four years time...” Gordon Brown [www.hm-treasury.gov.uk/newsroom\\_and\\_speeches/press/2004/press\\_94\\_04.cfm](http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_94_04.cfm).

should be a large regular committed rolling procurement fund, with IP in the hands of more players (including PPPs<sup>586</sup>) and more ability to allocate IP to manufacturers, long-term contracts to incentivize capacity (a form of pull), and less power concentrated down to a few points in the decision-making process, with more open and democratic decision-making instead and more risk-sharing,<sup>587</sup> more competition at the production stage, and less attention to an elaborate ex post R&D subsidy scheme.

### **8.7. Precommitment risks: Some lessons from economic history**

This section flows from feedback the author made to a comment by Owen Barder on his vaccine blog<sup>588</sup> pertaining to the value of precommitments, following the award of the 2005 Nobel Prize in Economics to Thomas C. Schelling and Robert J. Aumann.<sup>589</sup> Schelling, a game theorist, has written about how individuals and society can be better off if they deliberately limit their choices in advance via a precommitment. As Owen put it “This is a key idea in monetary policy (many governments seek to tie the hands of their central banks), the theory of bargaining, and industrial organization (firms may invest in capacity to precommit a market position and deter rivals).” Barder then linked this thinking to vaccines. First, allowing donors to enter into long-term contracts with vaccine suppliers of currently existing vaccines, will “greatly increase the value for money for the purchaser and make the producer better off than a scenario in which precommitment is not possible.” Second, and completely differently, that if donors precommit to buy not yet existing vaccines – for example, for malaria or HIV, this will “stimulate more R&D by the private sector than if they wait until the vaccine is developed.”<sup>590</sup>

However, the economic literature and practical experience of precommitments has other pertinent lessons to teach us too. Rather than spelling out every implication for vaccines, the reader should read this section thinking for themselves how this applies to different kinds of vaccine commitments and ‘precommitments’, from the purchase of currently-existing vaccines on the one hand, right through to the APC promise to pay mostly large subsidies on purchases of newly-created vaccines many years in the future with the subsidies designed to collectively repay all the private R&D costs of all vaccine developers, including the costs of developing all follow-on vaccines:

- 1) Many promises/threats will not be credibly stuck to and therefore will get no reaction. The whole point of the example of a firm investing in capacity to precommit a market position and deter a rival, is that the firm could not simply

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<sup>586</sup> There is a tradeoff in here somewhere, of rent-seeking and time-inconsistency versus the efficiency (or perhaps lack thereof) of PPPs.

<sup>587</sup> But *not* all risk taken off the firms.

<sup>588</sup> <http://blogs.cgdev.org/vaccine>

<sup>589</sup> [http://blogs.cgdev.org/vaccine/archive/2005/10/schelling\\_and\\_a.php](http://blogs.cgdev.org/vaccine/archive/2005/10/schelling_and_a.php)

<sup>590</sup> It should go without saying that this is a pretty meaningless point of comparison to compare a financial mechanism to. It is better to compare the efficiency (including risks) of alternative mechanisms, for every dollar of present discounted cost of using each mechanism, at achieving the desired goal. That is the only thing that really matters. Not the status quo of doing nothing. No other proposal for how to spend a few more billion dollars on vaccine R&D would get away with this as a comparison.

promise it would do something, or make a threat: It needed to back that threat up with a costly action to make it a credible threat. The firm may not even want all that capacity (in fact that is the whole point of the comment... it is capacity that it may never use if the rival stays out). But the cost of this capacity is the cost of creating credibility (though a more sophisticated analysis would analyse whether it really is worth the cost, there being several scenarios). Indeed this is why banks also have to hold costly reserves (money they could make more on by increasing their loans); they need to sustain this cost in order to sustain the 'precommitment' equilibrium of a non-collapsing bank.

- 2) It only makes sense to commit to something that it is optimal to commit to. For example, it is now widely understood that the European Stability and Growth Pact was badly contrived. Countries therefore do not suffer too much from breaching it and may even feel completely justified in breaching it. Therefore the pact fails to achieve its desired impact.
- 3) In many cases the precommitment simply can't be sustained. Economic history is littered with examples. The UK was forced out of the European Exchange Rate Mechanism in the early 90s because the precommitted equilibrium that had the UK in it became increasingly unbelievable to financial markets; collapse was inevitable and self-fulfilling. This was not without first a great deal of cost to the UK Treasury trying to defend its 'precommitment'.

Similarly, many of the financial crises of the 80s and 90s had at their heart a precommitment that could not work – whether it be the Russian default, or a variety of Latin American and other defaults. In mid-2005, Argentina finalized the largest debt restructuring in history for the largest sovereign default in modern history (of over \$100bn), with an estimated loss to bondholders of about 70% of the original value of the bonds – because its precommitments were ultimately not credible.

Similarly, banks are sustained on a 'precommitment'; a promise to pay anyone who asks for their money back, even if the bank has leveraged those deposits to make big loans. Yet, bank runs and financial collapses have been common throughout history when this 'precommitment' breaks down. At some point, markets realize that the only rational thing is for a bank or banks to default, and then default becomes self-fulfilling (the 'bank run').

At least in bond markets, the government can keep trying to issue fresh bonds to put off the moment of default, and Central Bankers can keep trying to pump liquidity into a faltering bank system to try to put off a bank run. Viewing APCs correctly as financial contracts (a promise to repay the 'debt' owed to vaccine developers), clearly reveals their ability to suffer 'crises' and collapse just like any other similar financial contract. How does one 'put off' the day of default of an APC, compared to, say, the default of government debt or a banking system? To avoid the embarrassment of having to 'bail out', how does one avoid the most

likely trajectory of a period of non-reaction to the APC contract followed by the contract being left in place and for all of the other R&D incentive devices having to be later ramped up. These other incentive devices would still have to work around, or in spite of, the badly set contract, and policymakers would still have to run the institutions upholding the contracts? Or does the fund ‘collapse’ into the hands of one developer anyway?

- 4) It is especially dangerous if not enough is known to set the terms of the precommitment in the first place, because all of these self-fulfilling pressures really start to bite. Those running the precommitment and private players find themselves reacting to a badly-set precommitment. But revising it later will simply destroy credibility and may even backfire.
- 5) Badly-set precommitments can set the stage for perverse behaviour. For example, revising up an APC that has been set too low will act like an extra discount rate making early investment even more expensive. Why invest more, when slowing down your response gets you an even better expected payoff (in NPV)? Tremonti, in spite of this simple economic logic, argues that “It is possible to maintain incentives for vaccine innovation by *increasing* the size of a specific vaccine AMC at a later stage.”<sup>591</sup> Financial markets will see the illogic of this claim even if Tremonti does not.
- 6) Even when a precommitment seems to be working as intended, there may be side-effects way off somewhere else. A central bank ‘ties its hands’ and gets inflation stability, but the inflationary pressures show up elsewhere – in asset prices (house prices say), which cause a ripple of effects (some good, some bad) elsewhere.
- 7) Sometimes a precommitment requires quite a bit more than meets the eye. Let us think of US bonds/debt (a precommitment to pay back money borrowed). The US issues debt (think how the following does *not* apply to APC ‘debt’) that people are willing to hold because:
  - a. The US always has tax-raising powers to make good on the debt, and this helps to reinforce the precommitment (even if it never uses the powers, it is the fact they are there as a back-up that matters, since it is all about the beliefs of financial markets);
  - b. It can issue more debt to pay off the first debt (indeed even pass the debt on to as yet unborn generations – It’s not as if they get a say in it – though we might have to pay them a bit more interest, and there are eventual limits to this);
  - c. The debt can easily be priced. It is a relatively simple underlying flow, and the market for pricing it is very liquid with plenty of buyers and sellers at any one time, and markets that have built up and that have learnt, over two centuries, how to handle it;

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<sup>591</sup> Tremonti, G. 2005, *ibid.* p8.

- d. There are usually limits to how much debt a country can issue, but this is bound by the chances of the country declaring bankruptcy. The logic is that the cost of bankruptcy is so bad that this helps to sustain the ‘precommitment’ equilibrium (it’s that ‘cost of an action’ thing again, here an action that a country only ‘might’ have to take, rather than an action it actually does take). If the US even showed hints of defaulting on its debt, the future costs of issuing bonds – that is future borrowing costs to the US – would spiral massively; current interest rates would shoot up and there would be appalling consequences for the economy *today*, never mind in the future. This huge adverse consequence disciplines the government to not even hint at not repaying, and this reassures bond holders. Observe how this works to push interest rates up if bond holders come to expect that the government will tolerate higher inflation as a way to eat into the government’s debt helping the government to not repay by the backdoor, since this is a form of default. In the US case, the dependence of the US on global confidence is so high, that it is practically inconceivable that it would default short of Armageddon (unlike Argentina perhaps), so this makes it much easier and cheaper to get people to hold US debt in the first place.
- 8) It can sometimes be statistically difficult to detect causation. Is central bank independence a cause of inflation stability, or does inflation stability tend to create political regimes in which central bank independence is much more likely to happen? Is inflation low because central banks tied their hands? Or is it that recent economic events conspired to create more stability and central banks take more credit for it than they should? Is low and stable inflation more by ‘luck’ than central bank acts? If so, will it last? When luck runs out (if it does) this harms the central bank’s credibility. Another lesson why terms need to be set right: Once things stay to go awry, a central bank starts to lose its valuable credibility, sometimes quickly, and this reduces its room for efficient maneuver and the power of its policy decisions in the future to have an impact.
- 9) It takes time to build up credibility, as most central bankers will tell you. It can also be destroyed quickly by mistakes.
- 10) You can get stuck with a precommitment that is harmful or not working, simply because the harm of defaulting on it is even greater, or there is a desire to avoid litigation, etc.
- 11) Keeping a precommitment going can be costly. Russian bonds in the mid 1990s were returning 60% per year (i.e. costing the Russian people that!) because of the default risk. In the case of an APC, the risk that the APC would be allowed to collapse or not pay out as intended, would translate into very high required capital costs, and very low R&D power. But this ‘cost’ does not really show up as a financial cost to governments – it falls on to those who do not get their vaccines

translated into a smaller chance of getting them, and higher pressures to accept lower quality vaccines.

- 12) The risks of malaria, HIV, and TB vaccine APC precommitments could not be hedged away. Unlike scientific risk, APC risk is less obviously statistically random. This risk is only ever likely to be asymmetric. A large pharmaceutical firm normally hedges by holding a portfolio of products. Biotech risk is normally hedged via Venture Capital, VC, firms on capital markets. However, no financial market would arise to hedge the APC risk since actuarially fair terms could not be set. Besides, if it were known that a hedge was on anyway, there would be an incentive to abuse the hedge, and, thus, those providing the hedge would not profit from creating the hedge in the first place.

Thinking of how the 12 points might affect the two cases of vaccine commitment mentioned by Barder: In the case of currently existing vaccines, it is clearly inefficient not to have longer term contracts in place. Terms can be set well (information is known enough to set them well). Terms can benefit all. As Barder puts it: “Precommitment can greatly increase the value for money for the purchaser and make the producer better off than a scenario in which precommitment is not possible.”<sup>592</sup> It’s a ‘win-win’. Reneging on the precommitment is a bit dumb. The problems only really start to bite for the second case of early-stage not-yet-existing vaccines like malaria, HIV, and TB. Yet we are told that it is “especially perverse”<sup>593</sup> to suggest that a vaccine precommitment had been untested against possible adverse consequences and failure.

### **8.8. Biotech and emerging developer risks**

It is said that a scheme based on subsidy payments at the end of the whole R&D process would create *de facto* markets for intermediate research outcomes. Standardly, market ‘deals’ struck between large and small companies at each stage of the R&D process are driven by a *real* market at the end, and are *struck over time*. So long as the real market is definitely there, the fact that deals are struck *over time* (rather than once and for all at the start) is no big problem. However, if large pharmaceutical firms strike deals *over time* under an APC, they have more of an option on the APC, and if it fails to work well or even collapses they are much more shielded.

Indeed, a disproportionate amount of the risks of such APC schemes – especially in the case of complex early-stage products – falls onto biotech firms. After all, they have to sink investments *before* later big pharma players do. In a sense they have to ‘go first’ in trying the scheme out. When commentators say “Let’s just try it!”<sup>594</sup> they really just mean let certain investors “just try it” first. Most of the discretion in the mechanism hits after biotechs and VCs have invested (basically running up to and including purchase decisions); there are big risks to biotechs and VCs of time-inconsistency and later capture

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<sup>592</sup> [http://blogs.cgdev.org/vaccine/archive/2005/10/schelling\\_and\\_a.php](http://blogs.cgdev.org/vaccine/archive/2005/10/schelling_and_a.php).

<sup>593</sup> Barder et al. 2005, *ibid.* p4.

<sup>594</sup> Chirac, P., 2004, *ibid.*

by larger firms influencing the mechanism away from those who have taken longer-term risks; there are higher chances of biotechs active at early stages suffering ‘crowding out’ than those operating later in the process; and if the program fails, biotechs pay the heaviest price.

**Large pharmaceutical firms are more shielded from APC scheme collapse**

Given the way that large pharmaceutical firms are able to hold off committing to products until they reach later stages of clinical trials, the rational response of a large pharmaceutical firm to worries about the ‘mechanism risk’ of APC schemes – particularly that generated by the committee-driven ‘tendering’ mechanism which is nothing like a standard tender and not obviously ‘competitive’ – might simply be to leave more risk on the shoulders of biotechs (this behavior may have strong option value). The options value to VCs from waiting is also especially high for highly uncertain payment schemes, such as the APC schemes currently being proposed. There *is* an option value to *not* waiting, but this is likely to be much smaller than the option value of waiting if the mechanism may collapse or be poorly set up.

And one only has to read the CGD, Berndt et al., and Tremonti reports and papers to see the painfully inept financial thinking that VCs would have to face, to realise how poorly set up and run they would expect APCs to be. This further contributes to the potential self-fulfilling collapse scenario of such schemes for malaria, HIV, and TB (including collapse down to repay just one first-move firm). Biotechs need prices to be real in later rounds of the process. The longer the horizon, the greater the chances that such schemes will not work as intended and that the payment for their outputs will not exist.

Should the APC obligation start to become a liability rather than an asset, it will harm a firm’s ability to get hold of finance for other projects. This also suggests that biotechs will have to decide whether APC obligations are too risky to add to a portfolio and whether APC-only based biotechs would have to be created. This is another reflection of the non-hedgeable nature of APC risk.

**Locking out certain players?**

This is all aggravated if the incentive mechanism narrows down the number of players. Key to APC subsidies is the holding back of finance by a committee in order to incentivize ‘effort’ and ‘quality’. Such schemes favor (though facing them also with heavy risk) those with large free cash-flows (‘deep pockets’) and good access to developed economy equity finance (i.e. large pharmaceutical firms in industrialized economies), even if they do not really want them.

However, this risks being self-defeating if it locks out those who are already struggling most in their access to finance, for example, small innovative biotechs operating under the current ‘blockbuster’ framework: “Hundreds of smaller biotech companies may have great proposals, but hardly any have access to the hundreds of millions of dollars needed

to bring a new drug to market.”<sup>595</sup> Half the drugs in clinical development belong to biotechnology companies many of which are spin-offs from publicly-funded and university-based research. Most of these drugs are found in just a handful of biotech groups. Kaper et al. observe that “Biotechnology companies are changing the landscape in vaccine development, but investment dollars from VC are not flowing like they did a few short years ago, and the biotechnology industry (and, hence, vaccine development) is feeling the repercussions of those cutbacks. Moreover, collaborating with contract research organizations, which often assist biotechnology companies in vaccine development and data management, is extremely complex and expensive.”<sup>596</sup>

Large pharmaceutical firms regularly express a lukewarm, indeed cold, attitude to APCs for early-stage vaccines like HIV, malaria, and tuberculosis, even though the logic seems to be favoring them. This lukewarm attitude combined with the financial restrictions on biotechs suggests that dollar-for-dollar compared to alternative funding routes APCs are poorly-targeted instruments. Others may be at least as well or better placed for vaccine R&D.

### **Developing country developers**

For complex vaccines such as malaria vaccines, developing country manufacturers may not yet have the skills to do the R&D and it may be that if we want a malaria vaccine we need to involve one or more of the major manufacturers. However, this situation is rapidly changing. For example, the new meningococcal serogroup A vaccine designed specifically for countries in the African meningitis belt is being developed in India with support from the Gates Foundation and technical backup, the major pharmaceutical manufacturers having turned down the opportunity to do this with Gates support. This is not an easy vaccine to develop but manufacture is being done very effectively by an Indian manufacturer which, at best, will make only very limited profits. Given the 20 year horizon for malaria, HIV, and TB vaccines, we should take great care not to prejudge what emerging and developing country manufacturers might be capable of one day.

### **More direct funding to biotechs and PPPs as a priority?**

Again, this hints at the budget constraint. Is it better, given the constraint, to put \$1bn directly into biotechs and/or PPPs, or go via the APC paid at the end to feed them the present discounted value of \$1bn? It is not obvious that a regime based on such subsidy schemes would work for vaccines at an early stage in their development if such vaccines are highly dependent on small and new biotechs, not-for-profit, developing country, and university-based research. The key point is that the *marginal impact* of a given dollar spent on an APC on the financial resources made available to biotechs, emerging economy pharmaceutical companies, developing country researchers, and other researchers is lower compared to the marginal impact on the financial resources made available to large industrial market pharmaceutical firms, and compared to other finance mechanisms that might have been used instead to help the former groups. Should

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<sup>595</sup> Mills, L., “Great science not all that matters.” Financial Times Special Report into Biotechnology, 10 November 2004, p5.

<sup>596</sup> Kaper et al. 2005, *ibid.* p15.

Biotechs rely on APCs to tackle their funding problems? Or would a PPP funding route be a more direct and efficient route?

Interestingly, an approach that is less dependent on end-product subsidies, and that is more reliant on funding into intermediate stages and biotechs with less payment ‘at the end’,<sup>597</sup> might encourage large pharmaceutical firms to take more of the risk and show interest earlier in the process.

The huge reputational and time-inconsistency risks from being the ‘last firm in the chain’, may mean that even if the overall subsidy is made bigger, firms may not necessarily want to expose themselves as much to it as advocates claim. This suggests that the ‘right partnership arrangements’ would help to get even big pharmaceutical firms more ‘safely’ involved. If so, the notion of a large APC subsidy is, yet again, barking up completely the wrong tree even for ‘big pharma’.

A different configuration of sources of R&D funding and a different industrial structure (both interdependent) might change the shape of some of these financial constraints and would be worth investigating in more detail (once again, huge flows of sponsor resources into APC activity have crowded out other thinking):

- 1) The more players in the market, the stronger the incentive for firms to work on vaccine R&D, since success replaces products of *other* companies;
- 2) An IP system that better works to allow firms to acquire technology that might undermine those firms experiencing (and causing) a ‘replacement effect’ (see below. This refers to firms working on vaccines that replace profitable drugs. If these are profitable markets for them, this raises their own capital, i.e. financial, costs for vaccine R&D);
- 3) Finance mechanisms that give differentially greater impact to biotechs, not-for-profits, and all those working on ‘replacement’ projects, enabling them to take projects further without needing to rely on firms causing/suffering from ‘replacement effects’;
- 4) A ‘demonstration effect’ of the purchases of current vaccines that in part unlocks credit constraints (i.e. makes finance cheaper) of biotechs, not-for-profits, and emerging developers, by ‘demonstrating’ that the ‘replacement effect’ is now weaker;
- 5) Positive ‘demonstration effect’ caused by investments into healthcare infrastructure too.

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<sup>597</sup> This is a budget constraint issue; the usual response of the APC advocates is to vacuously argue that they are not against either.

**Milestones: but no panacea**

One way to overcome the excessive risks placed on biotechs of schemes that may collapse or fail to work as promoted is to use some sort of milestone system. At first, milestones for biotechs were ruled out of APC schemes. Then milestones were ruled in, but it was not explained how they would work. Would milestone payments be drawn down from the eventual pot of APC subsidy funds? If so, how is the draw-down judged? Underlying science would need to be understood when setting terms at the start. What happens to the incentives of others as the pot shrinks? Especially if the draw-down is done badly. What if there is heavy rent-seeking over milestone decisions?

Ordinarily, milestones are a natural arrangement between larger and smaller biotech players, *when there is a market*. The request (in biotech feedback to CGD) by firms for milestones as part of the APC *itself* indicates that they do not view an APC as creating anything like a genuine ‘market’,<sup>598</sup> and it reflects the worry that larger firms may prefer to hold off on ‘signing’ promises that would affectively gamble on the APC scheme working and make them the ‘back up’ if it fails.

Milestones *within* the APC itself are a way for biotechs to avoid having to rely on a scheme that needs to maintain belief about the efficient and fair functioning of a committee in 20 plus years time, and to overcome the failure of larger firms to sign long-term deals with smaller firms that simply transfers this risk onto larger firms.<sup>599</sup> When firms have raised the issue of milestones, it is not wise to simply ignore them. If included within the APC itself, somehow, the expertise for inserting and running milestone payments has to be found in the public/foundation/sponsor sector. Distortion at intermediary stages distorts overall incentives. As Mahoney put it: “The complexity of the overall agreement, in at least some cases, would be extraordinary and would require great expertise in vaccine R&D...For example, who would adjudicate whether a milestone had been reached when there was disagreement?”<sup>600</sup>

Light complains: “Interim and milestone payments were suggested but rejected as part of push grants, not pull AMCs. There are good reasons for using such payments in both initiatives. The final [CGD] report keeps repeating that the process is open to all, but the contractual terms allow only cash-rich corporations to gamble for years for a possible big payoff and exclude future biotech companies that discover a vaccine after the initial contracts are signed.”<sup>601</sup>

Milestones within the APC were ruled out in the final CGD report.

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<sup>598</sup> If they did, they would accept it at face value and do milestone arrangements between each other and ‘big pharma’ and not be quite so fussy now.

<sup>599</sup> One remembers the option cost of taking on this risk.

<sup>600</sup> Mahoney, R, CIPIH Forum, 21 December 2004.

<sup>601</sup> Light, D., 2005, *ibid*.

### **8.9. Multiple APCs generate non-hedgeable risk**

It has been argued that multiple APCs could be wheeled out at the same time for a range of things: “Potentially, advance purchase commitments could be used to encourage research not only on vaccines, but also on other techniques for fighting disease.”<sup>602</sup> However, we already found that each APC – and, remember, we are thinking here of APCs as repayment devices for sunk R&D costs and not as standard large procurement devices to repay manufacturing costs – will be difficult to hedge. Standard tools of financial analysis – such as CAPM (Capital Asset Pricing Model) – would also undoubtedly rule out a mass role out of APC schemes because of the way such schemes would generate non-idiosyncratic – hence non-diversifiable – risk: A fault of one APC is very likely to show up on another APC, especially if politicians and lobbyists make a mess of it. Given the behavior of politicians and lobbyists even before any APC is launched, this is already looking to be highly likely.

Normally firms would find ways, through portfolios of products, to diversify away the idiosyncratic risk of the science. This can’t be done en masse on risky financial instruments when the risks are highly non-idiosyncratic. This will be magnified, the greater the amount of payment going through the end market subsidy. Given that it may not show up for many years – and the recent race to put in place APCs for malaria, HIV, and TB has been so desperately intellectually poverty-stricken, with no desire to critically stress-test the working of the idea – these risks will be high, and would be perceived to be high by financial markets.

Nevertheless, the Tremonti Report claims to have shown that “maximum effectiveness is obtained by establishing an overarching AMC”<sup>603</sup> with multiple AMCs tailored to the development of each vaccine. Tremonti does not, however, explain whether one committee runs the whole overarching AMC or whether each AMC gets its own committee; either approach clearly raises a range of problematic issues. Tremonti makes no attempt to judge from a financial perspective the ‘riskiness’ of such ‘overarching’ schemes.

The risk will not be diversifiable and will have to show up in the required rate of risk premium (i.e. extra return above and beyond market risk) for investing in any investment depending on such schemes for financial success. This extra risk premium is on top of the real 8%-11% (11%-14% nominal) required rate of return of ‘big pharma’, but would add even more to already high rates of return for ‘small pharma’. Burying all talk of problems may be good for lobbying, but it shows reckless disregard for the way financial risk works, and, paradoxically, undermines the very scheme being promoted.

There has been talk of applying APCs to a wide variety of cases, in defiance of this financial logic. Would a system based on lots of APCs – irretrievably fixed contracts with a wealth of new institutional structure to support them – actually work and get global

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<sup>602</sup> Appendix 7, p39, No. 10 Policy Unit website, <http://www.pm.gov.uk/output/Page3704.asp>.

<sup>603</sup> Tremonti, G. p13, 2005, *ibid.* referring to section II.2.1, that does not seem to contain anything relevant to this claim. For an idea never used before, ‘is’ is a little strong.

financial backing and investors interested? Again, the risks will vary by disease and state of science and the timing of the setting of APC terms. Targeting the big three – HIV, malaria, and TB – with APCs is almost certainly a disastrous financial strategy. It has always puzzled this author why when embarking on a 20-30 year scheme that will put risk on to some investors more than others, and has lots of potential for self-fulfilling collapse of R&D, that there has not been more of a desire for the application of even rudimentary financial thinking.

### **8.10. The beneficial impact of competition on risk and the costs of finance**

We have seen the way that rent-seeking behavior can feedback to generate less R&D, and lower incentive to cut production costs. But can lack of competition also increase costs in other ways? This section argues that lower competition may also raise the private financial costs of individual companies developing vaccines.

If equity markets correctly price all future expected discounted profit flows, then a firm working on projects that generate the mere *possibility* of reducing overall profit flows by ‘replacing’ some or all of its profitable treatment programs (profitable in the expected sense, which may be an important sense for an expanding treatment market), will pick this up in a depressing affect on its equity valuation. This will increase the firm’s capital costs for vaccine projects. This leads to firms requiring a higher rate of return on such projects. This also has implications for vaccine R&D finance when we encourage both malaria vaccine R&D and malaria drug R&D and treatment programs, since the expansion of the latter can increase the financial cost of finance for the former (the author hazards a guess that it is even worse for HIV). This has not been worked through in any of the analysis this author has seen, but it takes the vaccine ‘package’ thinking to a new level.

This is controversial, but should not stop us from tackling it. If such a ‘replacement effects’ is part of the problem in raising private finance for the R&D of malaria vaccines, then better policy will result from considering rather than from ignoring it. The fewer the number of firms being relied upon for treatments *and* vaccines, the larger the ‘replacement effect’ and the lower the incentive to invest in vaccine R&D.

Even if biotechs and not-for-profit firms are marginal, competitive, players and do not suffer from the ‘replacement effect’ themselves, if they cannot raise finance to take a vaccine ‘all the way’, their need to turn to firms suffering from the ‘replacement effect’ feeds the ‘replacement effect’ onto them. An incentive device that relies on ‘trickle down’ from big pharmaceutical players to smaller players may be blunter than one that feeds more finance directly to the smaller players.<sup>604</sup>

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<sup>604</sup> With the subsidy pool at the end, and the eventual product price able to be adjusted downwards (since there is a budget constraint).

This bites even for markets not competing against vaccines. For example, if vaccines weaken pricing power in markets where there are both treatments and vaccines (this weakening only has to be tiny for vaccines given the size and duration of treatment programs elsewhere and the marginal size of the vaccine market), or if vaccine research for a subunit vaccine or clade for a low value treatment market might produce results positively impacting high value treatment markets for other subunit vaccines or clades.

### **8.11. All risks show up in financing costs: A clarification**

Caricaturing<sup>605</sup> the risk observations made in Farlow 2004, 2005, and elsewhere, led to the following highly inaccurate portrayal of the position being taken (the reader can make up his or her own mind, from all of the above discussion of risk, and from all of the earlier discussion of capital costs and the role of private sector players, what the argument actually being made by the author is):

“Farlow (2005) argues that it is more efficient for the public sector to fund research up front than to incentivize the private sector [‘through APC subsidy payments at the end’, a crucially missing phrase<sup>606</sup>] since capital costs are lower in the public sector [though, Kremer, Towse, and Williams could not find a specific quote to insert at this point, since Farlow had never made nor relied for his argument on such an observation]. Thus with long development periods and high costs of capital the out-of-pocket costs of research are dwarfed by ‘capital costs’, and hence using the public sector to fund public or private researchers on an up front ‘push’ basis will be cheaper because it avoids these costs [a point contradicted by the author’s very public pronouncements on the issue<sup>607</sup>]. The logic of Farlow’s position that governments should undertake investment projects since they have a lower capital cost implies that governments should not merely develop vaccines and drugs for malaria but also should develop pharmaceutical products for developed country markets and indeed undertake all investment. It is widely recognized that such a strategy of government undertaking large-scale investments in economic sectors where the private sector has substantial expertise runs the risk of introducing considerable inefficiencies. Indeed, in recognition of this the UK government has been moving out of those sectors of the economy where there is substantial private sector expertise and has been seeking ways to involve the private sector in bearing risk where it is better placed to respond efficiently to the incentives provided.”<sup>608 609</sup>

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<sup>605</sup> The author has got quite used to having his position caricatured by now. Given time constraints in a very busy schedule, it can be difficult keeping up, so this has only really got the attention it needed now. The passage remains posted on the DFID consultation website (nothing of this author’s is listed that might have enabled balance or a defense).

<sup>606</sup> See how subtle caricaturing of a position can be?

<sup>607</sup> [www.economics.ox.ac.uk/members/andrew.farlow/FarlowDNDi2005.ppt](http://www.economics.ox.ac.uk/members/andrew.farlow/FarlowDNDi2005.ppt)

<sup>608</sup> Kremer, M., Towse, A., and Williams, H., May 2005, *ibid.*

[www.who.int/intellectualproperty/submissions/MichealKremerKTW\\_CIPIH\\_submit\\_2.pdf](http://www.who.int/intellectualproperty/submissions/MichealKremerKTW_CIPIH_submit_2.pdf)

<sup>609</sup> As another example of this misunderstanding – or deliberate caricature –, for some reason, Barder et al. 2005, *ibid.* rebuffed the observations of the Farlow et al. coauthors with lines like: “We understand that there are people who, for respectable motives, are opposed to intellectual property rights as a way to create incentives for innovation, and who do not want to encourage the pharmaceutical industry to develop new vaccines on a commercial basis,” (p2). However, Barder et al. had spent no time doing the very things they

**The issue is whether the incentives provided are efficient**

Of course, the bone of contention is not whether the private sector is better placed to respond efficiently to the incentives provided, but whether the incentives provided for them to face are efficient: An entirely different issue. The logic would seem to be that if you argue that an APC mechanism is itself very risky and inefficient and will simply not work remotely as described and harm the private sector, you must somehow be against the private sector, and that to be pro the private sector must, logically, mean only one thing – to be totally unthinking in one’s support for the CGD notion of how to repay private firms their R&D costs via an APC. It is taken as axiomatically obvious that anyone wishing to get the private sector more engaged in vaccine R&D must think that APC schemes are the only way to do it. The reader can see that the whole point of the current report, and all the other papers this author has written on this topic, is to explore how firms are likely to respond to particular ways of paying them, and to get more firms involved.

Who funds R&D of malaria, HIV, and TB vaccines, when this funding is paid, and who does the research are completely separate issues. When Zandonella argues in support of these elaborate ex-post APC subsidy schemes for HIV vaccine development on the basis that “Private sector investments are needed because [HIV] vaccine development requires expertise not found anywhere else,”<sup>610</sup> this is a meaningless observation. The logic in the Kremer et al. quote above, and Zandonella, can be turned on its head. It seems to imply that ‘all investment’ should get an APC top-up to the extent we are unhappy with the speed of development (i.e. of many diseases, such as Alzheimer’s and cancer). But it would seem that only the poor get these risky and untried instruments.

Those promoting APCs spend far more time arguing in favor of huge increases in ‘publicly funded’ research than Farlow and Farlow et al.<sup>611</sup> (APCs are huge publicly funded schemes run by publicly appointed committees) and less time worrying about whether it is likely to be efficiently used. All parties have surprisingly similar views about the role of those with private sector expertise, just very different views on how to get them interested, what risks they should face, how to pay them, and what they get at the end of the process.

**Politicians are not the ultimate judge**

An APC is a long-range investment instrument. If investors won’t touch it, it won’t work. If investors see that key features have not been worked out or have even been deliberately fudged, that marketing and spin are used to sweep critical analysis aside, that unfavorable feedback is suppressed, and that ‘deals’ are being done behind the scenes with favored

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criticized several of the Farlow et al. authors for wanting to discourage, while several of the authors of the Farlow et al. paper (though not this author) had more combined lifetimes of activity doing just that. And, in spite of themselves promoting ideas that are *totally* and very expensively publicly-funded, they argue that “Furthermore, we do not believe that a purely publicly-funded approach is a practical option,” because it would need “resources which do not seem likely to be available even on the most optimistic assumptions,” (p3).

<sup>610</sup> Zandonella, C., 2005, *ibid*.

<sup>611</sup> Farlow, A.W.K., et al. 2005, *ibid*.

players, why should they react? At the end of the day, as Barder et al. put it, it is only “any firm that can persuade an investor”<sup>612</sup> that such a scheme will work, that will be able to invest in light of it. Yet, for some reason, APC advocates have never viewed APCs as extremely long-range financial instruments, that therefore require extremely professional handling if financial investors are not to be put off. Indeed there is no evidence at all of any application of basic financial economics in the key APC papers. Amongst all the questionable calculations and the ignoring of key practical problems, perhaps in the attempt to win politicians over to APCs for malaria, HIV, and TB vaccines, it is forgotten that politicians are not the ultimate judges of such schemes. Advocates can obfuscate their way around awkward practical issues, but they can’t hide from the most rigorous judges of all – financial markets.

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<sup>612</sup> Barder et al. 2005, p9.

## 9. 'Innovative' Financing Mechanisms

### 9.1. What does 'stimulate the market' mean anyway?

#### 9.1.1. A wide spectrum of interpretation

The Malaria Vaccine Technology Roadmap talks about creating “mechanisms to stimulate the market,”<sup>613</sup> and there is much talk of “Innovative Financing Mechanisms”. However, so far this is very narrowly defined.

Reference is only made (by various stakeholders in the ‘commercialization’ section of the Malaria Vaccine Technology Roadmap) to the need to “secure advance purchase agreements for future vaccines”<sup>614</sup> with ‘novelty’ only acting *through purchases* and only via APCs. There is no reference to the problems of the underlying financial instruments/contracts driving R&D for these extraordinarily complex problems, and no reference to the possibilities of ‘novel’ financial instruments/contracts to mitigate some of *these* problems, and no reference to the layers of problems of APCs themselves.

Furthermore, the meaning of the term ‘APC’ is not itself pinned down even though a call is made to “muster global political will”<sup>615</sup> to “secure purchase commitments for the vaccine(s)”<sup>616</sup>. There are many ways to improve the market and to create more ‘market based’ incentives, short of the APC subsidy schemes being proposed by CGD and Tremonti, since the ‘market’ already fails in many other ways.<sup>617</sup> And we have repeatedly found that the sort of purchase schemes being advocated have very few genuine ‘market’ features about them anyway.

#### At one extreme

At one extreme, “innovative financing mechanisms” could refer to potentially extremely elaborate ex post subsidy schemes run by committees determining which products get funding<sup>618</sup> with the committee allocating a fixed pool of subsidy across products over time, based on expected information and contracts set up ex ante. ‘Effort’ and ‘quality’ would be incentivized by rules “tailored to the particular scientific and economic risks and costs associated with a vaccine against specific priority diseases.”<sup>619</sup> <sup>620</sup> Long-term

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<sup>613</sup> MVTR p32.

<sup>614</sup> MVTR p33.

<sup>615</sup> MVTR p33.

<sup>616</sup> MVTR p6. And remember, yet again, this not referring to a commitment to purchase per se, but commitment to a mechanism with fixed prices and disbursement rules.

<sup>617</sup> Farlow, A.W.K., July 2005, Section 3 discusses a wide range of pull initiatives. Though – carefully reading between the lines – the current paper is full of thinking about market risk reduction, and hence about how to get more ‘market pull’ for any given public expenditure.

<sup>618</sup> Tremonti, G., 2005, *ibid.* p16.

<sup>619</sup> Tremonti, G., Background Papers, 2005, p11. Also p14 also explains: “AMCs will need to be sized and tailored to the specific risks and costs that manufacturers face for a given vaccine/disease.”

<sup>620</sup> Though we found it difficult to find much being driven by purchasers given the lack of any relevant price signals, and a strong element of self-fulfilling pressure.

supply (including prices) and access said to be disciplined by threats in contract terms set at the start and punishments at the end.

**Tremonti fiddles<sup>621</sup>**

As Tremonti observes, even for cases that “face huge scientific and technical challenges,” such as malaria, HIV and TB, the provisions made “must reflect [in explicit legally enforceable terms] the specific market risks and scientific challenges faced by the industry in the discovery and development of the target vaccines.”<sup>622</sup> Tremonti, however, also recognizes that a great deal of the outcome will be determined by the discretion and abilities of the committee running things: “The AMC must also be periodically re-evaluated to determine if initial estimates on what constitutes an adequate size and price continue to hold true,”<sup>623</sup> and “the terms of the framework agreement, specifically the vaccine eligibility requirements, would be re-assessed periodically by the IAC [the committee running the scheme] to take into account additional information that becomes available. The terms of the agreement could be revised accordingly – although not to raise the bar in terms of the requirements for target vaccines.”<sup>624</sup> Since “The proposal is that *private* investment would underpin R&D by *private* firms,”<sup>625</sup> this would also refer to monitoring, and repayment side-devices to remove ‘crowding out’ and to create more of a level playing field between developers (discussed in more detail below).

Tremonti reveals all the monitoring of private investors the committee would have to do to achieve this,<sup>626</sup> something that early APC proposals downplayed. Supposedly this is done while avoiding a range of time inconsistency, rent-seeking, and asymmetric information problems, and without firms facing any increased risk from the committee. At least Tremonti reveals the hugely statist credentials of the APC proposals being promoted to G8 leaders.

**At the other extreme...**

At the complete other extreme (since there are things in between) the phrase “innovative financing mechanism” could refer to a commitment to carry out proper demand forecasts, ADIPS, and sufficiently large procurement funds to mass purchase products through a competitive process and to use the products with less restrictions on access. There would be no especially large role of a committee setting and policing ‘advance’ contracts and short- and long-run price in advance. There would be less prejudgment of R&D costs – indeed with pricing mechanisms set in place to extract information when it is needed and when it is available, with (in the most extreme case) much R&D of vaccines funded through PPPs, and a very democratic and open decision-making process (more so than at present) driving choice of vaccine candidates. There would be ‘other’ novel financial

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<sup>621</sup> Well, he is a Northern League politician, but his job *is* based in Rome.

<sup>622</sup> Tremonti, G., 2005, p7.

<sup>623</sup> Tremonti, G., Background Papers, 2005, p5.

<sup>624</sup> Tremonti, G., Background Papers, 2005, p38.

<sup>625</sup> Barder, O., CIPIH Forum, 19 November 2004.

<sup>626</sup> See for example Tremonti, G., 2005, *ibid.* p11.

instruments (and non-APC forms of public funding<sup>627</sup>), to help redistribute risk and to remove risk, with the terms of these set to insure firms but also to incentivize them (by leaving appropriate risk on their shoulders). There would be no attempt to reallocate R&D subsidies ex post through a mix of rules and discretion across products, and no need to extract from subsidy payments to avoid crowding out. There would be more access to technology and know-how by a wider range of players from the start, and competition in the end market to drive prices lower. This may involve commitments on capacity, and commitments to purchase products in exchange for financial help toward sunk capacity and a deal on IP; but these are very different from ‘APCs’ as currently construed.

These pretty much describe the two extreme alternatives on the table, and the second route potentially involves private players at least as much as the first route.

### **Pricing regimes**

When the Roadmap argues the need to “Develop a viable pricing model for developing world vaccines/drugs,”<sup>628</sup> the above two scenarios also delineate a range of pricing models available: Under the first ‘extreme’ APC case, eligible-country prices are high at first, becoming low later with contractual threats used to achieve this. Non-eligible country prices are set at what the companies can get outside of the APC, based on the hold of these companies over IP, and their pricing power. The second ‘extreme’ achieves early low and always a low price for poor eligible markets and possibly for less poor, otherwise non-eligible, markets (or an arrangement to give firms IP rights in the non-eligible markets), and competition between suppliers to drive low long-term price in both the eligible and non-eligible markets.

The notion of ‘market pull’<sup>629</sup> has become so vague that it could refer to a wide variety of interpretations as to how much of the cost of R&D is paid through end subsidies attached to purchases, and how much IP is given to the ‘winner(s)’. The IP arrangements have implications also for pricing policy in ‘non-eligible’ countries, and follow-on vaccines. From previous (and later) discussion, it is clear that the first extreme of paying R&D subsidies through ‘purchasers’ at the end, does not create anything remotely resembling a ‘market’; the only true markets are genuine ones. The second extreme makes more use of markets, and the information advantages of markets, at several levels, but especially towards the end of the development process. Under the first extreme the notion of a ‘market’ is really just a veil for the decisions being run through a committee via goals set by others elsewhere.

Unfortunately, recently, such narrow notions of what is “innovative” financial thinking have encouraged us to stop thinking about many aspects of the problem. The attention to ‘APCs’ has deflected us from a proper investigation of risk and the creation of financial instruments to tackle it.

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<sup>627</sup> An APC is itself totally publicly funded, with the richer developed world paying, with emerging economies (including China, India, and Russia) facing standard monopoly prices and forms of price discrimination.

<sup>628</sup> MVTR p33.

<sup>629</sup> MVTR p32.

**Confusions**

Indeed, what is being proposed is becoming rather confusing. APC advocates argue for a \$6bn or so APC for malaria on the assumption that it would bring in “up to two” large pharmaceutical firms.<sup>630</sup> This is puzzling. It hardly describes the first extreme above. Either firms are making high-risk high-reward gambles, with low probabilities of success for each gamble, necessitating multiple developers. Or the notion is that by the time things have narrowed down to one or two firms, the probability of success is high for each gamble. The latter interpretation would mean that a large proportion of the APC payment is related to production costs. But this would hardly necessitate a price-fixed instrument set 20 years in advance of the availability of the information that would enable it to be set efficiently, and would generate all of the inefficiencies we described above regarding such instruments, including poor discipline on price and problems with long-term access, and so forth. Probabilistically, neither is it clear how this motivates private finance into multiple parallel avenues of research, needed to generate the high chances of a high ‘quality’ vaccine. It does, though, rather beg the question of what \$3bn-\$6bn could do in bringing forward these ‘highly efficacious vaccines’ if these were instead the target from the start and this level of funding directed at those players working towards that goal.

**Malaria, HIV, and TB are different**

As one correspondence put it well: “It is crucial to separate out clearly the issues facing malaria, HIV, and tuberculosis vaccines from those facing Hib, pneumococcal and rotavirus vaccines. Several companies have developed or are developing the latter vaccines following the conventional route because there is a substantial market for them in industrialized and middle income countries with the potential for major profits. The issue here is how to make these vaccines affordable in the countries where they are needed most. As R&D costs can be paid off by rich countries, the critical issue is the true cost of vaccine manufacture which is dramatically less than current prices. Advocacy in developing countries, increasing market volume, encouraging developing country manufacture and some kind of subsidy for the poorest countries is the way forward in these cases and should be doable. The GAVI supported pneumococcal, rotavirus and newly formed Hib ADIPs are charged with encouraging this process and are making progress. But these are entirely different from what is being proposed for malaria, HIV, and TB vaccines.”

One correspondent was scathing about the way Tremonti simply mixed all vaccines together in a deliberate attempt to confuse finance ministers, but also perhaps to make it easier to attack those pointing out problems with malaria, HIV, and TB vaccine APCs.

**Some Questions:**

These suggest the following questions:

- i) How much R&D costs are repaid through such ‘purchase commitments’ and how?

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<sup>630</sup> Tremonti, G., Background Papers, 2005, p23.

- ii) Does it refer to novel financial instruments (mixes of debt/equity, or new forms of venture capital with social returns part of the return, or PPP instruments) or does it refer only to R&D product-based region-based subsidies paid at the end? There is no talk of ‘financial instruments’ in the Malaria Vaccine Technology Roadmap, seemingly implying only one ‘novel’ ‘finance mechanism’ is of interest;
- iii) If it is based on blockbuster-style payments, might this conflict with collaboration, and create great reputational risks for firms? Do firms really want to set themselves up for 1990s AIDS-style standoffs and price disputes, with a new set of countries (South East Asia, at least, for malaria, and Russia, China, India and others for HIV)? Or is there only part-payment for a result? If so, how much of the result is based on private equity finance, and how much is not? How much IP and monopoly power does the ‘winning’ firm get? Since Russia can’t easily fit inside a HIV APC, due to the need for the APC to become huge to incorporate it, but it can fit inside a PPP, would the latter be a better way to incorporate Russia into a global effort to find HIV vaccines (and avoid the problem, discussed shortly, caused by a 5% HIV prevalence threshold triggering eligibility for Russia, China or India, with all its perverse impacts on incentives).
- iv) What are the institutional details?
- v) Is it flexible or fixed? What are the implications for risk and for capital costs?
- vi) If it is referring to a mechanism that pays out a subsidy only on certain purchases, does this create conflicts if ‘price’ under alternative mechanisms is set in a fundamentally different way? What if the ‘collaborative’ or PPP parts of the overall process work better on the basis of lower prices (maybe to encourage some countries to contribute to R&D efforts in the first place) but this is aggravated by processes, such as APCs, based on high prices?
- vii) Do quantities really get set by ‘country level’ choices however dysfunctional these may be, however much such choices should be coordinated with other parts of an overall package, and however much this might lead to self-fulfilling affects pushing results off in the direction of inferior vaccines? Indeed, we found that the logic did not work to drive ‘efficient’ choice anyway.
- viii) How many developers are encouraged? There is extreme scientific uncertainty about what is a ‘good’ route. There is great need for multiple follow-ons. And there is high global payoff to success. So, any mechanism needs to keep alive multiple parallel paths, and must be expected to do so right till the end of development. If even at \$5bn-\$6bn, a malaria APC only leaves room for at most one follow-on vaccine developed from all the push funded activity, and maybe even no room for any follow-on vaccine, what does that do to (and say about) the power of a malaria APC?
- ix) What does the phrase “commercially viable”<sup>631</sup> mean? The conclusion of this author is that APCs would be one of the least ‘commercially viable’ options for firms working on vaccines for malaria, HIV, and TB. He certainly would

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<sup>631</sup> VMSR p1.

not recommend to investors to back any malaria, HIV, or TB vaccine project that relied on an APC for its financial success.

### **9.1.2. Paying for ‘a good vaccine in the future’ is not the same as setting up an APC**

The confusion and the simplistic nature of much of the APC thinking being fed into the promotion effort, show up in some of the malaria files. For example “Commit now to pay for a good vaccine in the future”<sup>632</sup> is given a 5 star rating.<sup>633</sup> But the far more important, and challenging, “Articulate need for hybrid, market push/pull stimuli,”<sup>634</sup> is given just one star. Unfortunately, one could not even begin to set the terms of the former without knowing how the latter would work.

Similarly, a call is put out by some stakeholder voices to “Advocate for APCs”<sup>635</sup> even though it is clear that many participants do not even understand what an APC is – certainly little understanding of the sort of APC currently being heavily promoted. It makes about as much sense as a call to “advocate for world peace”. We all agree that world peace would be a jolly good idea. Achieving it in practice is a little bit more challenging.

Given that IAVI was advocating back at the 1997 Denver G8 for a HIV APC, the level of ignorance as to what a HIV APC would have to look like is quite shocking. IAVI continues to rely for its interpretation of what an APC actually is on others, principally the limited group of the key individuals advocating APCs for malaria, HIV and TB through CGD. Advocates talk about ‘educating’ the world about APCs, when they have, largely, failed to first ‘educate’ the malaria (and HIV and TB) community about what exactly are the pros and cons of what they are proposing.

If the notion of ‘purchase commitments’ refers an elaborate advanced subsidy scheme and its set of supporting institutions, and it does not refer to a commitment to purchase with an emphasis on capacity and access, it would be a shame to have the former foisted on the Roadmap supporters if they were really imagining the latter. Nobody disagrees that one of the failures in the past was the under-use of products, but that is a totally separate issue from R&D. Perhaps before the “associated public relations campaign”<sup>636</sup> to promote APCs, we should all know a bit more about what the PR exercise will be in aid of?

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<sup>632</sup> RMSR p31.

<sup>633</sup> As an indication of the degree of importance.

<sup>634</sup> RMSR p31.

<sup>635</sup> RMSR p34.

<sup>636</sup> MVRM p34: “Advance purchase commitments can be encouraged by defining minimum criteria for the vaccine and by launching an associated public relations campaign.”

## **9.2. Why are there no APCs for Alzheimer's, cancer, obesity, and the common cold?**

### **Misidentifying the problem?**

We have to be extremely careful when we interpret failure of “market forces”<sup>637</sup> as meaning that the “market [is] not big enough.”<sup>638</sup> Recent policy advice has tended to presume that it is principally the poverty of potential recipients that holds back the successful development of malaria, HIV, and TB vaccines, and *not* the complexity of the science, and the difficulties and failures of the mechanisms we are trying to use to tackle the problem. Indeed, the scientific difficulty is deliberately trivialized away<sup>639</sup> so as to make purchasing power the *only* real issue.

To what degree does this purchasing power reasoning ever hold? The potential markets in the US alone for drugs and vaccines even partially effective against Alzheimer disease, or a vaccine 100% effective against the common cold would be huge. A drug that greatly cut back-pain would save firms tens of billions of dollars per year globally. Insurance firms and employers would save billions a year. Why are there not much stronger incentives to develop treatments, even vaccines, for Alzheimer disease or the common cold?

If we look at other diseases of the rich world, for which one would expect high purchasing power, there are *many* areas that are neglected relative to their health impact and potential value to society. Kaplan and Laing, after an extremely thorough analysis, list the following.<sup>640</sup>

- 1) Infections due to antibacterial resistance;
- 2) Pandemic influenza;
- 3) Cardiovascular disease (secondary prevention);
- 4) Diabetes (Type 1 and Type 2);
- 5) Cancer;
- 6) Acute stroke;
- 7) HIV/AIDS;
- 8) Tuberculosis;
- 9) Neglected diseases;
- 10) Malaria;
- 11) Alzheimer disease;
- 12) Osteoarthritis;
- 13) Chronic obstructive pulmonary disease;
- 14) Alcohol use disorder: alcoholic liver disease and alcoholic dependency;
- 15) Depression in the elderly and adolescents;

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<sup>637</sup> MTRM p2.

<sup>638</sup> MVTR p7. This reminds us, incidentally, that such subsidy schemes are supposed to *add* to the *already existing* market. Like all subsidy schemes, as far as possible, subsidies must not go to those who do not need them, or to those who would have bought the product anyway.

<sup>639</sup> Kremer Appendix 3 in particular started this all off.

<sup>640</sup> Kaplan, W., and Laing, R., “Priority Medicines for Europe and the World.” WHO, November 2004, ‘Preliminary’ list taken from p45.

16) Postpartum hemorrhage.

If something far more fundamental is causing a failure to research the high-impact diseases of the rich, to ignore this problem when analyzing the highly complex high-impact diseases of the poor – such as malaria, HIV, and TB – will lead to failure to tackle this for the poor too.

### **Why not set up an APC for Alzheimer disease or cancer?**

Why *not* set up an APC for Alzheimer disease or cancer? The terms would be set on the basis of the *extra* market size needed to stimulate an Alzheimer's or cancer breakthrough, based on the expected scientific complexity of the problem and expected costs of development of such breakthroughs (and all follow-on products). Perhaps \$20bn or \$30bn would do it? This would still be fantastically cost-effective (by the Berndt et al. methodology for sure, given that Alzheimer's or cancer APC advocates would be using up to £100,000 per DALY in their underlying cost-effectiveness calculations for the US and other wealthy countries that would stand to benefit).

Maybe we could set up an Alzheimer's or cancer APC to be even cheaper? Just “make the *revenues* from R&D investments [on a set of Alzheimer's or cancer breakthroughs] similar to *revenues* realized from investments in typical existing commercial pharmaceutical products,”<sup>641</sup> and base it on the “\$3bn per disease”<sup>642</sup> methodology of CGD. As CGD explain it: “Our recommendation [of \$3bn per disease for HIV, malaria, and TB vaccines] is not based on any estimated cost of vaccine R&D.”<sup>643</sup> Isn't this methodology applicable to Alzheimer's too?

Kremer even argues that “there are limitations” to the use of APCs,<sup>644</sup> because “this approach does not address the case of products like cancer drugs, for example, for which there are large markets in the developed world.” But, surely, if cancer drugs and cancer vaccines are being neglected too, and if the logic of APCs is completely sound, why ever not push for an APC to bring about more cancer drugs and cancer vaccines? What about an APC for flu? Kaper et al. observe that “Development of an influenza vaccine that can reduce community spread or cover the drifted strains that appear in the midst of flu season would have a considerable impact.”<sup>645</sup> Perhaps Berndt et al. should try their analysis on all of the above diseases and not just malaria, HIV, and TB, and suggest the APC sums needed in each case?

If it really was “simple, easy to understand, and practical to implement,”<sup>646</sup> it would be an outrage not to have APCs in place for Alzheimer's and cancer and a range of other high-impact health problems (by now the reader should have worked out that APCs are not comparable to orphan drug and similar legislation). Why would America – perhaps in an

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<sup>641</sup> Berndt et al. 2005, *ibid.* p1.

<sup>642</sup> CGD, April 2005, *ibid.* Chapter 5 heading, p48.

<sup>643</sup> CGD, April 2005, *ibid.* p49.

<sup>644</sup> Kremer, M., 19 November 2005, *ibid.*

<sup>645</sup> Kaper et al. 2005, *ibid.* p10.

<sup>646</sup> Barder, O., CIPIH Forum, 19 November 2004.

extension to the recently announced Kerry-Lugar Bill – not put the highest of priorities *now* onto APCs for such conditions? If the advocates' claims were true, it would 'cost governments *nothing*' (a big political selling point) till Alzheimer's or cancer was cracked, and the solution would arrive decades ahead of when it otherwise would. What could be a more popular domestic policy? After all, we know that APCs are "potentially a powerful mechanism" as G8 leaders put it in their Ministerial statement.<sup>647</sup> Why is there not more of an outcry that Americans lose out on this "powerful" and "highly cost-effective" mechanism that is only applied to the challenging diseases of the poor (or of the less poor through to the rich in the case of HIV)? Do the diseases of the rich *not* deserve the same mechanisms as the diseases of the poor?

As Towse is quoted as saying, "The right design for an AMC might be determined only through the action of setting one up,"<sup>648</sup> since they have never been used before on anything. But why do we advocate experimenting with schemes on the poor that we are not prepared to experiment with on the rich? Barder, Kremer and Levine put it well: "We do not understand the position of those who advocate one system for development of new medicines for themselves and their children, and quite a different one for the children of the poor."<sup>649</sup> And Kremer put it better still: "If the system is not good enough for rich countries, why is it good enough for poor countries?"<sup>650</sup> (though, obviously, all these authors were not referring to the imposition of their proposal on the rich).

#### **More clues from HIV?**

HIV gives us further clues as to this misidentification of the problem. There *is* a large potential global HIV vaccine market, and not just a market for the very poor, and yet we see that only a tiny fraction of global HIV vaccine research is ultimately funded by private investors, and the little we do see is usually heavily subsidized, and depends on the salability of its results to public- and foundation-funded projects and so does not even reflect the influence of the ultimate, potentially large, 'market'. We will shortly see that there is also more of a market for malaria vaccines than often claimed. If the 'current' market is doing nothing, how can adding a bit more to it suddenly transform the situation for developers? Should we even be distracting ourselves from taking alternative routes by the very notion that an APC will radically transform the situation?

Failure of 'market forces' in the case of HIV may be referring to failure to coordinate on complicated science, failure to incentivize information sharing in a world where equity finance requires a high degree of privacy, failure to develop the right financial

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<sup>647</sup> [www.hm-treasury.gov.uk/otherhmtsites/g7/news/conclusions\\_on\\_development\\_110605.cfm](http://www.hm-treasury.gov.uk/otherhmtsites/g7/news/conclusions_on_development_110605.cfm).

<sup>648</sup> Zandonella, C., 2005, *ibid*.

<sup>649</sup> Barder et al. 2005, *ibid*. p4 (adopting by now a pretty standard technique of conflating meanings, with 'orphan drug with genuine market' treated the same as 'R&D subsidy scheme with no market'). Using 'children' to defend a proposal against those questioning it, rather than providing concrete evidence of effectiveness, reached its low-point in a DFID file under the subheading "Are there any outstanding Issues?" The line used to avoid addressing a range of awkward outstanding issues was: "work undertaken by the Centre for Global Development has established that, in principle, APCs could work...Most of all it benefits the children who receive vaccines sooner." [www.bvgh.org/documents/DFIDAPC2-pager.pdf\\_p5](http://www.bvgh.org/documents/DFIDAPC2-pager.pdf_p5). Observe that the quote refers to developing vaccines, not the procurement of currently-existing vaccines.

<sup>650</sup> Kremer, M., *The Lancet*, Vol. 365, 2005, p753.

instruments to handle risk, failure of sponsors and policymakers to prioritize research activity and to efficiently spread the research emphasis, failure of markets for intermediate products/knowledge, and many other things.

Masking this with a big ex post subsidy at the end is hardly the most obvious solution, even less so when it brings with it a range of costs and inefficiencies. We are told that “Research has shown that *the major obstacle* to the development of vaccines for these diseases [HIV, malaria, TB] is the absence of a market...,” (emphasis added)<sup>651</sup> even though no such research has ever existed, and the solution then offered has nothing to do with creating ‘a market’ anyway. The poverty of recipients of a potential malaria vaccine is a factor, but clearly it is far from the only or even overriding factor. To argue that ‘but for’ the purchasing power of an APC we would have malaria, HIV, and TB vaccines, is to seriously misidentify the underlying problem, and to seriously mislead policymakers and distract them from tabling the decisions and legislative ‘Bills’ they most need to enact.

Even *if* the lack of purchasing power did hold, this would still not be a strong stand-alone argument for a particular mechanism to pay for R&D, since the poverty of recipients would still mean that developed country tax payers would pay for the outcomes for the poor, however achieved. Therefore, it is the efficiency of the mechanism used to achieve the outcome *only* that counts.<sup>652</sup> If ex post APC subsidies are the most efficient mechanism to achieve this goal, they should be used. But if they are ultimately high cost, inefficient compared to alternatives, and difficult to set up and run, they should not be used. Poverty does not come into it.

#### **‘Big pharma’ may be rationally responding**

If, on account of their capacity to bring products to market and because of scale issues, ‘big pharma’ is to play a role in bringing malaria, HIV, and TB vaccines to market, the risk is that they are doing everything they want to do at the moment, and that it is not ‘lack of a sufficiently large enough market’ but lack of the scientific breakthroughs they need to scale up their response, and the huge range of problems they would face (discussed in this report) even if they do scale up their response. In the case of HIV, this is massively compounded by the extremely poor demand data on potential uptake of an HIV vaccine and by the unquantified, but likely relatively high costs of distribution and use,<sup>653</sup> and a huge range of other issues not amenable to an APC-fix. If policymakers set about creating new institutions and mechanisms based on tackling an incorrectly identified problem, they should not be surprised if investors do not respond – or even rebel<sup>654</sup> – and the policymakers waste a lot of their and other peoples’ time.

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<sup>651</sup> Senator Kerry, on launch of the “Vaccines for the New Millennium Act.” 14 September 2005, *Congressional Record*, largely under the influence of recent APC advocacy.

<sup>652</sup> Farlow, A.W.K. 2004, *ibid.* Section 3.

<sup>653</sup> Large-scale adult and adolescent vaccination in high prevalence countries and costly distribution to high-risk groups in lower-prevalence settings.

<sup>654</sup> This is not an idle comment. Several leading ‘big pharma’ executives have expressed horror to this author at the notion of an inadequate, yet expensive, badly-set up APC (given recent analysis, how could they be inspired to have any confidence that it will be set up otherwise?) that they are duty bound not to respond to, but that will drag their reputations down when they do not respond.

### **Why no event studies?**

Will investors respond to APCs for malaria, HIV, and other diseases? After all they are “potentially a powerful mechanism.”<sup>655</sup> Like any ‘potentially powerful’ new financial initiative, it should be possible to measure some of the ‘potential’ now. If APCs are expected by financial markets to work, they will create shareholder value, and this would show up in share prices *now*. This is a standard financial phenomenon.

A standard technique in financial economics is to do ‘event studies’ to see how financial markets respond to news about new policy initiatives. If “research has shown that *the major obstacle* to the development of vaccines for these [HIV, malaria, and TB] diseases is the absence of a market...,”<sup>656</sup> then removing that obstacle with an APC should completely transform the situation, and this year’s G8 announcements and the various announcements of IAVI, the World Bank, the Gates Foundation, MVI, the Italian Minister of the Economy and Finance, Giulio Tremonti, on behalf of the G8 Finance Ministers, etc. would have seen movement in the share prices of all those companies potentially benefiting from such a ‘powerful mechanism’, and have seen fresh private investment flooding into malaria, HIV, and TB vaccine research. Why is nobody looking?

An event study of an announcement related to an APC (even if not an actual APC) that even allows for the APC idea to be abandoned if the event study result is not favorable enough, should still yield a useful result, since if APC proposals are as powerful as the advocates claim, this power would swamp the risk of abandonment (indeed the test allowing abandonment would be credible enough to boost the response). No doubt, malaria APC advocates have sensibly put in place the systems for detecting crucial evidence of market sentiment, with event studies and various other mechanisms proposed to study private investor sentiment (to avoid relying just on claims about what that response would be, that we will later find to be extremely dubious indicators), and they will report back on these undertakings in the next year or so. We know from previous similar proposals that APC-type schemes do not add to shareholder value. We repeatedly hear from industry that APCs for malaria, HIV and TB vaccines will not add to shareholder value either.

### **The danger**

The danger is that by misidentifying the problem, key systems capacity of a huge range of organizations is exhausted, and institutional and human capital wasted in a fruitless effort trying to set up an APC subsidy scheme and a system of prices that cannot even be known, and rules that mean nothing,<sup>657</sup> and institutions that are incapable of doing what they have been asked to do, while the measures that could have been truly helpful are left undone, the real problems are not tackled, time is lost, and more die. This, in this author’s

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<sup>655</sup> G8 July 2005, *ibid*.

<sup>656</sup> Senator Kerry, *ibid*.

<sup>657</sup> Others worry too. VMSR p6, in the Section on ‘Market forces’ there are complaints that the whole process is shaping up to “Focus on price (and not the solution) too early in the process.” But this is what the APC literature is forcing us to do.

mind, is the biggest risk of the current agenda and why he has spoken out so much against it.

### **9.3. 'Collaboration' and private finance**

#### **9.3.1. Collaboration, information sharing, and competition: An unresolved puzzle**

The Malaria Vaccine Technology Roadmap frequently calls for 'collaboration' and forms of information sharing. The following are just a selection:

"Many of the priority activities contained in this roadmap can *only be accomplished by collaboration*. Such coordination can help to accelerate the development process and create conditions that allow new vaccine candidates to emerge and progress through pre-clinical and clinical research phases in the most efficient manner possible."<sup>658</sup>

There is need for: "extraordinary collaboration between different groups,"<sup>659</sup> and for a paradigm shift from the "culture of competition" to the "culture of collaboration" among both scientists and funders.<sup>660</sup>

There is need for "greater levels of coordination and information sharing than has been seen before,"<sup>661</sup> and one of the key challenges is: "Improving information sharing among all stages of vaccine research and development to facilitate learning."<sup>662</sup>

We hear that: "A novel approach to knowledge management and sharing is imperative."<sup>663</sup>

The Bethesda meeting pointed out the very practical implications of this: "When vaccines fail in the development process, 90% of the time it is because of poor validation of assays,"<sup>664</sup> and yet "It takes great cooperation to develop assays that everyone will accept... requiring the contribution of reagents and antigens, buffer recipes, and monoclonal, as well as someone to do tests."<sup>665</sup>

Kaper et al. argue for "multidisciplinary centers that coordinate collaborations between academia and industry [that] could help carry vaccines from the bench to the clinic, a breach that is often difficult to traverse."<sup>666</sup>

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<sup>658</sup> MVTR p4, emphasis added.

<sup>659</sup> RMSR p1.

<sup>660</sup> RMSR p12.

<sup>661</sup> MVTR p15.

<sup>662</sup> MVTR p36.

<sup>663</sup> VMSR p6.

<sup>664</sup> RMSR p5 Bethesda meeting.

<sup>665</sup> MVTR p6.

<sup>666</sup> Kaper et al. 2005, *ibid.* p26.

In regard to malaria vaccine(s) in particular, Kaper et al. point out many practical details: “Testing two different vaccine formulations in a heterologous prime-boost strategy, which can be very effective immunologically is also legally problematic, as it is often difficult for two separate companies to reach a legal agreement on applying two experimental products together. One solution to the problem is to wait for one product to be licensed and allow the other company to use that product off-label. However, this process could take many years, and it is possible that neither product would be licensed without the other.”<sup>667</sup> Furthermore, there are “many innovative approaches available for vaccine development, but there are few ways to make head-to-head comparisons of delivery systems, vectors, etc., because it is not in the interest of any party to develop these modes of comparison. Validated assays, common reagents, and common peptides are needed in order to make effective, meaningful comparisons of approaches to vaccine development and intellectual property issues that inhibit comparisons should be resolved.”<sup>668</sup>

Kaper et al. observe that: “Taking a vaccine concept from basic research to development requires that coalitions of investigators work together toward their common goal. Large-scale projects that combine the efforts of multiple investigators have proven more effective in producing vaccines than have small, disconnected ventures. Collaborative efforts help investigators learn from one another and ensure better transparency of clinical findings. Lack of collaboration, results in wasted and redundant efforts. Multidisciplinary centers to coordinate effective collaborations between academia and industry could help carry vaccines from the bench to the clinic. These types of partnerships are not common in many areas and should be encouraged. Funding agencies can encourage multidisciplinary collaboration in research through requirements in their requests for proposals... International collaboration is an increasingly important issue in vaccine work and productive cooperation should be encouraged.”<sup>669</sup>

The director of GSK’s Diseases of the Developing World (DDW) Drug Discovery unit, Federico Gomez de las Heras, put it thus: “In the diseases of the developing world, the problems are so big that collaboration – putting together all the different capabilities of industry, government, academia, and PPPs – is necessary.”<sup>670</sup>

But not all think this way for malaria, HIV, or TB vaccines. Ernst R. Berndt writing on behalf of the Center for Global Development, observed: “It is of course possible for people to believe sincerely that society’s arrangements for funding medical R&D are all wrong, and that instead of competition between firms, we should have collaboration...”<sup>671</sup>

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<sup>667</sup> Kaper et al. 2005, *ibid.* p14.

<sup>668</sup> Kaper et al. 2005, *ibid.* p22.

<sup>669</sup> Kaper et al. 2005, *ibid.* p23.

<sup>670</sup> Quoted in Thayer, A.M., “Fighting Malaria.” *Chemical and Engineering News*, 2005, Vol. 83, No. 43, pp. 69-82. <http://pubs.acs.org/cen/coverstory/83/8343malaria.html>.

<sup>671</sup> Berndt, E.R., WHO Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, [www.who.int/intellectualproperty/forum/en/Discussion2\\_text.pdf](http://www.who.int/intellectualproperty/forum/en/Discussion2_text.pdf), 17 December 2004.

**Collaboration is perfectly consistent with competition**

Collaboration is perfectly consistent with competition and the involvement of commercial players. The human genome project was a highly competitive yet collaborative effort.<sup>672</sup> MMV is heavily involved with commercial players and looks likely to beat its goal to register at least one new effective and affordable drug before 2010; it may actually have as many as three or four by 2010. This is a seriously impressive achievement, based on extremely restricted funding, in creating a continuous supply of new-generation drugs to meet the challenge of changing resistance patterns. Indeed, it is fairly key to the thinking of this author that APCs will fail badly on the competition and commercial front compared to potential alternatives, and that we need more of both ‘collaboration’ and ‘competition’ and a greater *variety* of involvement of commercial players.

We are informed that “Better collaboration” is to be welcomed,<sup>673</sup> and yet that “collaboration has proven challenging,”<sup>674</sup> and “collaborations between the public and private sector can be very fruitful in vaccine development, but conflicts of interest can impede these partnerships, making the transitions from academic research to clinical development to commercialization extremely difficult.”<sup>675</sup> Into this, advocates pitch models and funding proposals that make no concessions to the problems of collaboration, and, indeed, we will find below, even aggravate it.<sup>676</sup>

Light argues that: “Going after a big contract designed not to pay a penny until a company has invested a decade or more in discovery, development, testing, and approval is a less cost-effective way to commit billions of dollars than to do what Gates and others are doing already: Funding the best basic research ideas (including from private-sector teams), creating PPPs and other bridging organizations, and bringing the best experts together in a global research community...Nothing [in the CGD Report] is mentioned about the daunting scientific barriers to developing a vaccine for either malaria or HIV-AIDS. The Kremer model assumes that creating a large purchase will induce a solution; but scientists who have done the research say that the scientific obstacles may be insurmountable because the targets are multiple and evolving. This observation leads to a more serious weakness in a global competition for a big contract: it rewards scientific secrecy rather than sharing, whereas the cooperative push efforts in recent years have fostered partnerships and sharing...The more cooperative government, university and nonprofit research teams will probably get nothing under the advanced commitment model. The big trade-off question gets buried by emphasizing that advanced

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<sup>672</sup> There are of course nuances to this, with one camp talking up the public-sector side of it, and another the private-sector spur, and therefore disagreement as to exactly what the case shows.

<sup>673</sup> MVTR pii.

<sup>674</sup> MVTR p36.

<sup>675</sup> Kaper et al. 2005, *ibid.* p15.

<sup>676</sup> Reports, such as that of CGD, added comments about the need for integration with PPPs only towards the end of the process, and never tackled how it was to be done. See Kremer Appendix 3 where each project has no information link or collaboration link to any other project – a model that is not particularly appropriate to malaria or any especially complex vaccine, though it underlies the whole CGD approach built upon it.

commitments are to be added to current push efforts to ‘complement’ them, as if committing a few billion dollars to ‘pull’ funding has no effect on ‘push’ funding.”<sup>677</sup>

### **9.3.2. The role and challenges of equity and venture capital finance**

The problem is that, for all the nice words about ‘sharing’, there is a fundamental unresolved conflict between the need to share information and the need for equity investors to protect the private value of information discovery that they have financed, so long as equity investors are being used as the source of funds to pay for R&D, as is the case for a malaria APC: APCs are essentially about paying returns to equity-based investors, and are, supposedly, essentially equity-based financial instruments themselves.

While there is a need to “find the appropriate balance between healthy competition and productive cooperation,”<sup>678</sup> this is easier said than done. In the case of very large ‘by-gones are by-gones’ investments (as typical in vaccine development) and heavy use of equity finance (as typical in private pharmaceutical finance), the very act of ‘sharing’ information can reduce the value of the equity of investors unless, somehow, the value of sharing can be captured in equity prices.

It is worth reviewing why equity finance arises in the first place as the core mode of finance for private pharmaceutical research, before moving on to review some of these informational problems.

#### **Why equity financed?**<sup>679</sup>

The fundamental problem in financing vaccine research, as indeed with any research, is the usual one of the ‘separation of ownership and control’ of those firms engaged in research. Those who own the firm face managers who control the firm, but the managers have most of the information, and getting them to reveal it is not always easy or even rational in many cases (since it reveals it to rivals too). This separation creates two co-existing and somewhat conflicting problems. Firstly, managers/scientists have a preference to invest in things that benefit them (a larger firm size, nicer offices, more staff under their control, higher pay, prestige projects, etc.). But, secondly, being risk averse, and certainly more risk averse than shareholders, they wish to avoid risky R&D. Normally, leveraging<sup>680</sup> would be useful to mitigate the first problem, but it is of limited use in the case of R&D-intensive firms. The knowledge asset created by R&D investments is intangible, often contains a lot of ‘know-how’ (vaccines especially), is partly, if not largely, embedded in human capital, and is often very specific to the firm. With banks and debt-holders reluctant to invest where there is no physical asset to secure loans<sup>681</sup> (and given that the sunk costs associated with vaccine R&D investments are

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<sup>677</sup> Light, D. *ibid.*

<sup>678</sup> MVTR p39.

<sup>679</sup> See Farlow, A.W.K., 2004, Section 12 for more of this.

<sup>680</sup> I.e. the use of debt. The unique thing about debt is that it has a default state. The price of equity, however, can move up and down without triggering ‘equity default’.

<sup>681</sup> Williamson refers to ‘re-deployable’ assets (those the value of which is almost the same in alternatives to the current use) as more suited to a governance structure based on debt. Williamson, O.E., “Corporate Finance and Corporate Governance.” *Journal of Finance*, 1988, Vol. 43, pp. 567-91.

higher than for ordinary firms) capital structure is therefore less leveraged (i.e. less debt-based) than average.

Servicing debt also requires a stable cash flow. Often R&D must be sustained at a certain stable level to be productive and it would make R&D even more expensive if it had to compete with this cash flow requirement. Again, this tends to reduce the use of debt finance for R&D, and again this may raise the cost of capital if alternatives are more expensive.<sup>682</sup> Furthermore, if bankruptcy is a possibility, managers may avoid variance-increasing R&D projects that shareholders want.<sup>683</sup> This leads to fewer long-term projects, and this too mitigates the use of debt.

So, the apparent solution to the first problem that would seem to suggest reducing free cash flow would simply force the use of high cost external finance – which makes R&D more expensive.<sup>684</sup> The optimal solution is to somehow increase the long-term incentives of managers rather than reduce free cash flow. This leads to the conclusion that that part of research, here vaccine research, that is privately financed will be largely based on equity forms of finance. This encapsulate why pharmaceutical R&D in general takes place in equity-based firms, older firms with already established cash flow records, or newer firms with access to venture capital – but certainly not debt-backed or bank-financed firms.

But this leads to a new set of problems.

One reason many companies do not do certain kinds of research is not because of the lack of an end market *per se*, but because it is hard to communicate to equity-based markets the value of research and hence to raise the finance for it. Problems with asymmetric information and moral hazard create an extra gap between the private rate of return and the cost of capital when the innovator-investor and financier are different. Firms therefore do not invest in innovations that would pass the private returns hurdle.<sup>685</sup> The ‘lemons premium’ is higher for R&D than for ordinary investment because the difficulty of separating good from bad projects in investors’ minds when projects are long-term R&D investments is much greater than with short-term low risk projects.<sup>686</sup> This is likely to be extreme in malaria and similar vaccine research.

The asymmetric information problems is made worse by the fact that many firms are also reluctant to release information to financial markets, afraid of revealing information to competitors. This reduces the quality of information signals that financial markets need to

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<sup>682</sup> It depends on the tax treatment of debt versus equity, etc.

<sup>683</sup> Intuitively, the variance sometimes leaves them in a default state in the debt contract. Equity investors however can hedge via a diversified portfolio, so should be less (if at all) concerned with variance *per se*.

<sup>684</sup> There is also good empirical evidence that limiting cash flow in R&D intensive firms is less desirable as a method to reduce the agency costs of the first problem.

<sup>685</sup> Kremer mentions that in private correspondence with Jon Horton of GSK, Horton remarks that firms “like to see a return on investment by the end of year 3.” (Kremer, M., No. 10 Policy unit, Appendix 1, p5). This is all part of the same problem.

<sup>686</sup> Leland, H., and Pyle, D., “Information asymmetries, financial structure and financial intermediation.” *Journal of Finance*, 1977, Vol. 32, pp. 371-387.

base investment decisions on.<sup>687 688</sup> In worse-case scenarios the problem bites so severely that projects disappear altogether. This is particularly aggravated by the long gestation periods of pharmaceutical projects and is especially bad for projects that would actually require information revelation and sharing (such as HIV, malaria, and TB research). There is a tendency in the APC/subsidy literature to talk in the mantra of ‘efficient financial markets’ where none of these difficulties arise, and to treat finance as simply a veil behind which real economic activity takes place. This is where a rôle for venture capital, VC, comes in.

### **The use of venture capital**

Sometimes the arm’s-length market-based financial systems of the US and UK are contrasted with the bank-centered capital markets of Continental Europe and Japan. VC is a combination of the good bits of both. It gives the strong incentives for manager-entrepreneurs of the stock-market, and the monitoring of the bank-based system. The optimal form of the VC contract is actually a complex debt-equity hybrid;<sup>689 690</sup> more like debt when the firm does badly, but more like equity when it does well.<sup>691</sup>

The VC solution to the financing of vaccines has its limits however. VC tends to concentrate on few sectors at a time and also tends to make investments of a minimal size that may be too large for some start-ups and smaller ventures. VCs also require a thick, active market in small and new stocks (NASDAQ and EASDAQ for example) to provide an exit strategy for early-stage investors, so they can move on to new projects, and to enable successful entrepreneurs to regain control of their firms (and to give entrepreneurs incentives to start up in the first place). VC also tends to be pro-cyclical (though it is hard to disentangle the direction of causation). Empirically, even though there is a great deal of entry to the VC industry, returns in the industry are still high, suggesting a high required rate of return. The financial side of an APC does not automatically solve these particular problems. And, we will see, the modeling of APCs has largely ignored many of them.

### **Some lessons**

This suggests a few lessons for us in the context of malaria vaccine R&D. First, efficiency of finance was always defined above relative to a given informational structure. Once we worry about the problems caused by the narrowing down of research leads and the conflict between equity forms of finance and the need for collaboration, a more open information structure, with, of necessity, less strictly equity-based finance, may possibly improve efficiency if it allows better collaboration, but the thought is not much developed (see Farlow 2005, various, that start to play with this idea). Second, the

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<sup>687</sup> Bhattacharya, S., and Ritter, J.R., “Innovation and Communication: Signaling with Partial Disclosure.” *Review of Economic Studies*, 1983, Vol. 50, No. 2, pp. 331-46.

<sup>688</sup> Anton, J., and Yao, D., “The Sale of Ideas: Strategic Disclosure, Property Rights, and Contracting.” *Review of Economic Studies*, 2002, Vol. 69, pp. 513-531.

<sup>689</sup> Aghion, P., and Bolton, P., “An Incomplete Contracts Approach to Financial Contracting.” *Review of Economic Studies*, 1992, Vol. 77, pp. 338-402.

<sup>690</sup> Dewatripont, M., and Tirole, J., “A Theory of Debt and Equity: Diversity of Securities and Manager-Shareholder Congruence.” *Quarterly Journal of Economics*, 1994, Vol. 109, pp. 1207-1054.

<sup>691</sup> Since this is incentive compatible.

kind of instruments that may do most to help financially are not ones that save all payment up to the end, since that aggravates some of the information revelation problems that put investors off in the first place. Similarly, having pay-at-the-end instruments such as APCs that are supposed to entice players early in the process requires some notion of milestones, and we already saw that this has its problems (and that CGD eventually left milestones out of their report). To this author, this suggests more finance direct to earlier players, and financial instruments that enable the right mix of equity finance and information sharing.

### **Giving a price to information**

Encouraging firms to share information requires them to believe that they can internalize the value of the released information in contracts, traded perhaps on a knowledge market, with use of the information policed out of the hands of those who did not pay for its discovery. However, we know that such markets struggle to work in some of the complicated settings typical of malaria vaccine research, for all kinds of reasons – such as insufficient market liquidity,<sup>692</sup> bargaining problems, transactions costs, information that is hard to quantify and price, difficulty in making long-term contracts long enough, science with feedback loops and ‘public good’ aspects, etc.

From an Industrial Organization perspective too, the success of one firm may depend on the lack of success of other firms. While the Roadmap claims that “Improved coordination and information sharing can help to ensure that all efforts yield the maximum scientific learning, capturing important information relevant to the *strategic goals of the community whether or not the particular candidate being investigated proves to be successful*,” (emphasis added) no explanation is given as to why equity financed (i.e. APC-financed) firms would do such a thing, given that in furthering the “strategic” goals “of the community” the firm also furthers the strategic goals of its competitors.

One response might be industrial structures with fewer and larger players, having control over research routes so as to more easily internalize the value of information. But this is itself inefficient for a process that relies on multiple research routes to develop high-quality, multiple, evolving products.

Again, is collaboration *easier* if firms are not relying on the expected very large subsidy in the end market?<sup>693</sup> Given the mechanism for distributing APC subsidy payments, there may be a strong incentive to ‘hold out’. For example, existing developed economy patent holders, facing potentially emerging-economy competitors, can exploit ‘secret’ know-how (as well as more general technical know-how, and undisclosed test or other data), including refusing to contract to transfer necessary know-how, creating a barrier to entry and a higher expected subsidy payment.

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<sup>692</sup> Not enough buyers on both sides of deals, such that the market ‘dries up’. This is also a dynamic issue over multiple periods, such that success in most periods, but failure of liquidity in just a few periods, can be damaging for investors, i.e. the (expected) chain of investors needed to make things work breaks down.

<sup>693</sup> Remember that if there truly are multiple competing players, firms always require back in the expected sense many times their actual costs, and most get nothing.

How are the “wins of collective [compared to the] losses of the individual,”<sup>694</sup> captured in a financial instrument? How does one mix equity-based competition with information sharing? This problem is aggravated as the level of sunk costs rises. Sharing may require firms not to be too exposed to such losses. What novel financial instruments could be created for encouraging information sharing, even in situations where such sharing destroys company value? The author does not pretend to have the answer (see Farlow 2004, section 12, that explores a bit further how to reconcile ‘collaboration’ with a role for equity finance, and Farlow May 2005 Section 5 for finance as part of a “Global HIV Vaccine Enterprise”).

The intuition for a solution is that the ‘sharing’ bit should not be attached to the equity bit, and that equity finance should only get attached to the bit that can be made exclusively a ‘private good’, and that if sharing increases risk to firms and makes their finance more expensive, the novel financial instrument should reflect this by making its terms of finance cheaper to those who share. This suggests that APCs are too blunt, and that something more subtle is needed, possibly better PPP financial contracts as allocators of risk, and the use of truly *new* and *novel* financial instruments.

### **First and second goals**

We can think of this in the all too familiar setting of the first and second malaria vaccine goals. Even if ‘sharing’ may “help *the community* fully capitalize on learning opportunities,” would an individual firm really ‘share’ all information in light of the second goal, even if this is privately costly for the firm in light of the first goal (and the sunk investments, supposedly, of the many firms pursuing the first goal)? Imagine a firm sharing in a way that risks increasing the chances of another goal-1 vaccine or of the goal-2 vaccine being achieved by *someone else* and thus undermining the value (e.g. the lifespan) of the goal-1 product the original firm is working on. Given the practically non-existent commercial pull of the second goal, there is even less incentive to create the commercial contracting to create financial value to such acts of sharing anyway. The value of secrecy for earlier goals is much more salient to investors than the heavily discounted dim and distant value of sharing towards the second goal.

### **Getting around these problems by assuming them away**

Unfortunately, recent APC models have got around these tricky issues by simply presuming them away. The underlying science of models like Kremer Appendix 3 is non-collaborative, with no information spillovers across vaccine developers, no ‘know-how’ monopolies, no externalities, and no technological feedback loops (the modeling uses what Farlow 2004 termed ‘single route’ technology) and information is strangely ‘open source’ in the way it is set up.<sup>695</sup> And there are a range of other limitations, including no financial constraints, no investment hold-ups, no strategic behavior (this might surprise many), no concentrations of market power based on IP ownership, etc. In other words, it

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<sup>694</sup> But how would the firm charge for this? And how does it extract the total value from all the ‘collective’ (it has provided something of public good value to many, say, but how does it extract optimally from each?). The standard argument would be via IP, license fees, etc.

<sup>695</sup> Farlow, A.W.K., 2004 discusses this underlying assumption of open source technology in the underlying Kremer model, and the way it is then used to justify essentially 100% closed source solutions.

is not presumed that knowledge markets would arise to overcome the problems; it is assumed that there is no need for such markets in the first place. Such models are not going to be particularly illuminating for describing projects involving science with lots of feedback loops, ‘collaboration’ and the sharing of information, such HIV, malaria, and tuberculosis vaccine R&D.

#### **9.4. Impact on goal-2 vaccines of the premature emphasis on goal-1 vaccines**

The Malaria Vaccine Technology Roadmap argues that “exploring novel vaccine concepts can lead to highly efficacious vaccines by 2025.”<sup>696</sup> However, we have seen that the commercial incentives on the goal-2 vaccine will be weakened by the heavy discounting of future payments, the high expected production costs of goal-2 vaccines, the risks that policy makers will not put in place the funds to fully pay for goal-2 costs, and worries that all the APC subsidy pool will be consumed on goal-1 vaccines anyway.<sup>697</sup> It will be non-commercial activities that will drive efforts towards the second goal.

This creates concern for the impact on goal-2 activities when ‘commercial’ emphasis is placed on goal-1 activities. The phrase ‘commercial’ is in quote marks since it really just refers to the way all funding may get biased towards the first goal, even though this may be through the statist pressures of an APC scheme and not strictly standard ‘commercial’ pressures.

#### **Wide stakeholder worries**

All of the malaria files (the Roadmap, The Stakeholder feedback, the MVI files, etc.) reveal wide worries already about the lack of access to data and key technologies:

The Bethesda Stakeholders meeting pointed out that the low level of commercial interest had kept IP costs relatively low, but that APCs could “push to increase patenting, raising transaction costs, particularly for combination vaccines,”<sup>698</sup> while lowering the incentive to ‘share’ information (or to combine vaccine concepts) for goal-2 vaccines. Similarly, APCs “could unnecessarily increase patenting and transactions costs,”<sup>699</sup> though setting them too low would also be harmful, given the perverse incentives created by having to raise the size of subsidies in response to a lack of response<sup>700</sup> and the low likelihood that there would be the political will to put together a funding mechanism that will dramatically rise in size over time to ‘catch up’ with what is needed.

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<sup>696</sup> MVTR p7.

<sup>697</sup> The usual response at moments like this is to say that the committee running everything will be able to resist the early overuse of a goal-1 vaccine and leave ‘plenty in the subsidy pool’ for goal-2 vaccines. But this author is not interested in what advocates would like to believe, but only the likely actual behavior in the cold morning light of day.

<sup>698</sup> RMSR p8.

<sup>699</sup> MVTR p34.

<sup>700</sup> Maurer, S., March 2005, *ibid.*

Even though private companies are found to be reluctant to take part in early-stage malaria vaccine development due to the risk, other researchers say that they are unable to get hold of the cGMP capabilities of these firms. Suggestions to tackle this included “open centers for formulation and process development that could be accessed by researchers in the public sector,” and “better mechanisms for researchers to access private-sector capabilities... under the right partnership agreements.” We need more work on how the nature of R&D partnership agreements will be affected by a mechanism storing up payments to the end. In particular, if it is determined that the chief driving force for R&D (and not production capacity) will not be APC-style subsidies, might this help encourage access to cGMP capabilities?<sup>701</sup>

### **A range of stakeholder quotes**

Some stakeholders went further, arguing “This is a public health market, not commercial.”<sup>702</sup>

There is talk of the importance of “efforts to reduce or remove sample access limitations”<sup>703</sup> with claims that “limited access to data slows research progress.”<sup>704</sup>

“Other challenges to vaccine design include access to adjuvants, platforms, and process development capabilities. Public-sector researchers need easier access to such resources, which typically reside in the private sector.”<sup>705</sup> Yet, the “availability of potent adjuvants outside of industry...[is] potentially controlled by commercial interest unwilling to license/share.”<sup>706</sup>

There is need to “facilitate access to enabling technologies not in the public sector...”<sup>707</sup> and the need to “facilitate procedures to overcome intellectual property barriers (academic and industry)”<sup>708</sup>

There are “Restrictions on development and partnerships imposed by intellectual property rights and licensing issues.”<sup>709</sup>

“IP issues restrict access to technologies (e.g. assays, models, adjuvants, etc.).”<sup>710</sup>

There are “prohibitive transactions costs” through the licensing process.<sup>711</sup>

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<sup>701</sup> Under more ‘open source’ type license agreements, with the open part of the agreements relating to the malaria vaccine uses?

<sup>702</sup> VMSR p7.

<sup>703</sup> MVTR p16.

<sup>704</sup> VMSR p7.

<sup>705</sup> MVTR p18.

<sup>706</sup> VMSR p10.

<sup>707</sup> RMSR p26.

<sup>708</sup> VMSR p9.

<sup>709</sup> MVTR p32.

<sup>710</sup> VMSR p5.

<sup>711</sup> MCTR p34.

There is a need to:

“Develop business plans for centralized, open centers for process development, assay and reagent standardization, and formulation.”<sup>712</sup>

“Encourage rapid and frequent data sharing.”

“Implement a web-based knowledge sharing process.”

“Clarify or pool IP that is malaria-specific.”

All these issues are more difficult to work through in an environment emphasizing the creation of large ex post R&D subsidies concentrated on goal-1 vaccines. If no commercial incentive could possibly be created now for the higher efficacy goal-2 vaccine, and would not be believed by developers anyway, why not think of better ways to use commercial players at shorter distances in light of goal-2?

### **9.5. The ‘option value’ of malaria vaccine R&D**

One financial issue never touched upon in the APC literature is that of the option value of malaria vaccine R&D.<sup>713</sup> One possibility is that APC subsidy schemes become part of a greater ‘investment option,’ as back-ups to other more lucrative but risky investments. This is especially problematic for HIV, given the different clades and the variable value of sub-markets. However, it is also a possibility for malaria.

First, malaria increasingly covers some richer markets, particularly in Asia, and there are potential markets for malaria vaccines for armed forces and travelers. According to Hay et al.<sup>714</sup> nearly 1 billion people are exposed to hypoendemic and mesoendemic malaria in southeast Asia, and 40% of the world’s population still lives in areas where malaria is transmitted, with this growing to half, or nearly 3.5bn people, by 2010. Snow et al.<sup>715</sup> conclude that whilst most clinical events attributable to *P. falciparum* are concentrated in the African region, 25% of the world’s clinical attacks were in South East Asia and the Western Pacific. By the time a viable 80% vaccine is ready, the potential richer markets paying for it<sup>716</sup> will be much richer than they are now.

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<sup>712</sup> MVTR p42.

<sup>713</sup> And neglected disease research in general, including HIV.

<sup>714</sup> Hay, S.I., Guerra, C.A., Tatem, A.J., Noor, A.M., Snow, R.W., “The global distribution and population at risk of malaria: past, present, and future.” *The Lancet Infectious Diseases*, 2004, Vol. 4, Issue 6, pp. 327-336.

<sup>715</sup> Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., and Simon I. Hay, S.I., “The global distribution of clinical episodes of Plasmodium falciparum malaria.” *Nature*, 2005, Vol. 434 pp. 214-7, [www.nature.com/nature/journal/v434/n7030/full/nature03342.html](http://www.nature.com/nature/journal/v434/n7030/full/nature03342.html).

<sup>716</sup> The word ‘it’ includes the possibility that a vaccine is different for a richer market, but that it benefited from the R&D for the poorer markets (i.e. there is some ‘option’ thinking going on).

In addition, it is no surprise that pre-erythrocytic stage (sporozoite and liver stage) vaccines are best supported financially, because they have a potential market in developed countries, for tourists, short-term visitors such as business people and field researchers, but especially for the armed forces, for which a temporarily effective ‘vaccine’ would have high value. Such vaccines may yield a beneficial result for the rich and military personnel without any viable use for the poor.

Second, malaria provides a good environment in which to test platform technologies (technologies usable across applications); the observation is that part of what is being tested in some vaccines may be the delivery technology or the power of the adjuvant, with the results sometimes profitable elsewhere even if the particular malaria vaccine candidate under observation is ultimately not particularly usable in poor countries.

Third, malaria vaccines for ‘richer’ markets would benefit from advances on vaccines for poorer markets. While *P. falciparum* is the most lethal species, and the most prevalent throughout the tropics and subtropics, there are other species of malaria too. This creates another route for certain kinds of vaccine R&D to have an investment ‘option value’. It is not clear how much *P. vivax* vaccine development would benefit from *P. falciparum* vaccine development. Cross-species challenge experiments in the 1970s using irradiated sporozoite vaccine showed that it would be difficult to achieve protection in a single vaccine against several species,<sup>717</sup> and R&D has thus tended to search separately for species-specific vaccines against *P. falciparum* and *P. vivax*. But *P. malariae* and *P. ovale* vaccines should be able to be built off successful *P. falciparum* and *P. vivax* vaccines.

We briefly review each of the three, non-*falciparum*, species:

### ***P. vivax***

It may be that one of the biggest option values on current vaccine research (outside of the military value of a vaccine and of the value of testing platform technologies) is on *P. vivax* (also called tertian malaria<sup>718</sup>). *P. vivax* has the widest geographical range – temperate as well as tropical and subtropical zones – of the malaria parasites that infect humans because of its ability to survive at lower temperatures within a mosquito. It is widely distributed throughout the world but predominantly in Asia, the Western Pacific, and the Americas, and preferentially infects only the young. *P. vivax* accounts for over half of all malaria infections outside Africa, and roughly 10 percent of infections in Africa,<sup>719</sup> although it is much less Africa-focused.

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<sup>717</sup> Clyde, D.F., “Immunity to *falciparum* and *vivax* malaria induced by irradiated sporozoites: a review of the University of Maryland studies, 1971-75.” *Bulletin of the World Health Organization*, 1990, Vol. 68(Suppl.), pp. 9-12.

<sup>718</sup> *P. falciparum* is malignant tertian malaria.

<sup>719</sup> Mendis, K., Sina, B.J., Marchesini, P., and Carter, R., “The neglected burden of *Plasmodium vivax* malaria.” *American Journal of Tropical Medicine and Hygiene*, 2001, Vol. 64, 1 Suppl, pp. 97-106.

*P. vivax* only attaches to human red blood cells possessing the Duffy blood group cell surface antigen.<sup>720</sup> West Africans lack genetic expression of this antigen, so it is absent from the region. *P. vivax* has recently made a comeback in Korea, Peru, Indonesia, and China<sup>721 722 723 724 725</sup> and produces approximately 75 million acute episodes every year.<sup>726</sup> What is the potential market for *P. vivax* vaccine(s)? Given that it is concentrated in non-African countries, how does this affect reasoning about ability to price?

### ***P. malariae***

*P. malariae* (also called quartan malaria) has a geographic distribution roughly the same as *P. falciparum*, but is much patchier in coverage. It has the distinction of decades-long persistence. It manifests acutely as a febrile illness with anemia. In the United States, *P. malariae* accounted for more cases of transfusion-associated malaria than any other malarial species in a 20-year review of cases.<sup>727</sup> In West Africa and Papua New Guinea, repeated and/or continuous infection with *P. malariae* is associated with childhood nephrosis,<sup>728</sup> which is usually steroid-resistant, and may progress to renal failure and death even after successful treatment

### ***P. ovale***

We know least about *P. ovale*. The parasite has a distribution over all continents, with sporadic transmission, but it primarily affects tropical Africa and New Guinea, where prevalence among children is between 2 to 10 percent, and sometimes in Asia and the western Pacific. It manifests as a relatively mild form of malaria closely resembling *P. vivax* and is rarely fatal.

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<sup>720</sup> Miller, L., Mason, S., Clyde, D., and McGuiness, M., "The resistance factor to *Plasmodium vivax* in blacks. The Duffy-blood-group genotype, FyFy." *N. Engl. J. Med.*, 1976, 295, pp. 302-304.

<sup>721</sup> Sleight, A.C., Liu, X.L., Jackson, S., Li, P., Shang, L.Y., "Resurgence of vivax malaria in Henan Province, China." *Bulletin of the World Health Organization*, 1998, Vol. 76, No. 3, pp. 265-270.

<sup>722</sup> Sharma, V.P., "Current scenario of malaria in India." *Parassitologia*, 1999, Vol. 41(1-3), pp. 349-353.

<sup>723</sup> Chai, J.Y., "Re-emerging *Plasmodium vivax* malaria in the Republic of Korea." *Korean Journal of Parasitology*, 1999, Vol. 37, No. 3, pp. 129-143.

<sup>724</sup> Roper, M.H., Torres, R.S., Goicochea, C.G., Andersen, E.M., Guarda, J.S., Calampa, C., Hightower, A.W., Magill, A.J., "The epidemiology of malaria in an epidemic area of the Peruvian Amazon." *American Journal of Tropical Medicine and Hygiene*, 2000, Vol. 62, No. 2, pp. 247-256.

<sup>725</sup> Barcus, M.J., Laihah, F., Sururi, M., Sismadi, P., Marwoto, H., Bangs, M.J., Baird, J.K., 2002. "Epidemic malaria in the Menoreh Hills of Central Java." *American Journal of Tropical Medicine and Hygiene*, Vol. 66, No. 3, pp. 287-292.

<sup>726</sup> Sina, B., "Focus on *Plasmodium vivax*." *Trends in Parasitology*, 2002, Vol. 18, No. 7, pp. 287-289. *P. vivax* invades only young reticulocytes and this limits the total parasite load and disease severity. The typical *vivax* malaria attack manifests as sudden, dramatic paroxysms recurring about every 48 hours, for several weeks if patients do not receive antimalarial treatment, followed by anemia. Occasionally there are severe and fatal complications from lung injury and splenic rupture. In rare cases, there have been cerebral complications. We know little about the effect of *P. vivax* malaria on pregnancy, though there have been reports of links to maternal parasitemia, anemia, and low birth weight. *P. vivax*, along with *P. ovale*, undergoes true relapse, that is reseeding of the bloodstream from dormant parasites (hypnozoites) in the liver.

<sup>727</sup> Guerrero, I.C., Weniger, B.G., and Schultz, M.G., "Transfusion malaria in the United States, 1972-1981." *Annals of Internal Medicine*, 1983, Vol. 99, No. 2, pp. 221-226.

<sup>728</sup> Heavy protein loss in the urine, peripheral edema, and renal impairment.

**The problems created by option components**

As well as being a potentially useful way to interest firms in researching neglected diseases, the presence of alternative markets and different technologies feeding off discoveries, does however create problems from a public policy and R&D perspective:

- 1) It adds to the difficulty of judging the genuinely additional R&D being incentivized that is targeted at a disease specifically for the poor. This intensifies the difficulty of using mechanisms that rely on sponsors tracking ‘additional’ R&D to work out how much more or less to pay via the mechanism;
- 2) It can be used to distort funding decisions of government and foundations towards highly expensive activity that, in terms of the ultimate goal of a vaccine for the poor, is less efficacious than alternative activities and funding mechanisms;
- 3) There is potential loss of important IP, that ends up having more value elsewhere but such that there is no, or less, ownership rights over it for the sponsors of the research. This may be especially so if APC end-subsidy schemes are mixed with expensive push funding. The product under trial may not be used in the way stipulated by the subsidy scheme and may never make a call on the subsidy scheme, yet the presence of the scheme (that forces firms to use equity finance) allows the firm to keep key IP while meanwhile fresh push funding is seemingly working towards the subsidy-based product but will never really benefit the sponsors.

There is, however, some sense in allowing firms to have multiple purposes for trials and to exploit this option behavior if it might benefit the malaria vaccine being targeted for the poor. Nevertheless, different instruments – e.g. PPP versus APC – have different implications for who controls the IP, and different implications ethically too. Again, the option value can have both beneficial as well as problematic aspects. The issue is how contracts deal with it and how different global methods of funding (APC versus PPP) affect the terms of those contracts;

- 4) It may mean that the poor do not get products or they get them with delay. For example, if firms have to supply both rich and poor markets and having to put capacity in place to do so, the expected cost, at the margin, of supplying the poor markets on top of the rich markets may be very high. The firm may prefer to supply, at lower capacity, the rich markets and still make a profit supplying at a high price, instead of putting in place sufficient capacity to supply both the rich and the poor markets and thus have to supply the marginal poor market ‘come what may’ even if it means loss of sales on the rich market. Since instruments like APCs are optional on the poor markets – firms do not have to supply – this helps firms to do this;<sup>729</sup>

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<sup>729</sup> This hints at the possibilities of perverse incentives too. If a firm has an HIV vaccine that meets the program’s requirements but for which there are more lucrative sales to be made elsewhere in markets that are non-eligible for the subsidy payments (at least in the early days and given low production capacity),

- 5) Will the Malaria Vaccine Technology Roadmap mechanism be able to benefit from all the R&D effort supposedly being stimulated by it? If firms invest in part because of the option value, at some point their (or early access to their) vaccine technology may be lost from the Roadmap mechanism, particularly if firms are being paid by instruments such as APCs and there is therefore much less control of funders over IP.<sup>730</sup>
- 6) This issue is becoming more pressing with the expansion of other vaccine activities, especially in response to large funding initiatives on biodefense preparedness, which is likely to both generate technology and data useful for neglected vaccine areas but also likely to feed off it in return. Again, this may have both beneficial as well as problematic aspects;
- 7) Vaccines may be developed that provide protection to travelers and the military, but that will need booster shots and drugs later. If these vaccines come in as too expensive to produce and use (given the need to combine with other measures), they may not be used in developing countries;
- 8) It suggests we ought to be very careful how we interpret lack of a market. Bluntly, the low level of current private activity for *P. vivax* may also be telling us something about the true balance between the difficulties of the science versus the lack of a market in generating low private malaria vaccine investment. It may also be suggesting a potential ‘option’ problem.

### **What is below the surface?**

It might seem that one could make ‘pull’ instruments, such as APCs, bigger to overcome ‘options value’ problems by reducing the relative value of the ‘option’ alternatives, but this needs a much larger APC from the start, many fewer markets relying on PPP (possibly destroying their ability to function), and it creates more ‘crowding out’ challenges. ‘Masking’ the options problem comes at a cost.

It is not clear how large this ‘option’ value is. If it is the case that we are misidentifying the true underlying problems, and it is the science and not the ‘market size’ that is holding private investors back, the size of the option value could be very large without showing, and it would be foolish to proceed without checking how much is hidden, as it were, below the surface.

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there may be little incentive to drive the production costs below the APC scheme’s price if it means the firm will look as if it is keeping an eligible vaccine out of the program. The claim is that a vaccine would be “available to all eligible countries at affordable prices” (CGD, April 2005, p38) both during *and after* the APC allocation is used up, and also available, at (tiered) monopoly prices, in countries *outside* of the mechanism (Russia, India, China for HIV perhaps?) while the mechanism is operative. But this does not have to hold, and certainly not if price is turning out to be higher than the legal contract stipulates. Incidentally this is another force pushing in the direction of higher cost products.

<sup>730</sup> The problems with option thinking were recognized (in private discussions) between the author and key individuals in the CGD/World Bank process, especially the problems for any funding scheme relying on less control over ultimate IP rights, but the problems have been left out of the recent debate.

The author has not touched on the ethical issues, but clearly the above is riddled with ethical problems when testing and subsequently using (or, indeed, not using) vaccines in developing countries.<sup>731</sup>

### **9.6. The option cost problems of 'new' technology**

Improvements in technology also potentially pose a challenge, which can also be thought of through the lens of option finance thinking. As Hoffman and Richie put it:

*“Our understanding of the relationship between host genetics and the response to infection is very limited. The elucidation of the sequence of the human genome and the development of scientific tools to use these data should lead to a better understanding of the role of host factors in determining the severity of disease associated with infection.”*<sup>732</sup>

*“In summary, whole-parasite-induced immunity could be directed at many of the 5000-6000 malaria parasite proteins. The malaria genome project and the single-nucleotide polymorphism (SNP) projects currently nearing completion may provide knowledge of all these potential targets and their variability at the epitope level, thereby laying the foundation for duplicating whole-organism immunity with subunit vaccines.”*<sup>733</sup>

There are three general approaches to malaria vaccine development. The most work and the most progress so far has been made in trying to get an immune response to a single or a few key antigens, with attention on getting antibody and CD4 T-cell responses, with interest too in CD8 T-cell responses. The second approach is to induce optimum immune response simultaneously against all of the 15-20 identified potential target proteins by immunizing with DNA vaccines or recombinant viruses and boosting with DNA vaccines, recombinant viruses, or bacteria, or recombinant proteins in adjuvant, with intent to elicit antibody and CD8 and CD4 T-cell response. The third approach is to try to duplicate the whole-organism immunity that is induced by immunization with radiation-attenuated sporozoites and natural exposure to malaria. However, achieving this depends on sequencing of the malaria genome and developing methods for exploiting this sequencing data.

That there are three competing approaches, and new technology on the way, does raise interesting and complex issues that, this author would argue, point away from an APC approach and towards more standard procurement approaches *alongside* a framework more able to deal with these risks, perhaps PPP-based.

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<sup>731</sup> One particularly knotty problem would arise if a vaccine is developed that has a military purpose based on technology that came out of this larger search for a vaccine, but where cost-effectiveness evidence indicates that it is not worth pushing through use of this vaccine, or a vaccine built on this technology, in a developing country setting (for example if it requires regular revaccination, or has efficacy or duration that is too low, or its use creates unwelcome epidemiological dynamics, or there are problems integrating with drugs, etc.).

<sup>732</sup> Hoffman, S.L., and Richie, T.L., 2003, *ibid.* p298.

<sup>733</sup> Hoffman, S.L., and Richie, T.L., 2003, *ibid.* p295.

### **Serious problems for private investors**

How should a firm – working on the basis of current approaches, finding itself with a ‘positive’ vaccine lead, discovered at the end of a period of historical R&D under-spend, with the chances of more concerted global funding to find a vaccine – respond if it is suddenly challenged to invest, in the expected value sense, billions of dollars *of its own funds* to take its lead forward? Given that only \$60m a year of public and private research expenditure is going into malaria vaccine research overall, this is a huge increase in *expected* expenditure for one firm. Should the firm be mindful that if new technologies lead to vaccines that work better, the funders might actually hope never to use any (or very little) of the vaccine based on the current approach? What if a firm invests heavily in response to the offer, only to see the government massively scaling up efforts on the competing newer approaches?

Conversely, what if funders ‘blow everything’ on the vaccine based on the current approach by offering an open-ended lump sum even if it turns out *not* to have been the best approach? How does it avoid disincentivizing private research on new approaches? How do the funders work out *in advance* how to optimally redistribute the overall payment and how much should they pay up-front for vaccines based on current approaches, so as to leave the ‘optimal’ portion over to be spent on vaccines based on newer approaches?

Of course, this problem never arises in the APC literature. We discussed above, and elsewhere (Farlow, 2004 *ibid.* Chapters 5 and 6), the way the key models (Kremer, Appendix 3) assume a constant state of science. There are no technological shocks or technological improvements *ever* possible. There are no ‘genomic revolutions’ or the openings of new scientific pathways to spoil the solutions of such models. Once this heavy simplification is dropped, things rapidly get very messy if APCs are the driving force. If things are about to get ‘technologically unlocked’ by breakthroughs in the malaria genome project, is it automatically obvious that we should be putting expensive APCs in place, pitched at the current players? And do firms really wish to be forced to risk only their own funds on *current* approaches?

### **9.7. Existing market size, and the exclusion of non-eligible countries**

The Roadmap points out that 70% of *P. falciparum* clinical disease is in Africa, but that 90% of all malaria deaths occur in Africa<sup>734</sup> where malaria accounts for at least 20 percent of all deaths in children under 5 years of age.<sup>735</sup> The other markets for *P. falciparum* vaccine are in parts of southern Asia, South America and other tropical

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<sup>734</sup> MVTR p1. Marsh, K., Forster, D., Waruiru, C., Mwangi, I., Winstanley, M., Marsh, V., Newton, C., Winstanley, P., Warn, P., Peshu, N., “Indicators of life-threatening malaria in African children.” *New England Journal of Medicine*, 1995, Vol. 332(21), pp. 1399-1404.

<sup>735</sup> UNICEF. *State of the World’s Children 2003*. 2002. New York: UNICEF.

regions of the world<sup>736</sup> but these countries tend to do better at preventing malaria deaths (30% of clinical cases causing 10% of all deaths). The WHO estimates about 90,000 malaria deaths in Southeast Asia, 56,000 in the Eastern Mediterranean region, 11,000 in the Western Pacific, and about 1,000 in the Americas.<sup>737</sup>

Recent reports however have made it clear that the non-African impact of *P. falciparum* is much greater than we had previously come to believe. And, over time, malaria is moving northwards and impacting more middle income markets. Snow et al.<sup>738</sup> observe how inadequate our measures of the global distribution of malaria are. These measures are needed in order to define populations at risk for appropriate resource allocation, and to provide a robust framework for evaluating the global economic impact of malaria. However, such measures are also needed for working out how to set the terms of instruments such as APCs, for which the market absent the APC needs to be known, so that the APC can be set big enough. This, incidentally, includes measures of ‘hidden’ option-based markets if there are ‘option’ elements to R&D. When Snow et al. observe that: “Inadequate descriptions of the global distribution of disease risk make it impossible to determine priorities and advise funding agencies appropriately,” this applies equally to the setting up of APCs.

By using a combination of epidemiological, geographical and demographic data., Snow et al. estimate that in 2002, 2.2 billion people were exposed to the threat of *P. falciparum* malaria, resulting in a conservative estimate of 515million (range 300-660 million) clinical attacks, producing figures up to 200% higher for areas outside Africa than extant WHO figures: “In reality, passive detection of disease events in most resource-poor countries is incomplete, even outside Africa.” At a regional level, Snow et al. found most clinical events attributable to *P. falciparum* were concentrated in the African region (70%), but that the highly populated South East Asia region and the Western Pacific contributed 25% of the world's clinical attacks. Other studies have also found that Papua New Guinea, the Solomon Islands and Vanuatu have malaria transmission characteristics similar to those in large parts of Africa.<sup>739 740 741 742</sup> It is therefore wrong to conduct analysis on the basis that *P. falciparum* malaria is only an ‘African problem’. In a

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<sup>736</sup> MVTR p4. RMSR p3.

<sup>737</sup> WHO. *World Health Report 2002*. Geneva: World Health Organization. 2002. Estimates for 2001.

<sup>738</sup> Snow, R.W., Guerra, C.A., Noor, A.M., Myint, H.Y., and Simon I. Hay, S.I., “The global distribution of clinical episodes of *Plasmodium falciparum* malaria.” *Nature*, 2005, Vol. 434, pp. 214-7, [www.nature.com/nature/journal/v434/n7030/full/nature03342.html](http://www.nature.com/nature/journal/v434/n7030/full/nature03342.html).

<sup>739</sup> Bell, D. R., Jorgensen, P., Christophel, E. M., and Palmer, K. L., “Malaria risk: Estimating clinical episodes of malaria (reply)” *Nature*, 2005, Vol. 437, doi: 10.1038/nature04179.

<sup>740</sup> Muller, I., Bockarie, M., Alpers, M., Smith, T., “The epidemiology of malaria in Papua New Guinea.” *Trends Parasitol*, 2003, Vol. 19, pp. 253-259.

<sup>741</sup> Over, M., Bakote'e, B., Velayudhan, R., Wilikai, P., and Graves, P. M., “Impregnated nets or ddt residual spraying? Field effectiveness of malaria prevention techniques in Solomon Islands, 1993-1999.” *Am. J. Trop. Med. Hyg.* 2004, Vol. 71, pp. 214-223.

<sup>742</sup> Maitland, K., Williams, T., Bennett, S., Newbold, C.I., Peto, T.E.A., Viji, J., Timothy, R., Clegg, J.B., Weatherall, D.J., Bowden, D.K., “The interaction between *Plasmodium falciparum* and *P. vivax* in children on Espiritu Santo island, Vanuatu.” *Trans R Soc Trop Med Hyg*, 1996, Vol. 90, pp. 614-620.

response to Snow et al., Nahlen et al.<sup>743</sup> agree that “Both groups agree that the burden of malaria disease outside Africa, especially in South Asia, is greater than was estimated in the 1990s.”

If the problem is so much greater outside Africa than we had thought, suggesting a much bigger non-APC market, should we not interpret the extraordinarily low levels of private sector investment as meaning a bit more than just that this is a disease of the poor? Is this not more evidence of potential misidentification of the underlying problem as being only about purchasing power and not about the complex scientific problem and our inadequacies in dealing with it?<sup>744</sup>

### **The problems of ‘adding’ market: non-eligible countries**

The point of APC subsidies is to create a “more valuable market”<sup>745</sup> by adding to what ‘market’ is already there. This needs those running the scheme to have some notion of what market is already there (or will be there) without the scheme. But, as Scherer puts it: “To be sure, some diseases occur primarily in the third world, but the magnitude of the problem that is uniquely without solution ought to be brought into sharper perspective.”<sup>746</sup>

Both the Malaria Vaccine Technology Roadmap (it seems at the moment) and the APC literature base their pull thinking on separating out and protecting for the ‘winning’ firm or firms the ‘richer’ non-eligible country markets and the associated IP and pricing power to such markets, ‘detaching’ these regions from any access to APC subsidy payments, and separating out within eligible countries those who will pay non-subsidized prices from those who will get subsidized prices.<sup>747</sup> Notice how the latter requires the mechanism to track every purchase. Since a huge amount of ‘windfall’ subsidy is attached to each purchase, and given the dangers of rent-seeking, it needs to be confirmed at point of use that it gets used for its legally defined purpose.

The term ‘market’ is interpreted to include the option-related markets that may require different vaccines to the APC vaccine, but that build off its technology in some way. The APC literature tends to interpret overall revenue earned by a vaccine (remember, since there are no costs in the methodology, this is not referring to investor ‘returns’) as being composed of a component from sales of pretty much the same vaccine to, for example, military personnel and tourists, with the rest topped up with APC payments on sales to eligible countries. However, an APC vaccine for, say, African children, is unlikely to be the same as that for US military or for South East Asia, with the latter needing more rounds of trials and different production facilities. This is on top of efficacy requirements

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<sup>743</sup> Nahlen, B.L., Korenromp, E.L., Miller, J.M., Shibuya, K., “Malaria risk: Estimating clinical episodes of malaria.” Comment in *Nature*, 2005, Vol. 437(7056), doi: 10.1038/nature04178.

<sup>744</sup> Given some of the potentially rich HIV markets, these arguments probably apply even more strongly to HIV.

<sup>745</sup> Barder et al. 2005, *ibid.* p2.

<sup>746</sup> F.M. Scherer, CIPIH Open Forum, May 2005.

<sup>747</sup> On the presumption there is a market for courses costing more than \$15 (or \$25 if that is chosen instead) inside these countries alongside the \$1 courses.

which may rule out entirely the use of a low-efficacy vaccine in some countries. One correspondent observed that there will be many years delay before any new vaccine developed for Africa would be trialled sufficiently to be EDL/EPI approved for wider use, but that this had not been fully absorbed by those designing an APC for a malaria vaccine for eligible countries. How is this all to be factored in many years in advance? Would it not be a bit expensive on the APC if it were clear that a targeted vaccine would have no non-eligible takers? Quite how one works out ‘market’, and hence needed APC, in these cases is not clear to this author.

### **Exclusion of middle-income countries including China for malaria and Russia for HIV**

Non-eligible countries, even if relatively poor themselves, must pay higher prices than the eligible countries – both before and after subsidized courses are gone. Many countries that are doing better than African countries at preventing death from malaria will pay (possibly tiered) ‘monopoly’ prices for any vaccine created, whether built off an APC malaria vaccine or not. In the Berndt et al. cost-effectiveness calculations, China is not included “because its GNI will soon surpass the \$1000 cutoff,”<sup>748</sup> and because “*falciparum* malaria, the most deadly form of malaria, is only a problem for a tiny fraction (less than 1 percent) of China’s population,”<sup>749</sup> (i.e. 13 million victims per year).

Similar thinking lies behind the work of mechanisms for HIV Vaccines. IAVI is currently working on the basis of a \$1000 cut off for eligibility for a subsidized HIV vaccine, and eligibility for countries between \$1000 and \$5000 only if HIV prevalence is greater than 5%,<sup>750</sup> which would rule out Russia, China, and India if their prevalence rates did not breach 5% or if their incomes breached the \$5000 limit. Indeed IAVI presumes that whatever happens to prevalence rates in China, it will not be eligible since its income will have breached the limit by the time a vaccine is available. Since the damage to health and economic costs and political instability<sup>751</sup> in Russia, China, and India would be high even at prevalence rates up to 5%, it would necessitate heavy purchases of vaccines in these countries (or not, if they are too expensive or there are problems with patents and generics) but not at APC prices. We need to worry about how to achieve this detachment of non-eligible countries and the potential negative consequences.<sup>752</sup> As one can no doubt imagine, it raises many issues – practical, ethical, reputational, economic, political. There is no evidence that the full implications have been thought through.

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<sup>748</sup> Berndt et al. 2005, *ibid.* p15.

<sup>749</sup> Berndt et al. 2005, *ibid.* pp. 15-16.

<sup>750</sup> Incidentally, if prevalence rates in these countries grow well over 5%, but investors only respond when this ‘market’ is clear, this suggests that the search for a vaccine will be well behind schedule relative to the prevalence rates. But nobody is suggesting an APC to cover for these worse-case scenarios.

<sup>751</sup> This may have an impact that is external to these countries and be less of a driver of purchases by these countries. Bluntly, it may be in the interests of others that Russia, China, and India have ready access to vaccines.

<sup>752</sup> This would still be much easier to do for malaria than would be the case for HIV (or the common cold or Alzheimer’s, etc.), though it may get more difficult over time.

### **Perverse incentives**

Indeed, this is riddled with perverse incentives too. For example, if HIV prevalence rates in Russia, China, and India are growing, this increases the chances of breaching the 5% mark, triggering Russia, China, or India becoming eligible for ‘cheaper’ subsidized vaccines under the APC. Under the IAVI proposal, a rising prevalence rate in these countries acts like an extra discount rate weakening private sector incentive to invest in vaccine R&D. If the APC is somehow to grow to counter this negative impact on incentives, this would require Russia, China, and India to agree to pay towards the APC scheme as their prevalence rates grow, but be subject to non-eligible unsubsidized prices at all prevalence rates below 5%. This is not likely to happen. The devil is always in the detail.

As another example, if access to a vaccine at heavily subsidized APC prices is related to levels of death or infection rates (as well as or instead of income) it is not clear how much this might interfere with incentives if an alternative is to heavily boost treatment and prevention. Boosting the alternatives and achieving lower consequent rates of infection carries a penalty that needs to be factored into the marginal cost of treatment. It is not clear that we should actually be adding perverse incentives to an already difficult problem.

Incidentally, since Russia can’t easily be fit inside an APC, because of the need for the APC to become huge to incorporate Russia in its terms, but Russia can fit inside a PPP-style set-up, would the latter be a better way to activate Russia into a global effort? This would avoid the problem caused by the 5% HIV threshold into the bargain. This author can’t understand why Russia, apparently, agreed to back the G8 APC program given how badly Russia would come off under an HIV APC, and all the perverse incentives and uncertainty it creates for Russia.

### **Focus on the parasite and not the geography**

Some Roadmap feedback argued that because of this geographic coverage “Some feel sub-Saharan Africa should not be the only target population”<sup>753</sup> and that we should focus on the parasite rather than a geographic region. This author concurs with this. However, an approach that targets the parasite flies in the face of approaches that rely on geographically splitting the market as required by APCs. Yet again we find the science being dictated to serve the political goal of the APC and not the other way around.

### **The role of Asia**

The Roadmap points to the need for “increased understanding of parasite antigenic variation and polymorphism” and argues that this will need “studies of parasite variation in endemic populations.”<sup>754</sup> One of the dangers of locking some countries into non-eligible status is that it risks pitching poor endemic regions against less poor endemic regions, with the first group getting product subsidies and the second group, who might

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<sup>753</sup> VMSR p9.

<sup>754</sup> MVTR p16.

be a useful resources for vaccine trials (think of HIV for example), getting nothing from the APC, and indeed having to face monopoly non-eligible-country prices.

Would countries in Southeast Asia and elsewhere take part in a large global collaborative effort to crack malaria, HIV and TB vaccine problems, only then to have to face higher prices than they otherwise would have to for maybe even a lower efficacy vaccine than a more collaborative route might have achieved? Indeed, at prices that may be higher for non-eligible countries by the way the market has been split by the subsidy arrangement. Would Asia be interested in 40%-50% malaria vaccine efficacy as a non-eligible market – especially if a different goal would have created a much more efficacious vaccine sooner than it now will be on account of the low goal-1 set to satisfy the APC? What are the consequences for deaths in Asia? What does Asia want? In the case of HIV, what do China, India, and Russia want?

### **Drug resistance in Southeast Asia and South America**

This is where the interaction between vaccine issues and treatment issues bites once again, and why this artificial separation into ‘eligible’ and ‘non-eligible’ countries also creates problems on the treatment front. As Arrow et al. point out, for antimalarial combination therapies to keep drug resistance at bay over the long-term, it must be used as first-line treatment for uncomplicated *P. falciparum* malaria as widely as possible.<sup>755</sup> Allowing monotherapies to persist *anywhere* in the world, will risk drug resistance. Historically, and according to our current understanding of the biology of drug resistance in low- and high-transmission areas, antimalarial drug resistance has emerged mainly in Southeast Asia and South America in areas of low transmission, and then spread to high-transmission areas, mainly in Africa. Unfortunately, artemisinin monotherapy is still widely used in Asia in the same areas where resistance to chloroquine and sulfadoxine-pyrimethamine (S-P) built up in the past. It follows that ACTs urgently need to dominate the market in low-transmission areas in Asia and South America as well as Africa.

However, the projected price of ACTs is still 5 to 10 times higher than the price of chloroquine or sulfadoxine-pyrimethamine (S-P) in Africa, making ACTs largely unaffordable there. Arrow et al. argue that the way for the global community to take definitive action would be by subsidizing the difference in cost between inexpensive but ineffective antimalarials, and effective ACTs, bringing the price of ACTs down to about the price of chloroquine (US\$0.10-0.20), so that consumers could freely choose ACTs over monotherapies.<sup>756</sup> This would cost at most \$300m-\$500m per year globally, and this cost would fall over time as the price of effective antimalarials comes down because of increased and more stable production, competition, and new technologies, even potentially including synthetic artemisinin,<sup>757</sup> and as economic conditions in endemic

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<sup>755</sup> Arrow et al. 2004, *ibid.*

<sup>756</sup> Arrow et al. 2004, *ibid.*, also recommend other supportive measures to keep monotherapies off the market.

<sup>757</sup> In December 2004 OneWorld Health received a US\$42.6 million grant from the Bill and Melinda Gates Foundation to support a partnership with the University of California, Berkeley (UCB), and Amyris Biotechnologies, to create a synthetic supply of artemisinin. OneWorld Health is leading a three-component research plan, in which UCB will apply synthetic biology to complete development of a process to produce

countries improve: “The window of opportunity to create a global public good – years of extended effective antimalarial drug life – is open now, but it may not remain open very long.”<sup>758</sup>

Arrow et al. argue that “Managed well, artemisinins could remain the first-line antimalarial for many decades.”<sup>759</sup> Indeed, in spite of extensive monotherapy in Asia, resistance has not yet developed, but artemisinins will begin to lose effectiveness and new drugs will eventually be needed. The R&D pipeline for new antimalarials has been invigorated by the Medicines for Malaria Venture (MMV), a PPP, set up in 1998, the WHO Special Programme on Research and Training in Tropical Diseases (TDR), and the Walter Reed Army Institute of Research (WRAIR). The financial needs of these are about \$60m per year, rising to \$80m per year as more drugs reach the stage of clinical and field trials. Though small, this is several times their current levels. Arrow et al. also recommend more support for these organizations to meet the MMV goal of one new antimalarial drug every 5 years, and WRAIR’s similar target, to join, or even eventually to supplant, artemisinins on the front line.

### **9.8. Mixing institutional structures**

Furthermore, what if, by forcing through mechanisms with different regional pricing implications, we end up with multiple institutional structures serving different markets. For example, what if South East Asia supports the notion of vaccine PPPs and lower prices from the start, but the plan is to cater for Africa via an APC with higher prices at the start followed by (supposedly) lower prices later, but with South East Asia under this APC scheme facing higher vaccine prices from the start and into the future too?<sup>760</sup>

Furthermore, the typical PPP contract with private players involves risk-sharing in exchange for some control over the IP, lower vaccine prices and access. How does this gel with a system based on the total ownership of the vaccine IP by the private ‘winner’ of the APC, with high prices for the first several hundred million developing country users of the vaccine?

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artemisinin from *E. coli*; Amyris will develop the process for production; and scientists at OneWorld Health will do the preclinical development and regulatory work to demonstrate bioequivalency between the synthetic and natural forms and secure a large-scale fermentation facility to satisfy global needs. The hope is that this will provide consistent, affordable supplies of artemisinin. See: Hale, V.G., Woo, K., and Lipton, H.L., “Oxymoron No More: The Potential Of Nonprofit Drug Companies To Deliver On The Promise Of Medicines For The Developing World.” *Health Affairs*, Vol. 24, Issue 4, pp. 1057-1063. <http://content.healthaffairs.org/cgi/content/full/24/4/1057?ikey=Kx5icW4Izo3tQ&keytype=ref&siteid=healthaff>

<sup>758</sup> Arrow et al. 2004, *ibid.* p5.

<sup>759</sup> Arrow et al. 2004, *ibid.* p10. The term “managed well” includes, for example: accurate surveillance of individual drug efficacy to ensure the best antimalarials for each country or region – in particular, the best partner drugs for artemisinins; and early warning systems to identify drug resistance, and replacement of a failing ACT partner drug thus protecting the artemisinin component itself. Pushing for a malaria APC regardless of the package of control measures it would have to fit into, has costs in terms of damage to efforts to tackle these resistance issues – and in terms of lives lost.

<sup>760</sup> Imagine what this does for the incentives of countries like Russia, China, and India to be part of such exercises as the Global HIV Vaccine Enterprise?

For PPPs currently working on the basis of IP-sharing arrangements, what are the legal and technical problems of switching over? One implication of the Kremer calculations<sup>761</sup> is that the APC achieves ‘additionality’ by being the only incentive device present (and we saw the way that Berndt et al. and CGD do all cost effectiveness calculations on the basis that all benefit of having a vaccine is ascribed to the APC as if only the APC is present at the time of such calculations). For a case with such a high PPP component and all of the associated problems this creates in the APC setting, one might hope that the claim about ‘complementarity’ might have actually meant something in practical reality. This rather contradicts the claim that this mechanism is *not* being promoted *regardless* of other approaches.<sup>762</sup>

Presuming follow-on malaria vaccines will be needed for all regions, some covered by the APC subsidy scheme and some not, and some covered by PPP-based products and some by APC-based products, a range of knotty issues arise:

- 1) What does the (complicated) IP regime look like?
- 2) How are clashes in IP systems resolved?
- 3) How concentrated is IP and how spread out?
- 4) In what ways does technology/IP transfer to emerging vaccine developers?
- 5) What legal jurisdictions over the ‘markets’ applicable to one scheme or mechanism does another scheme or mechanism have?
- 6) How are solutions enforced? In particular what are the problems when acting out disciplining ‘threats’ across institutions? Surely this causes potentially serious institutional/IP conflicts? Try thinking how an APC disciplines low prices after the first subsidy-yielding sales are gone with only some markets being applicable for APC payments.
- 7) Is it predictable how IP owners will be treated and how much investors should therefore invest?
- 8) If ever there are follow-on vaccines paid for via the APC scheme and payment is supposedly related to the need to demonstrate that the follow-on was based entirely on new independent R&D, how do firms demonstrate this without it forcing them to be more secret and keep their activities from being shared across firms in a PPP (especially late in the development process<sup>763</sup>)?
- 9) Do ‘winning’ firms want some of the PR disasters this will generate?
- 10) What if PPPs want to supply these other non-eligible countries at lower prices, undermining the APC subsidy scheme? These non-eligible countries were the base market on which the APC became ‘additional’, and this market needs some protection from being undermined.<sup>764</sup> How is a conflict prevented (and this not get fed back to harm R&D incentives)?
- 11) What happens if Asia, Latin America, Africa are a mix of eligible and non-eligible countries?

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<sup>761</sup> Kremer, M. No. 10 Policy Unit Appendix 7.

<sup>762</sup> Berndt, E.R., *ibid.*

<sup>763</sup> The later in the process, the higher the leveraged losses from this ‘sharing.’

<sup>764</sup> Again, even if it is not the same vaccine, option thinking goes through on vaccines that may not be the same actual vaccine.

- 12) What happens if serving these non-African markets requires a whole new set of EPI and other regulatory approvals?
- 13) Non-eligible countries must be stopped from using *vaccines that fail the APC scheme* but that were motivated by it,<sup>765</sup> since such vaccines destroy the value of investments being encouraged by the scheme (they destroy the market that the APC scheme vaccines were supposed to be additional to) and contribute to the self-fulfilling collapse of longer, more expensive, 'higher quality', R&D projects.<sup>766</sup> What rules could be used to prevent South East Asia from using vaccines that fall short of the scheme?<sup>767</sup> Who polices them?
- 14) Non-eligible countries must also be stopped from using '*me-too*' vaccines based on the vaccines being paid for via the APC scheme, and stopped from using the *technology or science* of subsidy-based vaccines for 'non-subsidy' based research or manufacturing processes. What problem does this cause? It is an extension of the 'market enhancement' problem to 'me-too' vaccines and to technology.
- 15) Tiered prices may be part of an efficient solution. However, does segmentation of the market into eligible and non-eligible segments enable higher prices to be charged to non-eligible countries than without the subsidy scheme in place? How will these countries react? This observation normally refers to the 'same vaccine' but it is perfectly good economic logic to visualize it as happening if there are different subtypes or different clades of a virus. It works through an investment 'option' component.
- 16) How exactly do PPPs and APCs schemes really integrate? The underlying models used to justify APC subsidy schemes (Kremer Appendix 3) strip out any interaction from the start. We have learnt next to nothing about the practical operation of mixes of schemes even for 'basic' existing vaccines, yet policymakers are keen to push ahead for malaria, HIV, and TB where the mix would be intense.
- 17) Not all vaccines are the same. That a market is 'additional' to an already existing market is itself highly variable across different vaccines (over generations, over the needs of different potential recipients for vaccines, etc.). Some vaccines will be disadvantaged by payments schemes based on 'an average', such that averaging across all markets (the APC methodology of working out how much 'additional' market is needed) will over-advantage R&D incentives to some and greatly disadvantages incentives to others.
- 18) An APC needs to guess at the start how much market to treat as non-eligible in order to work out its size. At least PPPs economize on this and reduce the need for those running the scheme (as opposed to the firms) to monitor and separate out the markets. PPPs are essentially more able leave it to the market to decide the value of the non-eligible market that is to be paid for separately, and not have to rely so much on pre-set terms and excellent monitoring.

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<sup>765</sup> As with all these observations, this also covers cases where it is the vaccine knowledge achieved via the sunk costs of firms, even if not the same vaccines as used in eligible countries.

<sup>766</sup> By making such projects much more expensive because of higher risks and capital costs.

<sup>767</sup> Russia, China, and India purchasing HIV vaccines for their non-covered markets?

**Difficulties in making the subsidy pool bigger to avoid institutional problems**

Maybe to avoid institutional overload and conflict, a malaria (or HIV or TB) APC might be extended to cover more of the countries that would otherwise be left out – so as to ‘encompass’ all markets under the same institutional structure and to try to avoid ‘crowding out’ and option value issues. How high are politicians prepared to allow the APC subsidy pool to grow to do this? What if firms are not happy at the inclusion of some countries that are then lost as profitable non-eligible countries after the subsidy pool has been drained, but that the firm is still obliged to supply at low long-term prices according to the contractual obligations? Firms would find themselves tied in to long-term low-price supply contracts in markets where this would otherwise not have been the case. What if, by then, there are ‘better’ vaccines, but no subsidy payments and these better vaccines are supposed to compete against artificially low-priced lower-quality APC vaccines, or do these better vaccines simply never get developed in the first place?

If a subsidy scheme was big enough to include China and other South East Asian countries, the fund would have to cover the profits that would have been made in South East Asia, and because there is a large ‘crowding out’ element (i.e. purchases that would have taken place anyway) there would have to be an agreement with China and South East Asian countries from the start to pay into the subsidy fund.<sup>768</sup> All sales would be subsidized sales even in markets that could pay more, reflecting the inefficiency inherent in any subsidy that fails to target those who really need it. Who pays these higher subsidy payments? US tax payers via any legislation pursuant to the Kerry-Lugar Bill?

If the alternative was a PPP-route from the start, and if this route was less risky and therefore had a lower capital cost element, and if this route is crowded out, then the expansion of the APC to cover China creates a new layer of crowding out. Perhaps it is best if we do not dwell too much on the extra IP problems created.

**9.9. Firm-level ‘crowding out’ of APC subsidies**

Like all subsidies, APC subsidies can end up poorly targeted. Such a scheme needs both to target the extra market needed on top of the current market, and also to target those who engage in *new* R&D motivated by APC subsidy payments. The subsidy should not pay for the markets or for R&D that would have existed anyway without the subsidy scheme. To the extent that a subsidy fails to hit those it is most intended for, there is a ‘crowding out’ of the power of the subsidy to motivate the act intended. This is on top of ‘rent-seeking’ behavior, which itself may be thought of as a form of crowding out, since it is a way to distort subsidy payments away from one set of players who need them to another set of players who do not, with the costs of rent-seeking eating in to the potential value of the subsidy and crowding it out. We saw ‘crowding out’ above in the shape of *purchaser* behavior. But we will now see it in the case of *sellers*.

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<sup>768</sup> The same problems hit when trying to expand out coverage of HIV vaccine schemes. What eligibility terms would put Brazil in but India out?

A similar situation happens in many other areas of economics. For example, it is difficult to target tax breaks to only those who need them, and not to the many others. If the tax break is supposed to incentivize a particular action, this action will be much more costly to achieve than if targeting were perfect. And social benefit systems have to create elaborate rules to target payments. But there is a crucial difference. In these cases, ‘crowding out’ happens at the time of the exploitation of the tax break or at the time of payment of the social benefit. In the case of an APC, crowding out happens all at the end of the process when many players (supposedly) have sunk their costs. Arguably, this is more risky, since it builds up to one large treatment of the problem at the end.

Crucially, from an investment perspective, it has to be *believed* by all investors that this targeting takes place. Indeed, investors need to know, in advance, that those setting up such a scheme will be able to design it to achieve this targeting at 20 plus year horizons. It is, as the reader can probably imagine, something this author would not advise any private investor should believe that any committee would be capable of; it is just another risk they will have to price in.

This was yet another set of issues that were ruled out in early models driving APC thinking (Kremer Appendix 3) which presumed these issues away by presuming that the scheme was not one funding mechanism amongst many. It is perhaps telling that the full recognition of the key role of this was only made three days before the deadline for CGD Working Group members to sign off on the CGD report.<sup>769</sup> These practical issues are only recently achieving attention, after most of the policy advocacy has already taken place and G8 leaders have gone with the idea.

Light observes: “To be fair to competitors, the payoff price should be adjusted for how much R&D was paid for by governments and foundations, because some risk much less of their own money, net of tax subsidies, than others. The CGD price of \$15 per course and \$3 billion might be much too high, or too low, by 2015. And no adjustments are mentioned [in the CGD Report] for external subsidies and other factors.”<sup>770</sup> Several correspondents have complained at the way the APC arrangement with GSK over malaria seems not to appreciate the need for GSK to “accept a large element of entrepreneurial risk.” Instead, big chunks of the risky part of the process have, and continue to be, covered from public and foundation funding, while other vaccine researchers who could use that funding to explore a wider range of competing leads go without or with much less than they need.

#### **A crowding out example**

Dealing with this ‘crowding out’ issue is also important for keeping the mechanism competitive and equitable, encouraging the speed of vaccine development. For example, imagine 10 firms are working equally hard on malaria vaccine(s), with a reward of just over \$6bn for the winner(s), but that one of them had 50% of its R&D costs offset by subsidies, grant support, non-private funding, etc. So as to maintain a level playing field

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<sup>769</sup> March 19<sup>th</sup> 2005. Internal correspondence to Working Group members.

<sup>770</sup> Light, D., 2005, *ibid*.

with all other players and to maximize the R&D incentives of private financiers, the subsidy payment to any firm would need to be reduced by *many times* the ‘push’ payments *it had ever received*.<sup>771</sup> In this case, the firms should have \$3bn (i.e. 50%) of the subsidy ‘reward’ denied to it, and left in the subsidy pool to be available to competing and follow-on vaccines. The problem, of course, is that for every \$1m that the firm can hide, it makes \$15m of extra subsidy payment, generating an extremely high incentive to hide what is going on.<sup>772</sup> This is another form of rent-seeking. How is efficiency of such mechanisms monitored if truthfulness is so heavily penalized?<sup>773</sup>

For this ‘crowding out’ to be removed, the committee would need to gather and keep high-quality historical evidence (for 20-30 years), to correctly ‘price’ streams of ‘other payments’ (e.g. it would need to define appropriate capital costs), and institute ‘repayment’ side-contracts that may not unfold for ten or twenty or more years. It would also have to release this information regularly, since the mechanism claims that to work out an optimal strategy, every firm needs to know how much genuinely new *privately*-funded activity is actually taking place by every other firm, how much will be removed from other firms and ‘returned’ to the subsidy pool, and whether therefore to increase or decrease its own activity.

#### **Dealing with this cannot be left to individual sponsors**

It is claimed by some APC advocates that individual funders can decide on how to handle these issues in order to create a ‘fair return’ to investors. As Kremer and Glennerster explain it: “The sponsor of a pull program might specify that if push funding had been allocated before the announcement of the pull program, the winner might [only ‘might’?] be required to use some of any pull revenue to repay part or all of the push funding it had received [we showed above that, logically, it should be *a multiple* all of the push funding it had received, if one is thinking of multiple parallel developers and an APC as an R&D device] ... Similarly, a sponsor might feel that if a product is already more advanced at the time the pull program is announced, fewer resources would be needed to incentivize the remaining research and development needed on the product [an allusion to the costs of development, even if all the CGD, Kremer et al., Berndt et al., figures are based only on revenues]. The sponsor might therefore specify a different schedule of payments for products that had already reached phase II or phase III trials before the commencement of the pull program.”<sup>774</sup>

However, and again thinking from the perspective of investors, this payment adjustment *should* be coordinated and not be left in the hands of individual funders. Investors need to trust over very long horizons that this is so, and that the system will be properly policed

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<sup>771</sup> Unless unequal access to push efforts can be made to be part of the efficient solution, a scenario that this author does not rule out.

<sup>772</sup> Throughout, this is being thought of as relating to pure R&D expenditure and not to the cost of setting up production of an already accepted vaccine.

<sup>773</sup> Remember, they started off presuming an auction to set the size given the difficulty of extracting information about what was an efficient level at which to set such an instrument. When this was found unworkable, contracts with monitoring and adjustment were incorporated. Now we find crowding out problems working against efficient monitoring.

<sup>774</sup> Kremer, M., and Glennerster, R., 2004, *ibid.* p107.

so that there will be no temptations for individual countries, firms, or foundations to ‘cheat’, otherwise this risk will undermine investment incentives. Think how this would have to be calculated in the light of R&D cost information, articulated, and fixed in advance for the sake of all other investors.

One of the paradoxes of APC subsidy schemes is that they were first proposed as ways to economize on monitoring and intervention, but then need so much monitoring and intervention to make them work. Pondering the statist credentials of the committee doing what Kremer and Glennerster have just described, a Soviet central planner would no doubt have been proud to have even got close to what they describe.

### **GSK**

Strictly speaking, if GSK were drawing from an APC (with the drawing of subsidy related also to the vaccine’s ‘quality’), the *proportion* of GSK’s overall research carried out before the APC was announced would have to be cut from any eventual APC payments,<sup>775</sup> as would any proportion of total funding accounted for by non-private funding of development from now on,<sup>776</sup> so that such APC payments would be reward for the *fresh* GSK equity finance genuinely brought into the project. Otherwise, the APC funding will simply crowd out funding that should have gone on alternative vaccine researchers elsewhere. In addition, those thinking of using private funding will realize that the value of the results of *their* private research spending (in the expected sense) is now lower. The overall malaria vaccine endeavor would be damaged at any given outlay of public funding. This would require that GSK be extremely transparent with the necessary information. Or will these issues just be ignored, even if this weakens the APC for competing developers?

Without such adjustments, the rational (and, to live up to the APC modeling, also the economically correct) approach would be for the PPP funding to now be withdrawn from GSK, setting them free to get on with their RTS,S/ASO2A project fully equity financed, in pursuit of the APC payments. And the PPP sponsors should be free to fund *competing* vaccines to support with their funding instead. It is not at all clear that when all risks are fully accounted for, and this reality is presented, that GSK would not prefer the PPP route were they actually to face the choice.<sup>777</sup>

### **Favoritism to large players**

One of the dangers is that this favors ‘large pharmaceutical’ players for early-stage vaccines such as those for malaria. Smaller firms, biotechs, and not-for-profit firms have many fewer ways to hide non-APC subsidies and financial support (if they can get them), and fewer ways to rent seek the setting of “different schedules of payment.” Indeed, many biotechs work on one area only, and their funding flows are less opaque than ‘large pharma’ players. This is on top of the bias against players who cannot maintain access to ‘deep pocket’ finance for the lengths of time required by the APC scheme.

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<sup>775</sup> Observe the disincentive to keep down the costs of later stages of development.

<sup>776</sup> Observe the incentives to distort this too.

<sup>777</sup> Of course, GSK may view themselves as not facing an APC at all as defined in this report, but see the APC as the veil for some other arrangement.

There are human capital limitations too: “The number of vaccines in the pipeline exceeds the available resources – particularly human resources – committed to malaria vaccine research right now.”<sup>778</sup> Industry, malaria, and public health figures expressed a concern to this author of another form of crowding out – that such schemes would tend to favor large pharma firms in taking human capital away from smaller firms and academic/publicly-funded research. To the extent that smaller biotech firms and other researchers are more innovative in this area, this crowds out and leads to a lower quality, higher cost outcome.

Observe how this problem arises because of the nature of the contracts (and another tradeoff): At the extreme of a standard competitive procurement contract, *only* the additional private funds needed to ‘finish a project’ need be extracted in the procurement process. In CGD-style APCs, the ‘Framework Agreement’ *is the tender*, and a highly complicated side device has to be appended to ‘the tender’ to achieve this standard property.

### **The dangers of favoring near-market over near-scratch malaria vaccines**

Observe how important it is to make sure that those developers ‘nearer to scratch’ are not disincentivized. Pull payments that are not appropriately adjusted to take account of all the financial help a firm has received will disproportionately benefit those nearer to market, even if they are not ultimately the ‘best’ vaccine (in the probabilistic sense). This further aggravates the ‘quality’ problem. The near-scratch developers who have poor vaccines would not get purchase funding anyway, so if we knew about them now, on an equal playing field as it were, their presence would make outcomes neither better nor worse than they currently will be. However, the near-scratch developers with ‘good vaccines’ would not make matters any worse, but would make matters a good deal better. There is option logic in pitching the pool of subsidy towards current whatever-quality vaccines, which indicates that one probabilistically forecloses on the chances of better near-scratch vaccines.

On the other hand, what if, instead, the size of the APC is set lower and more commensurate with those closer to market? Well, obviously, that is bad for the near-scratch developers! Clearly, the APC payments have to be commensurate with stage of development and other funding. Another job for the APC committee?

### **A simple example, with RTS,S as the case**

To visualize the problem better, let us think of a simple example. Imagine a range of developers at different stages of development of a malaria vaccine and think of R&D subsidies paid only after a ‘successful’<sup>779</sup> vaccine is produced. Should the GSK RTS,S vaccine be denied a large portion of the subsidy pool? The logic is simple. If, as a thought experiment, MVI, the Gates Foundation, the UK government, NIH, and all other funders were tomorrow to stop funding potential vaccines different to that of GSK, preferring instead that these firms respond only to the APC, but GSK’s RTS,S vaccine candidate

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<sup>778</sup> Rabinovich, R., 2004, *ibid.* p211.

<sup>779</sup> In quote marks, since a ‘successful’ vaccine is a tautology – it is the vaccine driven out of the incentive mechanism and accepted. By definition it is a ‘successful’ vaccine, even if something much better has been lost in its creation.

was treated the same as all others in terms of its access to the subsidies provided by an APC, this would massively favor the GSK vaccine candidate over others. Observe that because of investor expectations, even if the GSK candidate never pans out, this is damaging to other private developers and the creation of an ultimately useable vaccine.

GSK *should* only get a proportion of the APC subsidy pool (with this known by all in advance), so as to leave the optimal proportion of the subsidy pool for other developers. But how likely is this to be engineered? And how likely are policymakers ever to institute such payment adjustments (think of the accounting and monetary issues involved in doing this, and all the ‘rent-seeking’ incentives)?

The only logic to justify any argument that the GSK vaccine would not be disproportionately advantaged is the presumption that all other potential ‘vaccines’ will get the same levels of MVI, Gates, and public ‘push’ funding. But, was that not the whole point of the APC idea? That these funds are not going to be available in the quantities required? That there was a need to encourage more private funds to enter instead?

However one looks at it, near-scratch and near-market developers need the overall size and distribution of the APC to be modified commensurate with their current position. In real applications the likelihood is that these ex post funding adjustments would not take place. Failing this, for scientific areas with a complicated interplay of push and pull and a large push element, there is great risk that the exclusively pull-motivated will lose out to the favored push-motivated. The interplay between push and pull is all about balance, yet advocates have chosen to ignore, or obfuscate around, it. The problem of targeting purchase-based subsidies is highly variable across vaccines and stage of development. It is more easy to achieve for underused vaccines. It is more difficult to achieve for late-stage vaccines though it is probably still possible. It is extremely difficult to achieve for early-stage vaccines such as malaria.

### **9.10. Competition and procurement under different finance mechanisms**

APCs can be thought of as ‘procurement’ devices, based (loosely, we have now discovered) on what R&D a firm has previously done. Competition, and hence efficiency of R&D, however is much less driven in the ex post procurement process itself. Instead, APC advocates argue that firms instigate competition themselves in the R&D part of the process, such that having more firms active on the basis of more private funding equates to more competition, and that this – together with the legalistic long-term contracts – drives out lower prices. But this is more complicated than it at first appears. Competition is driven by:

- 1) The expected behavior of the committee running the subsidy scheme. We saw above that firms’ internal incentives to lower costs when facing time-limited subsidies and sole supplier contracts is not clear. Neither is it clear, if large sunk costs are building up in the system, how much of an incentive firms would have to distribute the IP and know-how in such a way as to have enough competition in

- the end market to feed these pressures to lower prices via external competition. This puts a lot of weight on expectations of the competencies of the committee;
- 2) Expectations (and worries) about the behavior of other firms (especially more influential firms) with respect to the committee, especially concerns about rent-seeking behavior at various levels;
  - 3) The pre-set price and quantity rules and eligibility conditions;
  - 4) The behavior of purchasers with a veto over the scheme, but facing non-existent price signals;
  - 5) The punishments in the long-term contracts.

At a deeper level, the issue is about what stage in the process competition can be relied upon both to arise and to serve a useful purpose. Alongside access to IP and know-how and suitable industrial structure in the end market, the power of competition and the bidding power of buyers is a useful device to help weaken the ‘crowding out’ problem, reduce the need for monitoring, and – alongside financial instruments to help to tackle the risks of large sunk costs and production capacity – to help allocate subsidy/procurement payments efficiently. We will not here pretend to explain precisely how it is done but, ignoring for a moment a range of R&D issues, some of the benefits of competition towards the end of the development process (and en route) are:

- 1) Good information on how to efficiently set terms; information is extracted through competitive tenders, etc.;
- 2) There is less rent-seeking. A reliance on the build up of private sunk costs may risk creating too many incentives to rent-see at several levels, and encourage firms not to ‘cooperate’ (it is too risky given their sunk costs). Taking away a chunk of the sunk costs, and reducing the ‘end-period reward’ needed (on average) to cover those sunk costs, makes it easier for competition later in the process to discipline rent-seeking;
- 3) It may increase ability to separate out the procurement/competitive process at the end from a more collaborative process en route, with players building up reputations for collaboration and performance en route;<sup>780</sup>
- 4) It is relatively easier to make the ‘new’ incentive genuinely ‘additional’. The pull instruments being currently proposed require lots of monitoring and the creation of side-instruments to try to achieve targeting and to avoid crowding out, but, realistically, none of this is that likely ever to actually take place.

The Malaria Vaccine Technology Roadmap could usefully think much more about exactly what is meant by ‘competition’ and especially about where in the process ‘competition’ is most likely to be created and to have greatest impact, and which financing mechanisms are likely to generate more or less competition. Under schemes that repay all R&D investments at the end, firms do not bid for a contract *before* sinking their investments; they sink their investments in order to bid. The firms able to take part are different too, affecting the amount of competition in the industry. Those who win standard ‘procurement contracts’ can use that to attract finance to cover their R&D; those

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<sup>780</sup> IAVI has, for example, been working with ‘social venture capital’ to achieve better access.

seeking the APC must already have good access to finance and ability to sink what will (in most cases) be irretrievably lost costs.

‘Crowding out’ is also handled differently. Under the ex post APC subsidy-based schemes, crowding out has to be judged in advance, to set size and terms, and kept track of over time en route to an eventual payout. Firms have to trust that the correct adjustments to take care of crowding out will be done. Any risk about this is bad for investment. A PPP route with procurement can leave more of this problem to be extracted later through fairly standard competitive processes, economizing on information and monitoring en route.

### **A tradeoff: corruption versus R&D costs**

The usual observation is that the monopsony buying power of institutions, such as the WHO, UNICEF, etc, drives prices too low to recover R&D costs. Firms may have the IP, but it is less valuable because of this monopsony buying power. This is compounded by the inability of UNICEF and others to negotiate long-term contracts; one senior figure, heavily involved in promoting APCs, explained in correspondence that the interest in APCs would greatly fall if UNICEF at last had the ability to negotiate long-term contracts, and that this was the more direct problem to tackle. The move to APCs is in part a reaction to real or implied institutional failures of the past, and an attempt to rebalance pricing power in the direction of firms. The problem is that the replacement has faults too.

There is a tradeoff between, on the one hand, the need to control the rent-seeking, corruption, and self-fulfilling pressures pushing in the direction of lower quality, inherent to APC subsidy schemes, by allowing more price-based bidding of purchasers and more competition, versus, on the other hand, the need to extract R&D costs. This is recognized by Kremer, Towse, and Williams:<sup>781</sup> “A strength of such bidding procedures is that they can address potential concerns over corruption in purchasing, but in some markets [such as in the case here] such bidding procedures can create substantial problems,” in the shape of time-inconsistency over investments and problems if institutions are not able to sign long enough deals on vaccine purchases.

Similarly, the Tremonti Report, at last, recognises that the APC subsidy scheme breeds corruption because most of the triggered payment for each product used is a top-up ‘windfall’ subsidy at the time of use<sup>782</sup> of a vaccine on top of the supposedly low manufacturing costs, and will require “all the economic, institutional and technical arrangements to combat corruption and ensure the actual delivery of vaccines and a strong public health and development impact,”<sup>783</sup> and “procurement systems that ensure transparency and avoid corruption,”<sup>784</sup> and contain “appropriate safeguards.”<sup>785</sup>

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<sup>781</sup> Kremer, M., Towse, A., and Williams, H., 2005, *ibid.*

<sup>782</sup> It *should* be ‘use’ and not ‘purchase,’ even if that means tracking each purchase to make sure it gets used.

<sup>783</sup> Tremonti, G, 2005, *ibid.* pii, and p12. Indeed, for efficient investment incentives, it would require the watertight *expectations* of this.

<sup>784</sup> Tremonti, G., 2005, *ibid.* p12.

The question is, what is the tradeoff between the different institutional failures? Where is corruption easiest to find and remove? Early in the development process before too many privately-sourced costs are sunk? Or, should limited on-the-ground systems capacity be absorbed in recording and tracing each use of the product, and other measures to tackle corruption created by an APC? What if the shift to APCs exchanges one set of institutional failures for another? How do investors respond? There is no free lunch. Someone pays. Yet current lobbying efforts brush these problems aside.

### **Good use of competition and bidding power**

Past successes were in part depended on achieving low prices, and establishing economic pressures to achieve this. Farlow July 2005 Section 3 reviews many cases and finds that a large procurement fund together with ability to compete on price helped increase access to vaccines and push production costs lower. Instead of trying to mend the problem by replacing the entire system from the end with a new risky institution, and contracts with threats, maybe it would be better to find ways to combine the mechanisms we do currently have that put heavy pressure on achieving low product prices, with a different sort of R&D mechanism (with its consequences for IP), with fresh large procurement funds, and ability for institutions to at last be able to sign decent length contracts if that is needed to get the lowest price? Why would one want to use APC subsidy schemes instead of working to correct current failure and put in place proper procurement funds?

The danger at the current juncture is that instead of having lots of firms competing at the R&D stage as claimed (and increasingly we find this hard to sustain) we end up with the number of firms heavily narrowed down to very few developers, and most likely to just one developer, and no competition. Meanwhile we throw the baby out with the bathwater, and entirely lose the useful power to push prices lower. To remotely achieve some efficiency of the APC subsidy mechanism requires an unwieldy mechanism at the end, generating high risk at the start. It would be useful to explore how to reduce that unwieldiness.

### **Pre-fixing APC arrangements crowds out certain ‘partnership’ models**

The Malaria Vaccine Technology Roadmap says that we should “Analyze best partnership models for vaccine development efforts,” and that this should involve an exploration of “past partnership experience, financial, political, legal, and IP issues.” It suggests we “evaluate and characterize options”.

The key observation here is that the nature of financial arrangements driving incentives is the mirror image of the arrangements over APC and PPP and any other institutional arrangements. To fix an APC subsidy scheme in place before sorting the PPP arrangements is to fix in on a financial structure that determines the range of “partnership models” available. It makes little sense to “advocate” for a woolly APC without first clarifying what these “partnership” consequences would be.

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<sup>785</sup> Tremonti, G., 2005, *ibid.* p12.

It would be especially negligent to pitch finance towards highly expensive APCs without first exploring what the impact of similar levels of funding would be on the current PPPs. The forthcoming work of the Pharmaceutical R&D Policy Project (PRPP)<sup>786</sup> at the LSE, under the direction of Mary Moran, will be critical to analyzing this, and policymakers should resist locking in anything until this evidence is available.

Perhaps before narrowing down to an irreversible device, we should take note of the advice of the Roadmap to “Explore all options for how vaccine[s] would be procured?”<sup>787</sup> If APC or PPP cannot be sorted out separately because of the need to crack the financial arrangements *together*, then neither should they be pushed through the policy process separately. Besides, instead of seeing the ‘the lack of a market’ as a problem – when really what we mean is that we do not know how big the market is – maybe we should be seeing this ‘lack of a market’ as an *opportunity* to creatively exploit? Maybe, paradoxically, it helps to make certain things more possible? Given all the difficulties we have found trying to work out how to artificially create ‘blockbuster’ markets through subsidies, perhaps we should not despair and instead first try to work out if we can exploit the situation? We will also find that there are also all sorts of genuine market forces we can take advantage of.

#### **APC = Advance Procurement commitment?**

Perhaps the word ‘Purchase’ in APC could be replaced with the word ‘Procurement’? That is, to clarify, that it is a promise to have large funds to procure vaccines, but that it does not refer to an elaborate, impossible to operate, and risky ex ante determined R&D subsidy scheme paid for through the product prices of the first small tranche of sales, with unrealistic threats to drive longer term supply, and all the while the risk that it is just a Rube Goldberg mechanism to pay off the first dominant firm.

But if so, why would one want to lock in prices at 10 to 20 years, generating all the faults we discussed above that arise when genuine price signals have gone, and with most of the advantages of procurement lost too. Is it better to promise that all the faults will one day be mended, or to actually set about mending the faults, via measures that generate a history of better use of previously developed products, stronger health systems, and the sort of systems that will *naturally* lead to large procurements?

### **9.11. The verbal evidence of firms: Does it mean anything?**

There have been mixed messages about what pharmaceutical firms think about APC subsidy schemes for malaria, HIV, and TB, and, indeed, neglected diseases in general. In particular, somebody is not telling the truth about the support of ‘big pharma’ for APCs.

Moran states: “We also considered the possibility of APCs to stimulate R&D-inactive multinational companies to enter the field; however, these companies were very clear that even large public purchase funds were unlikely to incentivize them to return to neglected

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<sup>786</sup> [www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm](http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm).

<sup>787</sup> RMSR p31.

disease R&D.”<sup>788</sup> Whereas Kremer et al. argue that: “Consultations undertaken by the Center for Global Development indicate private sector *interest in* advanced purchase commitments,”<sup>789</sup> (emphasis added). Similarly, Kremer, when asked “What do drug companies think?”<sup>790</sup> responded that pharmaceutical firms “like the mix of public-private incentives [APCs say nothing about this, and the interaction of the private APC bit with the public bit has been ignored by Kremer et al.<sup>791</sup>]. GlaxoSmithKline has been amongst the most supportive.”

This author has been told by leading figures in two of the big pharma companies (not GSK) that APCs, and especially for malaria, HIV, and TB, are not looked on at all favorably by the industry, and by a leading figure in GSK that even inside GSK an APC for malaria is seen as only the second-best of a bad range of options. At one of the two DFID consultation meetings, Rudi Daems, Executive Director, Policy and Corporate Affairs, Chiron Vaccines Division is reported as stating that “There is not yet a common industry position.”<sup>792</sup> This conflicted with the claim of Nancy Birdsall of CGD that “There is a broad consensus of governments, industry, development experts and the global health community in support of this initiative.”<sup>793</sup>

Others have told the author that the idea has dissenting voices within GSK too. Indeed, in a later section, we will see that CGD-style APCs for malaria, HIV, and TB vaccines would be a disaster for ‘big pharma’, including GSK, given the way a badly designed ineffectual carrot quickly becomes a rod to their backs, replete with reputational damage, even while harming PPP efforts. Lack of ‘big pharma’ support was even revealed in Kremer’s comment above. Why did he feel the need to single out GSK *in particular* if there were lots of ‘big pharma’ lined up to show support, especially given the sensitivity of GSK pushing for an APC for its malaria candidate? If more than GSK were in agreement, why not list them?

The problem with most of the firm-level ‘evidence’ of an interest in APCs, especially for malaria, HIV, and TB vaccine APCs – to the extent it actually exists – is that, like asking children in a sweet shop what they would like, respondents are more than happy to express preference for a bit of everything so long as the marginal cost to them of expressing this preference is zero.<sup>794</sup> Face respondents with a true (and not a hypothetical) budget constraint, real-world tradeoffs between a range of real options (if

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<sup>788</sup> Moran et al. 2005, *ibid.* p81 (though, in the context of drugs).

<sup>789</sup> Kremer, M., Towse, A., and Williams, H., 2005, *ibid.*

<sup>790</sup> <http://msnbc.msn.com/id/10206224/site/newsweek>, 19 November 2005.

<sup>791</sup> Given the number of times Kremer has openly disparaged and sought to create evidence to disparage public-private activity, this is also perhaps a bit rich.

<sup>792</sup> [www.dfid.gov.uk/consultations/amc-consultation-note.pdf](http://www.dfid.gov.uk/consultations/amc-consultation-note.pdf), p2.

<sup>793</sup> [www.cgdev.org/content/article/detail/5253](http://www.cgdev.org/content/article/detail/5253).

<sup>794</sup> For example, the DFID briefing note mentioned earlier (Kremer also had a hand in most of this DFID material) says that an industry group came to a “broad consensus that APCs are a useful addition to the armoury and are definitely worth trying.” DFID *ibid.* p5 [www.bvgh.org/documents/DFIDAPC2-pager.pdf](http://www.bvgh.org/documents/DFIDAPC2-pager.pdf). By now, hopefully the reader will know enough about what a genuinely operational APC would have to be to have any power as an R&D device and to attract *private finance*, to realise that the “worth trying” bit is, to say the least, somewhat disturbing.

you get X billion more of these you will get X billion less of those), then they are much more discerning in their expression of choice. And it has not helped that CGD, Tremonti, and others have repeatedly conflated widely varied vaccine issues, such that industry may respond positively to something that is mostly perceived as a procurement device for an already existing or near-to-existing product, with this support then used to justify an R&D mechanism for highly complicated vaccines that not only do not exist but are a decade or two off existing on best-case scenarios.

Economists are familiar with this problem from public choice theory. Asked about some hypothetical new public investment (more money into local schools, better street lighting, etc.), respondents are happy to express strong preference if their contribution to the investment is not affected by their response. Indeed, if they think it is personally costless but may generate a marginal positive impact in their favor, they will say yes to even globally wasteful policies. However, if their contribution goes up with their expressed preference, and their expressed preference is marginal in its impact on the likely outcome, then they ‘free ride’ on others and under-report their preference in order to reduce their financial contribution. Indeed, it is quite difficult to face firms with anything that is not a phony APC question, since it is very difficult to make anything real hang on the answer. It is remarkably difficult to achieve ‘truth telling’ as the dominant strategy amongst those who respond to questions completely free of any budget-constraint. It is quite shocking to see this basic problem in public choice analysis being regularly disregarded – indeed, openly exploited – in the PR literature surrounding APCs.

It is also clear that many firms have not had the true costs or the workings of the APC mechanism even explained to them before they are asked such questions – outside of reassuring comments that it is “simple yet powerful.”<sup>795</sup> The reliability of answers to such questions is highly questionable. Though Kremer and Daems indicate that “private sector interest” has a much more limited basis than has been regularly claimed.

As a correspondent, very involved in the World Bank process in late 2005 and early 2006, put it to the author: “I have made the point frequently with the WB folks that the process needs to engage really senior people from industry – CFOs and chief counsels from the few main vaccine companies – but this has not been done. So the AMC proponents are, I think, interpreting the vaguely positive but very general comments from mid-level big pharma folks in an overly optimistic fashion.”

#### **Ask them to act on their expressed preference**

It is notable in the papers so far produced to support APCs for malaria, HIV, and TB, that firms are not faced with a range of binding options. They are never asked an obvious corollary as a way to (partly) help overcome this revelation problem: Will they agree to legally obligate themselves to start investing much more in malaria vaccine R&D if such a subsidy scheme is put in place? Will they invest in a new vaccine institution? Will they legally bind themselves to privately finance a set of vaccine trials? If firms did face

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<sup>795</sup> Nancy Birdsall, Testimony to the Senate Committee on Foreign Relations, [www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf](http://www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf) p5.

genuine options with genuine financial implications for themselves, they would get their finance teams pouring over the proposal. This author is confident that the advice they would get from finance professionals would not be favorable, and that such firms would prefer, for the same cost to public funds, many other things before APCs would be on the agenda.

Neither is any attempt made by APC advocates to track private investments or financial market reactions in advance of APCs. Normally, asset prices and investments rise in advance of valuable policy changes (land prices rise even on the suspicion of major new infrastructure projects). We should already be seeing rises in private investment into vaccines being targeted for APCs and in share prices of those who invest in malaria vaccine R&D. Why is nobody looking?

### **A last contradiction**

Asked, in a recent article promoting an APC as a solution to the problem of a malaria vaccine, “Are there any precedents for your approach?”<sup>796</sup> Kremer responds positively: “Yes, in the U.K. in 1994 there was an outbreak of a bacterial infection causing brain swelling. The government said that if a treatment were produced, they’d buy it. It was, they did, and cases of infection went down by 90 percent.” Not only is this a completely inappropriate example,<sup>797</sup> but it even completely contradicts Kremer’s own previous assertions that this was not a good example to use to support the logic of APCs, since the UK Department of Health “did not offer a legal guarantee,”<sup>798</sup> and that outside of the unusual circumstances of this case “it is unclear that manufacturers would be willing to invest in R&D without legally binding commitments in cases where vaccine development was likely to take many years to reach fruition and where government priorities could easily shift.”<sup>799</sup> Why is Kremer holding this up as the *only* case of a successful application of this approach?

### **The time-inconsistency of verbal evidence**

Verbal evidence is itself open to a form of time-inconsistency anyway. The ex ante and ex post incentives of firms may differ radically, distorting their response to open questions about incentive mechanisms. Ex ante, before knowing their ‘drawing’ from the range of possible drawings of vaccine leads, a firm may prefer one incentive mechanism over another, especially mechanisms involving more sharing of information, PPPs, less emphasis on a ‘winner’, less desire for APCs, etc. However, once a firm knows its ‘drawing’ from the pool of potential vaccines, or, indeed, feels that it has some control over a process that is starting to favor it (including its ability to exploit push sponsors) it

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<sup>796</sup> “A New Drug Deal” *Newsweek* <http://msnbc.msn.com/id/10206224/site/newsweek>.

<sup>797</sup> Farlow, *Innovation Strategy Today*, July 2005, pp. 133-34, pp. 140-141, discusses what happened in the UK case of meningitis conjugate C, and why it was so distinctive, and completely unlike the APCs being promoted for HIV, malaria, and TB. Just a few: Much simpler science than malaria, HIV, and TB; all developers covered costs; all made sales and continued to make sales; no follow-on concerns; little risk; a great deal of the needed vaccine technology was already in place; price was not driven down to \$1 in the long-run and was not pre-agreed as APC advocates now propose for malaria, HIV, and TB vaccines; there was no pre-agreed legal APC-style contract, etc.

<sup>798</sup> CGD, April 2005, *ibid.* p59.

<sup>799</sup> CGD, April 2005, *ibid.*

may start to advocate for mechanisms that disproportionately (or the firm thinks will disproportionately) advantage its own vaccine lead (or its approach to a vaccine).

Imperfect competition (i.e. a limited number of big players) may affect response too. If large players can capture part of any overpayment, they will have some incentive to lobby (relative to what they would otherwise have preferred) for mechanisms that create overpayment. We need to constantly guard against this, and, indeed, build in protection against it from the start (like stopping firms from taking too influential a part in the policy-making process<sup>800</sup>).

And what about asking those in Russia, India, China, Latin America and all those who will fall outside the APC subsidy schemes for malaria, HIV, and TB what would suit them too, and what R&D approaches they would pay for and contribute to?

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<sup>800</sup> So, an end to conference calls in which Gordon Brown says things like: “Yes, GSK. And J.P. Garnier...there is, if you like, an understanding with the Gates Foundation and with the pharmaceutical company that the next stage would be an advance purchase agreement...” CGD news teleconference, 25 April 2005, with Nancy Birdsall of the CGD. See the full transcript of this below. To bore the reader, this is not an anti-GSK comment; it is a ‘fair and level playing field’ comment, because a fair and level playing field is crucial to malaria vaccine success.

## **10. The Kerry-Lugar Vaccines for the New Millennium Bill 2005**

There was a recent announcement of a Bill, the Kerry-Lugar Vaccines for the New Millennium Bill 2005,<sup>801</sup> to promote policy on some of the issues discussed in previous chapters. The preamble to the Kerry-Lugar Bill contains several positive pieces of advice on what needs to be done to bring forth the more rapid development and use of vaccines for several major killer diseases. However, our interest here is with the genuinely new initiatives the Bill is promoting, rather than with measures that it discusses that are going on elsewhere already but that the Bill is doing nothing to further. The Bill contains sections on PPPs (especially favorably described), a range of new tax credits for companies that invest in R&D for vaccines for neglected diseases, as defined in the Bill, and APC subsidy schemes. Were such a Bill to go through, what impact would it have on some of the issues being discussed in this report?

### **10.1. The promotion of APC subsidy schemes**

The Kerry-Lugar Bill spends most of its energy pushing for a system based on APC subsidy schemes, titling them ‘Advance Market Commitments’ (the language created by CGD), thus conscripting the language of the ‘market’ to promote what we have repeatedly found, and especially in the cases of HIV, malaria, and TB, to be highly ‘non-market’ based schemes.

The Bill contains a very puzzling section on ‘Advance market commitments.’ The relevant sections are:

“*On the date that the Secretary of the Treasury determines that a vaccine to combat a neglected disease is available for purchase, the Secretary shall establish in the Treasury of the United States a fund to be known as the Lifesaving Vaccine Purchase Fund...*” (emphasis added).

“The Secretary is authorized to expend amounts in such Fund for the purchase of a vaccine to combat a neglected disease pursuant to *an advanced market commitment undertaken on behalf of the Government of the United States.*” (emphasis added).

Furthermore, we are informed in a section titled ‘Authority to accept contributions’ that:

“The President [of the United States] may accept and use in furtherance of the purposes of this Act contributions from nongovernmental organizations, international health agencies, the United Nations, the Global Fund to Fight AIDS, Tuberculosis and Malaria, private nonprofit organizations that are organized to support public health research and

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<sup>801</sup> The proposed legislation can be found at:

[http://blogs.cgdev.org/vaccine/archive/2005/09/vaccines\\_for\\_th.php#more](http://blogs.cgdev.org/vaccine/archive/2005/09/vaccines_for_th.php#more)

programs, and any other organizations willing to contribute to the Lifesaving Vaccine Purchase Fund.”

## **10.2. Lack of credibility to investors**

The central concern of all those dealing with such subsidy schemes, whether for or against, is that the commitment will not be credible. This is the ‘time-inconsistency’ problem, the notion that if the purchase fund is set up *after* firms have sunk their R&D costs, they will suffer ex post opportunism in the hands of the funders. There are high chances of this, given that a firm’s out-of-pocket R&D costs will be a small fraction of the required payment from the fund, if the fund is supporting APCs as genuine R&D instruments encouraging multiple parallel developers per diseases, and not just providing the funds for one firm to cover its production costs. Even a small risk of renegeing on a few key terms will impose a huge financial penalty on private investors.

We ran a simple example in an earlier chapter just for illustrative purposes: If a firm (for simplicity we presume one winner, but the reader might like to think how the logic is affected if there are supposed to be multiple ‘winners’ over time) expects, say, a 75% chance of purchases at an agreed \$6.25bn (a figure for malaria taken from a previous CGD report), and a 25% chance of the committee renegeing and paying only half, then the ex ante expected value of investment has fallen from \$6.25bn to \$5.47billion. This still ‘looks’ a ‘very good’ deal from the public’s ex post perspective. The firm is getting a huge multiple of its out-of-pocket R&D costs and the firm is more than covering its capital costs; it is the ‘winner’ from a process involving a large number of parallel developers, with all the others ‘losing’.

But this is not a ‘fair’ return judged ex ante. Fighting ex post to get the ex ante ‘fair’ return looks ‘greedy’. If \$6.25bn *was* the risk-adjusted ‘fair’ figure required to generate optimal research intensity, and if we wish for vaccine development to not be slowed by this risk of renegeing, the promised payment by the sponsor has to *rise* to at least \$7.14bn<sup>802</sup> (assuming firms are risk neutral), generating a premium of \$890m to compensate for the risk of renegeing.<sup>803</sup> If vaccine developers are risk-averse, the figure must be even higher.<sup>804</sup> Sponsors pay more for the same level of research intensity.

We remember, yet again, that the main purpose of such APC subsidy schemes is not to pay the manufacturing costs of vaccines – that would not need a contract set 20 years in advance with prices and terms set before much of the science and financing costs became

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<sup>802</sup>  $x$  such that  $0.75*x + .025*0.5x = \$6.25bn$ , if vaccine developers are risk-neutral.

<sup>803</sup> The calculation also presumes that the probabilities are not altered in the process of adjusting up to \$7.14bn. This is unlikely to hold. If probability of renegeing rises with the APC size, the APC size will have to rise *even further* to compensate. Size settles at the stationary point (if there is one) in this process. This presumes that firms cannot easily hedge this risk, which this author presumes would be very difficult to do given the non-idiosyncratic nature of such risk, and given the moral hazard problems if policymakers were to believe that such risk is hedged.

<sup>804</sup> Vaccine developers have different required risk premia, with some – biotechs and emerging developers – would be especially badly hit. It depends on ability to hedge risk.

known, since this would be a highly inefficient price-fixing arrangement – but instead to repay the sunk R&D costs. In exchange, ‘winning’ firms get valuable IP, useable across all markets, both those that are eligible for APC subsidies, and those that are not eligible.

### **Developers tied in to contracts for 20-30 years**

Politicians can make promises, but the political process has a tendency to lose interest, and default on previous politicians’ promises. As the author was writing this chapter, the British newspapers were full of stories about the potential collapse of the G8 2005 debt right-off agreed in the summer of 2005, and its last minute rescue. Political commitments are shaky affairs. The debt right-off was agreed just a few months previously. We are talking here about extraordinarily complex commitments (because of the complex targets) over several generations of vaccines for several diseases, needing to last for 20 to 30 years.

In the APC literature of just a few years ago it had been claimed that funds would not need to be set aside in advance of the availability of a vaccine: “Such a commitment does not require money now.”<sup>805</sup> To have to set the funds aside ‘now’ would destroy one of the key justifications for deferring payment – the freeing up of *current* funding for alternatives, such as malaria drugs. It would also increase the costs of APC subsidy schemes if money needed to go into escrow accounts. Unfortunately, this claim has proved difficult to sustain.

Instead, the CGD report of 2005 concluded that the way to avoid sponsors needing to commit actual funds, would be if all vaccine developers, including all future vaccine developers, are contractually tied in to the sponsor from the start. Hence the CGD report contained contract term sheets, described by CGD as utterly crucial to the workings of the APC subsidy scheme. To the degree that these contracts are legally enforceable in a court of law, we are informed that money would not need be put into escrow accounts by sponsors of the APC. Farlow 2005 (WHO, and *Innovation Strategy Today*) and Farlow et al. 2005 argued that this creates as many practical problems as it solves, and is still not credible.

Therefore, according to the Kerry-Lugar Bill all vaccine developers would have to sign-on from the moment the scheme is set up or shortly thereafter. So as not to distort incentives, this would require all currently funded vaccine trials to be signed into the scheme from the moment of its inception. This would involve over 100 current trials run through eight different funding agencies: NIH and its intramural Malaria Vaccine Development Unit (MVDU), the European Commission (EC), the European Malaria Vaccine Initiative (EMVI), the Malaria Vaccine Initiative (MVI), the United Nations Development Program (UNDP)/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, the United States Agency for International Development (USAID), and the United States Department of Defense/Naval Medical Research Center. Future developers would have to sign-on from a moment

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<sup>805</sup> Kremer, No 10 Policy Unit, Appendix 2, p1.

before they invested anything in vaccine R&D (if those running the scheme allowed them to join, since this is not guaranteed).

### **Monitoring and intervention**

In exchange, all activity would, supposedly,<sup>806</sup> be monitored by those running the APC scheme, to judge if the scheme was working and to adjust terms if necessary (though earlier we found that this had big problems). CGD initially made light of this, but Tremonti makes it clear that it will be a significant role for the committee running the APC. As Tremonti puts it: “Another noteworthy task of the IAC [the committee running the APC scheme] will be suggesting [to] donors the split of each AMC commitment between the unitary prices and the number of doses,”<sup>807</sup> and that “the AMC must also be periodically re-evaluated to determine if initial estimates on what constitutes an adequate size and price continue to hold true,”<sup>808</sup> and “the terms of the framework agreement, specifically the vaccine eligibility requirements, would be re-assessed periodically by the IAC to take into account additional information that becomes available. The terms of the agreement could be revised accordingly – although not to raise the bar in terms of the requirements for target vaccines.”<sup>809</sup> Tremonti reveals all the monitoring of private investors the committee would have to do to achieve this,<sup>810</sup> and the essentially statist, non-market, credentials of such subsidy schemes. In this report we have many times discussed the adverse consequences of this asymmetric attitude to the ‘quality’ bar.

### **Were Kerry and Lugar told what an APC actually is?**

The Kerry-Lugar Bill proposes that funding is *not* put aside until a vaccine is developed. It is only “on the date that the Secretary of the Treasury determines that a vaccine to combat a neglected disease is available” that “the Secretary *shall establish* in the Treasury of the United States a fund” (emphasis added) to buy it. Therefore, if the CGD-style contracts are not in place, firms will not invest in response to the promised Kerry-Lugar funds;<sup>811</sup> it will be just too risky for them to do so.

The Kerry-Lugar Bill must therefore be implying (though it does not spell it out) that all current vaccine developers and all potential vaccine developers (wherever they are in the world, and before they invest a cent in malaria vaccine trials) sign into a mechanism, the purse strings of which are in the hands of the Secretary to the US Treasury and the President of the United States of America, run by a committee with powers along the lines of those just outlined by Tremonti.

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<sup>806</sup> Most of this is ‘supposedly’, since the political realization of the scheme will be very different from what is claimed.

<sup>807</sup> Tremonti, G. p11.

<sup>808</sup> Tremonti, G. Background Papers p5.

<sup>809</sup> Tremonti, G. Background Papers, p38.

<sup>810</sup> See for example Tremonti, G. p11.

<sup>811</sup> Various companies have privately expressed concerns (based on experience) that the US and other governments will renege on vaccine promises. We remember also that it is not just failure to buy a product, but failure to pay the price that covers the full risk adjusted return based on *all development costs* across multiple parallel developers.

Were Kerry and Lugar told about the key role of the APC contracts, the institutional structure to support the contracts, the committee determining returns to investors, and the locking in of all global malaria vaccine trials to such a highly interventionist mechanism being run through the US Treasury and the president of the United States of America? They do not mention it in their Bill.

Incidentally, once liability issues are finally and properly looked at (being signed into such legally-binding contracts carries obligations on both sides, as described elsewhere in this report) even the President of the United States of America might balk at this arrangement.

### **Tremonti complicates and contradicts Kerry-Lugar**

After the Kerry-Lugar announcement, The Tremonti Report was released, complicating yet further the situation facing the Kerry-Lugar Bill. Several of those who advised on the Tremonti wording had previously advised on the wording of the CGD report; indeed, the Tremonti background papers contained all the same contract term sheets as the CGD Report. However, the Tremonti Report proceeded to backtrack on the notion that all payment would be only at time of disbursement of vaccines. Tremonti suggested three options for sponsors to pay for the APC:

- a) Either full front-loading of finance at launch of an APC;
- b) Or financing through periodic contributions. This option would require a bridging facility to create extra funding in the case of early discovery, and some (so-far unmodeled) mechanism to reassure initial developers that they will be fairly treated and that follow-on innovators will not be disadvantaged. The intuition is that developers may have ‘got lucky’ early, having spent only a fraction of the potential APC fund. Repayment however needs to be based on the ex ante probabilities, and not on the actual outcomes. If the bridging mechanism is not watertight, firms who ‘got lucky’ too soon will have to push for extra funding even if this behavior looks ‘greedy’. These bridging arrangements have not even been sketched, even though any lack in their veracity would perversely harm R&D incentives. They are just another get-out clause from having to deal with an otherwise awkward and intractable problem;
- c) Or financing at time of disbursement.

The first two would have to be designed to hold the deposited funds in Trust funds for the duration of the scheme (30 years as suggested by Kremer and CGD) so as not to undermine incentives, and would also require mechanisms to reallocate funds if no vaccine was ever developed.

Tremonti simply ignores the (high) costs of options 1 and 2. And Tremonti ignores any conflict between these two options and any front-loaded efforts to develop vaccines and other health products for the poor. Tremonti seems to presume that in the face of financial constraints on drug and vaccine development, delivery, health systems capacity, etc., funders would still be able to siphon large resources into Trust funds that are committed

to a distant APC payout. Tremonti still requires all developers to be signed into contracts even before investing in vaccine R&D, as suggested in the CGD Report.

Tremonti also recognizes that the fiscal scoring of option 3 funding (and large chunks of option 2) is still an unresolved issue.

These various options also require a complicated understanding of how different countries would fare in a mixed system, and the reactions of vaccine developers to this. One can only conclude that this part of the APC proposal has become a mess – with the Kerry-Lugar Bill and Tremonti Report even in conflict – and more costly than advocates have been letting on.

### **10.3. Risks of the Kerry-Lugar Bill to investors**

We saw – given very difficult science in advance and many unknowns – how malaria, HIV, TB and other vaccine APC subsidy schemes would have to contain a great deal of discretion in the hands of a committee running the APC scheme. Given that there was already concern about the lack of accountability of a small committee and the risks that this would impose on developers, it is not clear how placing key funding powers into the hands of the Secretary of the US Treasury and the President of the United States would help mitigate this.

Would decisions about the release of funding really reside in US hands according to Kerry-Lugar, even under systems with discretionary aspects, all this monitoring, and several funding options at work? Observe how, even with the presence of other funding agencies, the Kerry-Lugar Bill risks making the US the lead decision-maker in funding decisions dependent on such subsidy schemes (and ‘lender of last resort’ if others fail to execute their funding obligations via one of the funding options Tremonti details):

- 1) Ex ante, how would a US company that has not quite made the efficacy conditions expect to get treated?
- 2) How would an emerging economy, developing country, or European firm expect to get treated in similar circumstances?
- 3) What happens to incentives of follow-on vaccines? Is the Secretary of the US Treasury obligated to ‘create’ more funds for an emerging firm’s vaccine to replace a US-based firm’s vaccine? Again, it is the expectations of this that feed back to impact R&D.
- 4) If emerging developers have to make investments even before being allowed to join the APC scheme, how does this not become a hurdle? Even small expectations of disputes and litigation over ‘qualitative’ issues (e.g. regulatory standards) and ability to join the scheme, may put off ‘pre-joining’ investment.
- 5) How could emerging developers trust that the Secretary to the US Treasury will handle ‘fairly’ all the non-APC funding a developer had received (including the denial of a multiple of APC funding, as discussed above)? Or would this just get ignored?

### **Worries of preferential treatment**

The sponsors, in this case the US Treasury, would clearly therefore have to be operationally independent of the committee running the APC. Yet, this is a committee with discretion. Does the Secretary to the US Treasury and the President of the United States do as the committee commands? Could the Secretary to the US Treasury and the President of the United States really be obligated to act against his/her/their wishes under duress? Do the Secretary to the US Treasury and the President of the United States not have some greater obligations than even the APC subsidy scheme? We saw simple cases above where small risks of renegeing on terms can be very costly in the ex ante sense, with literally hundreds of millions of dollars of losses from small chances of renegeing. And we also saw how just the uncertainty about this can be leveraged by certain players. How is it guaranteed that such a structure for raising payments will not create the expectation in investor's minds that some players will be treated differently than others?

How is funding not to be driven by political decision-makers and not instead by an open 'competitive' process (we are already seeing the dangers of this in the case of malaria). Is it also not a little unrealistic to believe – with funding organizations' reputations at stake, and with vital policy and financial interests that they *must* be able to exercise – that these organizations would really hand over independence? Who would have jurisdiction over non-eligible countries and non-APC scheme developers? What would be the involvement of the US Treasury and the US President? What about political rent-seeking and the temptations to favor political or commercial allies? What about project choices that reflect the preferences of bureaucrats? And priority setting that results in R&D being directed only at one type of country, one region of the world, one disease, or one company?

The pricing of the risk between these various cases tips the whole mechanism squarely in favor of US-based companies, and intensifies the rent-seeking incentives of a mechanism that is already stuffed full of rent-seeking incentives, and faces US politicians with a range of reputational risks.

### **Anti-competition problems**

There is a further serious problem that Kerry and Lugar may or may not have been aware of. Their proposed funding mechanism ceases to be a scheme open to all unless all are prepared to be signed into the underlying contracts and monitoring structures from the start. Since product subsidies would favor lower quality firms over higher quality firms that do not get subsidies (see above), either all should agree to join or all should keep out. To the extent the European and other initiatives do not wish to sign into such contracts and such extra layers of monitoring, this would make the scheme an anticompetitive device subject to various competition authority interventions.<sup>812</sup> If the Europeans and others wish not to be part of such a scheme, the presence of the scheme would damage them, and it would be legitimate to complain, especially if it harmed the chances of getting better quality vaccines. Indeed, no subsidy scheme should be allowed to pick off a few developers at a time, blackmailing the rest into joining for fear of being harmed.

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<sup>812</sup> Including to tackle the anticompetitive consequences of the 'options value' of the legislation.

Tarcisio Hardman Reis argues that finance by a government to advantage its own domestic private companies is a form of subsidy, and that such contracts “might be considered as subversions for the purposes of the EU and possibly represents unfair competition for WTO.”<sup>813</sup> Furthermore, Reis argues that there is no international organization that is properly empowered to define the companies that are subject to such contracts, and that this is unable to exist under WHO or WTO Constitutions.

Would the US really want to set itself up for this? Meanwhile, harming cross-country collaboration if the R&D community is split in this way? As Kaper et al. put it: “Collaborations between investigators from the U.S. and European Union are [already] problematic, as government grants often put constraints on expenditures. More harmonization is needed between funding agencies in order to foster these collaborations.”<sup>814</sup> Do vaccine scientists and the pharmaceutical firms themselves want this problem to be intensified, given future reputational risks?

We repeatedly saw the way it was important to create more active players, including from emerging and developing economies. Now we are told that the “Secretary of the Treasury determines” such matters. Is this likely to be a globally accessible initiative?<sup>815</sup>

#### **10.4. For whom will the Kerry-Lugar Bill purchase vaccines?**

The Kerry-Lugar Bill explains: “The term ‘developing country’ means a country that the World Bank determines to be a country with a lower middle income or less.”

This seems to indicate that the Bill is creating a fund to purchase, for example, HIV vaccines – in the hands of the Secretary to the US Treasury and the US President – that would deny subsidized sales to most of those countries that might benefit from them in, say, 20 years time, including Russia, China, and India. Either these countries would be customers at (tiered) monopoly prices of the firms being paid subsidies in other markets, who would own all the IP to the vaccine(s) favored by the subsidy scheme the US

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<sup>813</sup> Tarcisio Hardman Reis, CIPIH Forum, 16 Nov 2004.

<sup>814</sup> Kaper et al. 2005, *ibid.* p23.

<sup>815</sup> Given the crucial need to create for investors the impression of inclusiveness, competition, and a level playing field across all potential developers, CGD, astonishingly, held the launch party of their April 2005 report at Covington and Burling, one of the leading ‘big pharmaceutical’ legal practices, with the sponsorship of Merck. What are developing/emerging country developers to believe about the crucially-needed independence of the small adjudicating committees visualized as running such schemes many years hence, if it cannot even be clearly signaled at the launch party? And now they hear that everything goes through the Secretary of the US Treasury and the President of the United States. The issue here is not whether or not ‘corporate interests’ influenced the process, but the crucial importance of investor perceptions of a very wide range of potential investors facing a mechanism that already creates problems for itself with rent seeking and the strategic behavior of larger players. Since all of the emerging country developers and PAHO members had already fallen away from the CGD Working Group process by the time of the launch, this suggests that their interests were already not being well catered for before aggravating these perceptions even further. Furthermore, we will shortly see that Merck (along with GSK) was one of the two companies locked in the race to produce the first cervical cancer vaccines, with its vaccine Gardasil (submitted to regulators December 2005).

Treasury was funding (if these countries wanted the vaccine). Or these countries would have to rely on vaccines created outside of the subsidy scheme (but not generics of the subsidized vaccine(s) or vaccines based on the vaccines covered by the scheme, since this would be banned<sup>816</sup>).

How would such ‘non-eligible’ countries be encouraged to take part in such activities as the ‘Global HIV Vaccine Enterprise’ and various PPPs, if they know that they will draw the short straw at the purchase stage, and have to buy from companies who benefited from the results of the collaborative efforts that these countries had had an important hand in creating?

However, to include such countries in the subsidy scheme from the start would crowd out most of the private sales that such non-eligible countries might otherwise have made to ‘winning’ firms, and pass the cost on to US taxpayers in a much bigger required subsidy fund – a funding proposal hardly likely to get through the US Senate. The only alternative in this case would be for these countries to agree in advance to pay into this US-based fund, but how are their payments to be made credible if not physically paid into escrow accounts?

#### **Arguments over eligibility**

At the very least, by the time a vaccine is available, there would be an argument over the status of such countries. The stakes are high. If China and South East Asian countries, Russia, and India, and Latin American countries can be treated as non-eligible in HIV, malaria, and TB vaccine APC subsidy schemes, they will have to pay monopoly (possibly tiered) pricing for their vaccines. Indeed, given the limited level of the APC subsidy available, so long as there are enough poor markets to absorb the subsidy, the logic to a vaccine firm would be to not ‘waste’ the subsidy on sales to China, Russia, India, Latin America, etc., and thus lose non-eligible profits on those markets.

Would the President of the United States really become the funnel of funds from other organizations – including the Global Fund to Fight AIDS, Tuberculosis and Malaria, private nonprofit organizations, etc. – through a scheme that is biased to US-based companies and that is set up to deny payments to Russia, China, India, Latin America and others? Would the US want the political ramifications of this?

### **10.5. The narrow range of products covered<sup>817</sup>**

The Kerry-Lugar Bill covers HIV/AIDS, malaria, TB, and “any infectious disease”, which is then further defined down to mean something more limited: “infectious disease (of a single etiology), which, according to the World Health Organization, causes more than 1,000,000 deaths each year in developing countries.” To observe that the range of

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<sup>816</sup> Again, what kind of mess are large pharma firms also walking into here?

<sup>817</sup> The following section has benefited from the input of a wide range of public and industry experts on infectious diseases. If a reader is unhappy with what they think is more of an opinion than a fact, the author would gladly look into it and, if necessary, change the text. Sometimes these issues require insider knowledge, with all its problems and caveats.

coverage is narrowed down, is obviously not to downplay the importance of the coverage itself.

However, this excludes many infectious diseases that might cause much suffering and death in developing countries but that do not cause *sufficient* deaths, and it excludes all non-infectious diseases however many deaths in developing or other countries, and it excludes non-vaccine approaches to health problems. The “infectious disease” definition repeats the restrictions to exclude emerging and lower middle income countries too. So, what vaccines does this leave to be funded by the Kerry-Lugar Bill?

WHO estimates 1.75 million TB deaths,<sup>818</sup> 1.6 million pneumococcal-induced deaths per year,<sup>819</sup> 745,000 deaths from measles,<sup>820</sup> 450,000-500,000 deaths from Rotavirus (mostly in children under five, most of them in the world’s poorest countries),<sup>821</sup> 288,000 HPV deaths,<sup>823</sup> with about 3m deaths from HIV and about 1.2m deaths from malaria,<sup>824</sup> though the figures for malaria have been very imprecise in the past, ranging from 0.5 to 3.0 million deaths<sup>825</sup> – because there has been insufficient investment in proper documentation of the epidemiology and burden of malaria. Indeed, malaria-related mortality is particularly difficult to measure because the symptoms of the disease are non-specific and most deaths occur at home.

The Kerry-Lugar Bill thus covers vaccines for HIV, malaria, TB, and pneumococcal disease in ‘developing countries’ only (i.e. not even in lower-middle income countries). Given that HIV, malaria, and TB vaccines are a long way off ever being amenable to such a fund – and indeed the analysis in this report argues they are *not* going to be incentivized into existence by an APC – this only seems to leave the Kerry-Lugar Bill as currently potentially applicable to pneumococcal.

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<sup>818</sup> [www.who.int/mediacentre/factsheets/fs104/en/index.html](http://www.who.int/mediacentre/factsheets/fs104/en/index.html) (2003).

<sup>819</sup> [www.preventpneumo.org/disease/disease.htm](http://www.preventpneumo.org/disease/disease.htm) (2003).

<sup>820</sup> (2001 data).

<sup>821</sup> DFID data [www.bvgh.org/documents/DFIDAPC2-pager.pdf](http://www.bvgh.org/documents/DFIDAPC2-pager.pdf).

<sup>822</sup> WHO data (2001 data).

<sup>823</sup> [www.who.int/vaccine\\_research/diseases/hpv/en/](http://www.who.int/vaccine_research/diseases/hpv/en/) (no date). Though, one correspondent indicated that HPV probably has poor data to support a claim under the Kerry-Lugar definition. Another correspondent observed that mortality figures were only part of the story of human suffering from HPV, and wondered whether the interest in ‘only’ mortality figures was a good idea.

<sup>824</sup> WHO, 2002. “World Health Report 2002.” Geneva: World Health Organization. Worldwide total of 1,124,000 deaths due directly to malaria in 2001, with about 300-500 million cases of disease every year [www.bvgh.org/documents/DFIDAPC2-pager.pdf](http://www.bvgh.org/documents/DFIDAPC2-pager.pdf). Snow et al. 2003, in their work on the Burden of Malaria in Africa (BOMA) project, build on the MARA (Mapping Malaria Risk in Africa) risk mapping, and a wide range of other data sources, coming up with a best estimate of 1,144,572 deaths attributable directly to malaria in Africa in the year 2000. This is regarded as the most plausible current estimate. Snow, R.W., Craig, M.H., Newton, C.R.J.C., Steketee, R.W., 2003. “The Public Health Burden of *Plasmodium Falciparum* Malaria in Africa: Deriving the Numbers.” Bethesda, MD: Disease Control Priorities Project. These two differ in their distribution over age groups. Snow et al. calculate about 65 percent of deaths among children under 5, and the WHO a much higher 86 percent.

<sup>825</sup> Guerin et al. 2002. *ibid*.

### **Some big misses**

The term “any infectious disease” is not set to cover rotavirus gastroenteritis or human papillomavirus virus, HPV.

### **Rotavirus**

Rotavirus is endemic and infections occur in almost all children by the time they are two or three. The big difference is that in developed countries few deaths occur, with the problem showing up mainly in hospital admissions and medical costs, while in developing countries the disease is much more devastating because of the lack of prompt access to treatment and hospital care. About 40% of all hospitalizations among children aged under 5 years in developing countries are for rotavirus, as are about 40% of all diarrhoeal deaths.<sup>826</sup> A vaccine would save many lives in developing countries.

For nearly a decade, RotaShield was so clearly the dominant rotavirus vaccine that manufacturers of other candidate vaccines (SmithKline Beecham [GlaxoSmithKline], Merck) held back on their investments fearing they would simply arrive late in the market. The withdrawal of RotaShield encouraged these manufacturers to review their programs, to spot new commercial opportunities, and to push forward with new commitment and vigor. GSK reckon that the global market potential of a vaccine against rotavirus could reach almost \$2 billion a year.

As Glass et al. put it: “Withdrawal of the first rotavirus vaccine dealt a resounding blow. However, the results of and the reaction to the unfortunate problem of intussusception with RotaShield might be that the world’s children gain access to rotavirus vaccines sooner than expected. More vaccines from more companies – both multinational and local – are proceeding to development, which should ensure greater supply and distribution, lower prices, and more rapid local acceptance. These vaccines will all be tested in children in developing countries. Multinationals are competing with renewed vigor and can test their vaccines in the USA, an opportunity not available to them when the first vaccine was licensed and being used. Donor agencies have recognized that the prevention of rotavirus diarrhoea is a target worthy of their investments, and that the likelihood of success with live oral vaccines in the near future remains substantial.”<sup>827</sup>

Indeed, two new vaccines have been licensed literally in the closing days of writing this report. Merck’s new oral rotavirus vaccine, Rotateq, was submitted to the US Food and Drug Administration in April 2005, and approved 3 Feb 2006, with US distribution beginning within a week. At a cost of \$187.50 for the three-dose course, RotaTeq is one of the most expensive vaccines ever. By 2009, Merck forecasts that the vaccine could bring in as much as \$500 million in annual revenue. Although Merck has said that they are committed to making RotaTeq available at a discount in the developing world, they still need to test the drug in poor nations before the WHO will recommend its universal use; some oral vaccines that perform well in rich countries are not nearly as effective in

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<sup>826</sup> Glass, R.I., Bresee, J.S., Parashar, U.D., Jiang, B., Gentsch, J., “The future of rotavirus vaccines: a major setback leads to new opportunities.” *The Lancet*, 2004, Vol. 363, pp. 1547-1550.

<sup>827</sup> Glass et al. 2004, *ibid*.

the difficult settings of developing countries. However, testing in poor nations is still stuck in the planning stages.

On 27 Feb 2006 the European Medicines Agency approved GSK's Rotarix. Like Merck, GSK has pledged to make their vaccine available and affordable to developing countries, but has also not yet completed the necessary clinical trials. Rotateq and Rotarix are 98% and 85% effective respectively, and show no evidence of being associated with intussusception.<sup>828</sup>

GAVI selected diarrhea vaccines for special emphasis three years ago in an attempt to make rotavirus vaccine available to children in developing countries at the same time as those living in the developed world, but it is not proving easy. GAVI is already facing the tough challenge of delivering worldwide a \$3.50 vaccine against five other major killers. A big issue with vaccines such as Rotateq and Rotarix is going to be the price, and the finance of a sustainable and affordable supply of vaccines. Chapter 5 above argued that price was crucial and much more difficult, yet crucial, than the APC literature had tended to appreciate.

Tremonti<sup>829</sup> comments that “If an AMC were established now for rotavirus, it would be too late to influence the development pathway” but that it would influence decisions to conduct studies into the efficacy of the vaccine in different parts of the world and expand capacity. The provision of funding to purchase existing products “would provide a signal to industry that the developing country market for vaccines can provide a profitable return.” In other words, Tremonti describes rotavirus vaccine along the lines of good past practice<sup>830</sup> involving a decent-sized procurement fund, with a range of demand stabilizing initiatives (with the caveat that there still are struggles to make the product affordable in poorer settings), and not close to the language used to describe malaria, HIV, or TB vaccine APCs.

Both Pneumococcal and Rotavirus are seeing more than 2 suppliers within the next two years or so with or without any new Senate-approved mechanism. One commentator pointed out that rotavirus is more amenable to scale production than pneumococcal, and that at the moment there is probably more capacity than is being taken up due to lack of purchases.

### **HPV**

Two companies, GSK and Merck, have been locked in a race to produce the first cervical cancer vaccines. In December 2005, Sanofi MSD, a subsidiary of Merck submitted Gardasil to the European Medicines Agency for licensing. In early March 2006, GSK submitted its vaccine, Cervarix. Each claims it will tackle at least 70%-80% of cancer cases, with the exact figure – maybe higher – yet to be settled. No price has been settled yet, but some reports suggested that for the three dose course it would be about the same

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<sup>828</sup> Glass, R.I., and Umesh D. Parashar, “The Promise of New Rotavirus Vaccines.” *The New England Journal of Medicine*, 2006, Vol. 354, pp 75-77.

<sup>829</sup> Tremonti, G. Background Papers, 2005, *ibid.* p21.

<sup>830</sup> See Farlow 2005, *Innovation Strategy Today*, Section 3 for applications of pull initiatives for rotavirus.

price or more than the recently-launched rotavirus vaccines, at about \$180 (some suggest more) for the course.

If approved, these vaccines could have a major impact on women's cancer. Tremonti points out that "Both these products will likely be licensed within the next two to three years. There is a substantial developed world market for [these] products. However, the need for them is arguably greater in the developing world, where it is estimated that 80% of cervical cancer occur."<sup>831</sup> The figure is so much higher in developing countries because the quality of screening and awareness and detection of the problem is so much lower. However, as Kaper et al. put it: "Unfortunately, an HPV vaccine is probably going to be prohibitively expensive for use in the developing world, where it is needed most."<sup>832</sup> One correspondent observed that HPV, unlike malaria and HIV, is "much more stable" so that the need for a *set* of vaccines and follow-on vaccines was not the same as for malaria, and that the HPV vaccines are good-quality and will work, and this explains why a high price is chargeable. This correspondent queried the notion of heavily subsidizing a malaria vaccine that had none of these features.

In the cases of HPV and rotavirus vaccines, it is not just about money to buy the vaccines. As Glass et al. explain: "A major problem with [*Haemophilus influenzae* type b] vaccines was a lack of awareness of the disease even after the vaccine was licensed. The same may be true for papillomavirus and rotavirus vaccines. Although rotavirus is the commonest cause of diarrhoea in children worldwide, in most developing countries with high mortality from diarrhoea a diagnosis of rotavirus infection is rarely made."<sup>833</sup> The problem is that pediatricians and decision makers in these countries have no first-hand knowledge of the disease and do not appreciate its importance. An APC does not automatically get rid of this problem.

### **Both rotavirus and HPV left off Kerry-Lugar Bill**

Why *have* rotavirus and HPV seemingly been left out of the Kerry-Lugar legislation?

### **One big hit in the Kerry-Lugar Bill – pneumococcal**

With respect to pneumococcal, there is a childhood vaccine, Prevnar, that since being introduced in 2000 has proven effective against pneumococcus bacteria, and that Wyeth has been doing well from in non-developing countries (\$4bn over 5 years). However, at \$150 to \$180 for the three doses required, it has proved too expensive to use to treat many children outside of the United States and Western Europe. The recent Wyeth 7-valent conjugate pneumococcal vaccine formulation (in which the capsular polysaccharide has been linked to a protein carrier to enhance its immunogenicity) contains only seven serotypes that are most common in the United States, and would reduce disease burden by a minimum of about 50% in low-income countries.<sup>834</sup> There are 9-valent and 11 valent formulations in the Wyeth pipeline but these would only add small increments (a few percentage points) to reducing disease (greater strain coverage is a law

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<sup>831</sup> Tremonti, G. Background Papers, 2005, *ibid.* p22.

<sup>832</sup> Kaper et al. 2005, *ibid.* p10.

<sup>833</sup> Glass et al. 2004, *ibid.*

<sup>834</sup> Personal correspondence.

of diminishing returns), but recent results from large scale Phase III trials in South Africa and Gambia are encouraging. Unfortunately, there are some serious limitations on the conjugate vaccine, including “high manufacturing cost, making them inaccessible in the developing countries where they are most needed to reduce child mortality,”<sup>835</sup> and lack of effectiveness against some of the pneumococcal serotypes that most commonly strike adults.

Other manufacturers have similar pneumococcal products in their pipelines for supply in 2-3 years. There has been testing variously in the Gambia, South Africa, and Indonesia. GSK is strongly involved in a late-stage product. What is now Sanofi-Pasteur has/had a vaccine candidate that they Phase III tested in Indonesia but they were ambivalent about going forward with it.<sup>836</sup> These products are like Wyeth’s. Merck might re-enter if they see a good market but they backed off a few years ago, probably to focus on other late-stage products – MMRV combination, rotavirus, HPV. Production capacity is a constraint for the Wyeth product, mostly on the polysaccharide component.<sup>837</sup>

### **Emerging technology**

There is another group of pneumococcal vaccines with different approaches further back in the pipeline, that do not rely on immunity based on the over 90 pneumococcal polysaccharide-based serotypes, but instead induce responses to proteins common to all or most pneumococci. Because of mergers, it is less clear in which company the lead contender now resides.<sup>838</sup>

In recognition of the fact that current methods of vaccine production are complex and expensive, in April 2006 the Gates Foundation announced \$75m to a new PATH initiative to find a new method of vaccine development that will significantly reduce the cost of pneumococcal vaccines.<sup>839</sup> This seems to reflect the recognition that getting pneumococcal vaccine available in poor countries is not just because we do not have an APC to do, but because the current technology makes it a very expensive thing to do. For the 2 billion people in the world living on a dollar or so a day, cost matters. The goal of the PATH project is to explore a new approach that would stimulate immunity using basic proteins commonly found on the surface membranes of all pneumococcal serotypes. Once common proteins have been identified, the hope is that these ‘protein vaccines’ will be easily and inexpensively altered to match the specific strains of any given region. The new PATH initiative would also explore ways to help poor countries set up their own vaccine-manufacturing facilities

This provides a vivid illustration of a point made in Chapter 5 of this report: Efforts to achieve low costs in the first place are key to access. Yet, incentives to achieve low costs risk being distorted if large pre-fixed price subsidies are placed on some products. Will the subsidy get absorbed in repaying R&D (for a low cost product)? Or will it get

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<sup>835</sup> Kaper et al. 2005, *ibid.* p11.

<sup>836</sup> Personal correspondence.

<sup>837</sup> Personal correspondence.

<sup>838</sup> The author only has personal correspondence on this.

<sup>839</sup> [http://seattlepi.nwsource.com/health/265285\\_path03.html](http://seattlepi.nwsource.com/health/265285_path03.html)

absorbed in higher costs of a high cost product? And what about the use of legalistic rules to tie producers to long-term low prices even before conducting R&D as argued by APC advocates?

As Kaper et al. observe “It has proven to be very expensive to develop a pneumococcus vaccine, and prospective manufacturers face major financing, supply, and advocacy issues.”<sup>840</sup> In addition, those working on pneumococcal and rotavirus have expressed a preference to work within institutional settings that they are used to and understand and that are low risk, and they have made it clear that they want to avoid the new untested procedures and layers of uncertain new bureaucratic and institutional detail created by an APC. Indeed, some have argued that these products are so close to market that to shift responsibility for purchasing away from GAVI and onto an APC subsidy scheme and a whole load of new institutional detail will introduce a great deal of unnecessary delay. The problems and challenges in getting price low are tough enough as it is.<sup>841</sup>

Current pneumococcal and rotavirus can largely be catered for with large procurement funds and long-term contracts with competition to drive production costs lower. So, as an R&D device, what is the Kerry-Lugar Bill adding? Why not simply make the procurement funds available?

**At what level will the efficacy and price be set for pneumococcal vaccines?**

As Tremonti explains “proven technology exists for pneumococcal vaccines,”<sup>842</sup> though Tremonti ignores the issue of there being alternative potentially superior technologies (in the sense of technology more likely to achieve long-term affordable costs) further back in development. The issue therefore is whether the requirement for an APC subsidy payment (as an R&D device) will be set higher than currently existing pneumococcal vaccines to encourage better future vaccines, or will payment go to existing products?<sup>843</sup> If the efficacy is set at 50%, so as to allow the current pneumococcal vaccines through, how is the legislation being used for its claimed intent of using APCs to incentivize R&D of *new* vaccines? One correspondent even wondered, if an APC was designed to provide funding for current pneumococcal vaccines leaving nothing for these different approaches further back in the pipeline (i.e. an ‘APC’ that is *not* used as an R&D device on products much further back in the pipeline), whether or not it would harm investor incentives on these other products (compared to a rolling procurement fund open to all products with more emphasis on affordable products).

Thinking of this as a practical example of what might happen with malaria vaccines, if a fixed pool of R&D subsidy is made available via an APC: How do those distributing the

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<sup>840</sup> Kaper, et al. 2005 p11.

<sup>841</sup> Gillis, J., “Lives Lost As Vaccine Programs Face Delays: Efforts to Get Medicine To Poor Children Falter,” Washington Post, 19 December 2005, [www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069\\_pf.html](http://www.washingtonpost.com/wp-dyn/content/article/2005/12/18/AR2005121801069_pf.html).

<sup>842</sup> Tremonti, G. Background Papers, 2005, *ibid.* p22.

<sup>843</sup> Clearly, this is not a criticism of the use for existing products. The author has written plenty elsewhere in support of this. The issue is the degree to which the funds are being used for the claimed use to incentivize R&D, and the degree to which the instruments resemble a CGD-style APC with all the contractual aspects.

subsidy pool make sure that it does not all go on existing vaccines, leaving less than is optimal to incentivize follow-on vaccines? What if follow-on developers come to believe that this will happen anyway? How does the subsidy distributor credibly reassure the follow-on developers so as not to deter them from their investments in the first place, with the subsidy going on already existing vaccines in self-fulfilling fashion?

We saw above the importance of driving long-term prices lower. If one of the big problems with pneumococcal is achieving low price, will the fund enable better vaccines costing less to be developed for the future? How will it cause the prices of better efficacy vaccines to be driven down to a few dollars? Will the firms concerned be forced to sign long-term contracts to supply at very cheap prices even after the subsidy is gone, as repeatedly asserted as a “crucial feature” of CGD-style contracts? Or will they be allowed some lee-way on the pricing rule used? If so, how can it be maintained that APC contracts are the key to ending millions of deaths for HIV, malaria, and TB by securing long-term cheap supply?

The big question is – if this legislation is being sold to the public as a novel way to incentivize the R&D of new vaccines – will the new fund enable research and development of ‘better’ pneumococcal vaccines than developing countries would otherwise have got, or be used up to fund the already available vaccines? If the latter, how is it novel? If pneumococcal and rotavirus just need the same devices as previous successful programs, what is left for the Bill to attach itself to *as a novel R&D tool*? How would the APCs initiated begin to match up to the APCs that advocates are proclaiming for malaria, HIV, and TB: R&D devices for not-yet existent products?

### **It won’t tell us anything about malaria, HIV and TB**

Recouping all R&D expenditures plus all production capacity costs (including process development costs) from an APC subsidy scheme for eligible countries will be a very rare event. For pneumococcal vaccines, the need is much more production capacity, and only these extra production capacity costs will be legitimately ‘chargeable’ to the APC if no new strains need to be added to the vaccine to meet the target product profile – i.e. an APC would essentially be a capital investment instrument close to the time of uptake with no risk of failure. This is utterly unlike a research investment removed in time from possible uptake, with high risk of failure, as is the case with malaria, HIV, and TB. Indeed, Towse is quoted as observing that “a successful AMC for a late-stage vaccine will do little to actually prove that the commitment can motivate R&D for early-stage vaccines for AIDS and malaria.”<sup>844</sup> Indeed, it may contradict it, since such late-stage vaccines will teach us a lot about the difficulties (and impossibilities) in setting price years in advance. This has not stopped key advocates claiming recent initiatives as applications of a ‘novel’ new R&D funding instrument, and proof of its value for malaria, HIV, and TB vaccine R&D.

If the Kerry-Lugar Bill (and an APC) is ‘used’ for pneumococcal, this would therefore tell us nothing about the power of an APC to incentivize R&D for malaria, HIV, and TB

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<sup>844</sup> Zandonella, C., 2005, *ibid.* p21.

vaccines. Nobody has ever disagreed with the need for ‘pull’ instruments to create capacity and to help drive production prices lower. This author has written a lot about it (see Farlow 2005 section 3 for plenty of ‘pull’ capacity issues). The issue is about how much R&D can genuinely be pulled through via APCs, and whether all the fresh risk introduced by such schemes, when used to fund R&D, are worth the institutional effort and cost of setting up contracts 20 to 30 years in advance. If they are capacity devices, why set price and force firms to take those terms now? And why create an unbalanced sunk pre-set subsidy with all the distortions discussed above? Why push through a whole new set of complicated and risky institutions, and eat up the institutional and political capital of organizations like MVI, GAVI, the G8, the World Bank, and the Italian finance ministry, like some giant hammer to crack an otherwise – with political will and good global leadership – penetrable nut?

### **Is this even the best way for pneumococcal?**

One can completely understand the frustrations and financial need of those working on pneumococcal, and even the rational of using even inefficient policy instruments indirectly to force sponsors to ‘cough up’ (even though that means that most of the new funds created via the US Treasury just replace funds that should have been created anyway, and are therefore mostly fungible). But the Kerry-Lugar Bill, to the extent it will almost certainly hit delays and raise budgetary issues in the US Senate may delay, rather than speed, the needed funding for pneumococcal. If it was being used as an instrument to persuade the US into funding the roll out of vaccines, why was it pitched to miss HPV and rotavirus? Was it to avoid the chance of defeat in the Senate? Or was this just an error? Or is the rational that HPV and rotavirus do not really need these subsidy instruments anyway?

### **10.6. Will all ‘eligible’ products get funding?**

But is it realistic to believe that all products (including new generations of products) that are potentially eligible will get funding? That is, are there no limits on the Kerry-Lugar funds? Will the US Treasury sign up to a potentially limitless scheme?

The Bill points out that “For each fiscal year beginning after the date that the Secretary determines that a vaccine to combat a neglected disease is available for purchase, there are authorized to be appropriated out of *any funds in the Treasury not otherwise appropriated* such sums as may be necessary to carry out the purposes of such Fund,” (emphasis added), and that “The Secretary shall transfer the amount appropriated...for a fiscal year to such Fund...Amounts appropriated pursuant to this paragraph shall remain available until expended without fiscal year limitation.”

This seems to imply that funds are released in a fiscal year according to the vaccine then newly available, and that the funds can be spent over several years. But it says nothing about how *new* funds are created for each and every follow-on generation of vaccine – and the legal obligations to do so. Indeed, the section italicized in the last passage above seems to indicate some limitation on funds appropriable from the US Treasury for the purposes of this.

Is it realistic for firms to believe that a vaccine for *any* neglected disease (as defined in the Kerry-Lugar Bill, that we saw has already limited this definition greatly) whenever developed and however much has been spent from the subsidy ‘fund’ already, would nevertheless get fresh funds? Does the US become ‘funder of last resort’ if other funders fail to top up the funding pool? We are, after all, talking about horizons of 20+ years in the case of malaria (and HIV and TB) and we are interested in long-term R&D incentives of an evolving complex vaccine R&D process based on human-parasite interactions, necessitating generations of follow-on products.

We already saw the need for subsidy funds to grow in nominal terms by at least 11%-14% per year to equalize the value of the 2015 and 2025 malaria goals and of follow-on vaccines, if relying on large pharmaceutical firms to provide the investments leading to vaccines, with repayment of their investments via an APC. Will the US Senate allow such a subsidy scheme to feed through this funding mechanism so as not to harm goal-2 and follow-on malaria vaccines in general? Will the US agree to such a *growing* funding commitment at a time of growing domestic budgetary pressures?

What if there is a limit on the total size of the funds compared to the potentially eligible products (or firms suspect that this is the case, or there is no limit set but the limit is implicit, or there is no limit set but this is not credible)? The principles are the same for any fund that is not big enough to cover all the products that it might potentially pay for. For example, a country may offer to pay for the first of several products in the hope that other sponsors will pay for other products.<sup>845</sup>

But this has its flaws.<sup>846</sup>

- 1) There are insufficient R&D incentives for *all* diseases;
- 2) Those diseases with the easiest or most badly set terms, pick off the funds first;
- 3) The R&D for other, usually more difficult, diseases does not respond.

The chief lesson is this: The sponsor(s) need to spell out an efficiently-sized funding pot for each product target evolving over time to allow for follow-on investment – and then ring-fence it. The Kerry-Lugar Bill gives no hints that this is intended. Perhaps the spelling out of the cost implications would be just too much? Maybe policymakers really

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<sup>845</sup> “An advance purchase commitment from a single government would pave the way towards commitments from a broad range of governments and donors... One possibility would be for the United Kingdom to pledge to purchase the first vaccine developed [from a selection of diseases for which vaccines are being sought] and [then] seek commitments from other countries for subsequent vaccines...It is unlikely that vaccines for all three diseases would be developed simultaneously, but if donors wanted to limit their exposures, they could cap their total promised vaccine spending under the program, for example at \$520 million annually.” Kremer Appendix 7, p35, [www.strategy.gov.uk/downloads/files/Appendix%207.pdf](http://www.strategy.gov.uk/downloads/files/Appendix%207.pdf).

The wording in the Tremonti Report reveals that, at last, policy-framers have cottoned on that this is not true: “The specific risks and challenges for the development of each new vaccine require the design of *a separate AMC mechanism for each target disease*.” pii (emphasis in original). See also p7, p8, and elsewhere.

<sup>846</sup> Farlow, A.W.K. 2004, *ibid.* Section 8.7, pp. 126-128, “The Dangers of the UK (or any Single Government) Going it Alone.”

would be prepared to enact policy to pay only for the least efficacious early vaccine outcomes?

### **10.7. Tax breaks**

The bill includes a section on new tax breaks, which includes things like:

“Limitations on Foreign Testing – No credit shall be allowed under this section with respect to any vaccine research (other than human clinical testing) conducted outside the United States.”

This further intensifies the US-centric view of the Bill, and is a flat contradiction of the view previously taken by leading APC advocates that tax breaks are a very inefficient way to pay for vaccine R&D.<sup>847</sup>

Furthermore, “No credit shall be allowed under this section for pre-clinical research unless such research is pursuant to a research plan an abstract of which has been filed with the Secretary before the beginning of such year.” And the biggest tax break of all is a 100 percent tax credit on contracts and other arrangements for research and development of these vaccines and microbicides, an increase over the 65 percent credit now in the tax code. This, we are told “is designed to serve as an incentive to larger pharmaceutical companies to work hand in hand with the smaller biotech companies to pick up the pace of vaccine development.”<sup>848</sup>

#### **Low response to previous tax-breaks**

The legislation builds on legislation introduced in 2001 (Frist-Kerry), yet ignores the fact that even the current tax incentives have done little to stimulate privately-funded vaccine R&D for conditions such as HIV, malaria, and TB.<sup>849</sup> Logically, a newly instigated tax break should, for any given market size, have caused a surge in privately-funded R&D at the time. The fact that it didn’t, undermines the claim that “Research has shown that the major obstacle to the development of vaccines for these diseases is the absence of a market,”<sup>850</sup> but rather suggests that the problem is much, much deeper, at the level of the science and a wide range of risks faced by developers not amenable to an APC or tax-break fix. We showed in an earlier chapter that no such ‘research’ exists anyway.

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<sup>847</sup> “Currently, U.S. companies are eligible for a 20% research and development tax credit. A bill recently introduced in the United States Congress proposes increasing this credit to 30% for research on vaccines for diseases that kill more than one million people a year. One potential problem with such an approach is that firms doing research with only indirect implications for these diseases might try to claim eligibility for the credit, while focusing much of their effort on developing more lucrative products.” Kremer, M., *Creating Markets for New Vaccines Part I: Rationale*, p27, <http://adfdell.pstc.brown.edu/classes/readings/kre99a.pdf>.

<sup>848</sup> Senator Kerry, on launch of the “Vaccines for the New Millennium Act.” 14 September 2005, Congressional Record.

<sup>849</sup> ‘Privately-funded’ since private firms are very involved in much of the activity currently going on even if not all ‘privately funded’. The exclusive interest of APCs, however, is to create *privately-funded* activity and force firms to take entrepreneurial risk, and this is all that they should pay for.

<sup>850</sup> Senator Kerry, 14 September 2005, *ibid*.

Indeed the Bill spells out that “The term ‘qualified vaccine research expenses’ shall not include any amount to the extent such amount is funded by any grant, contract, or otherwise by another person (or any governmental entity).” That is ‘qualified vaccine research expenses’ are not non-privately funded PPP-based activities. This is sensible of any new tax incentive, since it helps avoid (but not completely) the ‘crowding out’ problem. However, the Bill thus first sings the praises of PPPs, and then proposes to enact tax incentives that favor those other than PPPs, and puts forward no practical funding proposals for PPPs.

About 50% of current vaccine research takes place in biotechs. Currently, ‘not-profitable’ biotech firms can only take advantage of tax-breaks to the extent that they can be bought-out by much larger pharmaceutical companies to ‘cash in’ on the value of the tax-break (the smaller firms amass the unused tax-breaks as an asset reflected in their equity valuations until taken over). Biotech research therefore needs to boost biotech share valuations in ways that appeal to large pharmaceutical firms. This is another route for the ‘replacement effect’<sup>851</sup> to enter. Again, dollar for dollar is it clear that the tax-break route is the most cost-effective at unlocking the credit constraints of biotechs?

### **10.8. Obligations to report on progress**

The Bill contains various obligations to report on progress:

The first obligation is to report within 90 days on the new tax breaks and the SBIR and STTR programs.

The second obligation is to report on the setting up of the funding commitment to AMCs:

“REPORT- Not later than 180 days after the date of the enactment of this Act, the Secretary shall submit to the appropriate congressional committees a report on the status of the negotiations to create advanced market commitments under this section.”

The third obligation is with respect to the ‘Comprehensive Strategy for Accelerating the Development of Vaccines for Neglected Diseases’: “Report- Not later than 270 days after the date of enactment of this Act, the President shall submit to the appropriate congressional committees a report setting forth the strategy described in subsection (a) and the steps to implement such strategy.”

There are no obligations to report on the progress of any new PPP initiatives. Neither are there any new PPP funding commitments to report on, in spite of growing evidence of the

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<sup>851</sup> See a previous chapter. It refers to what happens when a vaccine potentially replaces the non-vaccine product for the same disease of the same firm. In this case, even if biotech research boosts valuations, if they have not got the funding to go ‘all the way’, the need to turn to firms that suffer a ‘replacement effect’ will feed this ‘replacement effect’ onto the biotech.

value of some of these initiatives. In a recent article<sup>852</sup> McGee argues that “scientific advances and additional funding are revitalizing the field.... the field is also being energized by initiatives such as the Bill & Melinda Gates Foundation, which has provided hundreds of millions of dollars for vaccine research, particularly for diseases affecting the third world...The National Institutes of Health (NIH) is also helping jump start the field.”<sup>853</sup> This is all without facing firms with risky new APC subsidy instruments and contrasts starkly with the vague notion of ‘potential power’ ascribed in the literature to justify such subsidy schemes.

Thus, the Kerry-Lugar Bill puts its greatest reporting requirements onto the thing that leading APC advocates regard as one of the least efficient of ways to pay for R&D for neglected vaccines;<sup>854</sup> Farlow (2004) explains why the evidence that SBIR would crowd out private R&D for vaccines for neglected diseases is hard to sustain,<sup>855</sup> and thus provides some support for this part of the Kerry-Lugar policy proposals.<sup>856</sup> The next most emphasis is put on to the APC subsidy schemes. The next onto the details of the “Comprehensive Strategy”. There are absolutely no reporting requirements or indications of new funding commitments at all on the one thing – PPPs – that the Kerry-Lugar Bill takes most time to praise and finds most actual evidence of previous success.

### **10.9. A missed opportunity to boost efforts to roll out current products and to tackle resistance**

Had there been more joined-up thinking, this would have been a fantastic opportunity to help put in place the funding for the treatment roll-out proposed in Arrow et al. 2004 as part of a “comprehensive strategy” to tackle malaria.

As Arrow et al. put it “With the incentive of a secure and large market, producers already are promising that wholesale prices for a course of ACTs will fall to US\$0.50-\$1.00 (or

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<sup>852</sup> McGee, P., “Vaccines on the Road to Recovery,” *Drug Discovery and Development*, October 2005, [www.ddmag.com/ShowPR.aspx?PUBCODE=016&ACCT=1600000100&ISSUE=0510&RELTYPE=CVS&ProdCode=00000000&PRODLTT=V](http://www.ddmag.com/ShowPR.aspx?PUBCODE=016&ACCT=1600000100&ISSUE=0510&RELTYPE=CVS&ProdCode=00000000&PRODLTT=V).

<sup>853</sup> By providing \$20 million to \$25 million in funding to each of three or four companies that can bring new vaccine approaches into phase I trials.

<sup>854</sup> For a particularly scathing attack on the SBIR in the context of vaccine funding for neglected diseases see: “For an empirical argument that government crowding out effects on private R&D can be close to 100% please refer to Wallsten (2000).” (quote from Kremer, M., Appendix 2, No. 10 Policy Unit, p10, repeated Appendix 3, No. 10 Policy Unit, p20). The Wallsten study (Wallsten, “The R&D Boondoggle.” *Regulation*, 2000, Vol. 23 Number 4) looks at the Small Business Innovation Research Program (SBIR), covered by the Kerry-Lugar Bill, and the way it, according to Kremer: “seems to have crowded out privately funded research dollar for dollar.” The clue as to why it is not appropriate to apply this analysis to neglected disease vaccine research is in the subheading of the Wallsten paper: “Why is government subsidising commercially promising business projects?” – but there are many other reasons why this is an inappropriate study to use to argue against such initiatives for neglected disease vaccine R&D (see Farlow, A.W.K., 2004, *ibid.* Section 8).

<sup>855</sup> Farlow, A.W.K., 2004, *ibid.* Section 8.1.2.

<sup>856</sup> ‘Some’, since the crowding out argument is weaker than claimed by Kremer, but firms may still not respond if the science and complexity of the problem is too great.

possibly lower) within 2 years.”<sup>857</sup> Indeed, “A global subsidy near the top of the distribution chain will stabilize demand and create incentives for ACT production, resulting in lower prices,”<sup>858</sup> with the entry of more companies and the ramping up of production of current companies. The procurement agency would buy ACTs directly from manufacturers at competitive prices, then resell them to countries at a lower, subsidized price (ideally through a ‘virtual’ rather than a physical warehousing system). If 300-500 million episodes are treated annually worldwide – roughly equaling the number currently treated by chloroquine or sulfadoxine-pyrimethamine (S-P) – at an incremental \$1 per ACT course, an adequate global subsidy for ACT could be created for at most US\$300-\$500 million per year, falling if the price of effective antimalarials comes down significantly. It would be a true global public good, by preserving the effectiveness of antimalarials for all global citizens through the simple expedient of ensuring coformulated drugs (currently, ACTs) globally. It is worth reading a passage of Arrow et al. at length:

*“There is something of a chicken-and-egg quality about the current price of artemisinin, and the prospect for significantly lower prices. Lower prices can be expected in response to large-scale demand, which, in turn, will induce competition among producers. However, without assurances from the global community that there will be a market for large quantities of ACTs, manufacturers will not have the incentive to scale up production, and prices will not drop. In addition to competition driving prices down (i.e., companies being willing to accept lower profits per dose with higher volumes), technological improvements in the process could bring down the actual production costs, which would be passed along to purchasers in a competitive environment. The real price breakthrough will likely occur only when a fully synthetic artemisinin is developed, eliminating the growing and extraction process. The Medicines for Malaria Venture (MMV) has such a compound under development, which they predict could be available in 5-6 years. The ultimate price is not known, but it should be significantly less expensive than current artemisinins (assuming no premium for exclusivity). If the synthetic product is better than, or at least as effective as the extracted ones, the market would change dramatically. A global subsidy might still be needed, but it could be less than what is needed now.”*<sup>859</sup>

There is also much going on to help lower long-term prices, which would also be boosted by greater and more stable demand. As alternatives to growing *Artemisia annua*, biotechnology-based approaches are being explored to produce artemisinin. The Institute for OneWorld Health in collaboration with Amyris Biotechnologies, with a \$42.6 million five-year grant from the Bill & Melinda Gates Foundation, is exploring how to scale up a microbial process created by chemical engineers at the University of California, Berkeley. OneWorld Health will coordinate the clinical testing and regulatory issues. The hope is to create a stable, semisynthetic source of the drug and a major cost saving, although the ultimate saving will depend on the combination drug formulation. Similarly,

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<sup>857</sup> Arrow et al. 2004, *ibid.* p5.

<sup>858</sup> Arrow et al. 2004, *ibid.* p7.

<sup>859</sup> Arrow et al. 2004, *ibid.* pp. 63-64.

much better data on burden of diseases, along the lines of the Snow et al.<sup>860</sup> data discussed above would help avoid financing being driven by speculation, poor data, and even guesswork.

A similar range of supply constraints impacts on injectable forms of artesunate. This is produced in China, but there is no widely available version made to current Good Manufacturing Practices (cGMP) standards.

### **Worries about resistance**

At the same time there is a great worry about resistance, with chloroquine-resistant *P. falciparum* widespread across all malaria-endemic regions. Current heavily-used drugs come from a restricted range of chemical classes, quinolines and folate inhibitors, with the threat of cross-resistance among closely related chemical entities. The sequential introduction of monotherapy drugs has led to sequential selection and spread of mutant drug-resistant malaria parasites and the creation of multidrug resistance.<sup>861 862</sup> As Guerin et al. observe “Artemisinin-based combinations, which provide mutual protection against resistance, high efficacy, excellent tolerability, and reduced transmissibility, are judged the most effective strategy to provide highly effective treatment that will not fall to resistance.”<sup>863</sup> In June 2005 the WHO convened a meeting of growers and representatives from companies, government agencies, and nongovernmental organizations (NGOs) to discuss strategies to create a more stable and sustainable market for artemisinin-based drugs.

As Guerin et al. point out “*The current most urgent need in malaria control is to provide effective treatment. Antimalarial drugs that are effective against all malaria parasites are available now, and their lifespan of effective use will be greatly extended if they are used in combination. We already have several highly effective artemisinin combination treatments, although further development work in dosing, coformulation, packaging, and delivery is still urgently needed...For such discoveries to happen and for these drugs to become available to patients, an international commitment to provide adequate funding and coordination must occur at all levels from upstream research through development to deployment. But, in all probability, none of the potential new compounds will be available for general use for 10 years—even if they are safe, effective, and affordable.*”

If there is a crying need for a malaria purchase commitment at this moment in time, it is to ensure the financial sustainability of this. Unfortunately, just like the Hepatitis B case study that exited the CGD report at the last minute, this malaria treatment proposal contradicts key components of the malaria vaccine APC scheme being proposed:

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<sup>860</sup> Snow et al. 2005 *ibid.*

<sup>861</sup> Targett, G., Drakeley, C., Jawara, M., et al. “Artesunate reduces but does not prevent posttreatment transmission of *Plasmodium falciparum* to *Anopheles gambiae*.” *J Infect Dis*, 2001, Vol. 183, pp. 1254-1259.

<sup>862</sup> Nosten, F., Brasseur, P., “Combination therapy for malaria.” *Drugs*, 2002, Vol. 62, pp. 1315-1329.

<sup>863</sup> See also White, N.J., Nosten, F., Looareesuwan S, et al. “Averting a malaria disaster.” *The Lancet*, 1999, Vol. 353, pp. 1965-1967, and “Antimalarial drug combination therapy”: Report of a WHO technical consultation, April 4–5, 2001. Geneva: WHO, 2001.

- 1) It is a standard procurement commitment with competition to drive prices lower;
- 2) It shares out IP widely (the “no premium for exclusivity” bit);
- 3) It is a global solution covering all countries;
- 4) It involves no systems of monitoring to deal with crowding out and similar problems (public and private sectors of *all* endemic countries would be eligible to purchase ACTs at low, subsidized prices);
- 5) The subsidy goes in at one point and not through purchasers’ individual decisions (as Arrow et al. put it: “very high in the purchasing chain – above the level of individual countries”<sup>864</sup>) avoiding corruption and keeping transaction and monitoring costs down (contrast this with the monitoring and registering of every use of a malaria vaccine under an APC scheme, to try to prevent corruption);
- 6) It is both private- and public-sector friendly but, this author would suggest, more private-sector friendly than current APC proposals;<sup>865</sup>
- 7) It is cheap and indeed should decline in cost over time;
- 8) It is simple (in contrast to the fake-simplicity of the current APC subsidy proposal<sup>866</sup>);
- 9) It would work for sure (rather than be the CGD-inspired gamble that will fail).

But it lacks the ability to be ‘claimed’ as a self-generated novel policy success and it might even show up the current proposal. So, it gets overlooked, and even deliberately played down.

### **10.10. What is left?**

Given the highly favorable remarks on PPPs, given the complete non-event of malaria, HIV, and TB APCs – and the way they have recently crowded out the possibility of real practical action –, given the unproven, problem-filled, and certain low-power and riskiness of APCs, and given the lack of impact of previous incentives on encouraging private R&D towards vaccines, it is not at all obvious why the emphasis on new initiatives leaves PPPs out quite so conspicuously, and why malaria treatment is so overlooked. The most obvious policy initiative would be to make some concrete promises on PPP funding, malaria treatment funding, and turn the APC idea into a commitment to procure (as part of a package to create many suppliers) supported by financial instruments/incentives to help with capacity and risks, and get rid of the complicated statist scheme currently being heavily promoted.

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<sup>864</sup> The full line is: “Recognizing the many pathways by which antimalarials flow to consumers leads inevitably to the conclusion that external financing should be injected at a point very high in the purchasing chain – above the level of individual countries,” Arrow et al. 2004, p7.

<sup>865</sup> In many countries, the distribution and payment for malaria drugs is still primarily through the private sector. In Africa, more than 70% of antimalarial drugs reach consumers through the private sector (small pharmacies, and general store kiosks, and even street-side stalls). Waiting for the public sector infrastructure to be improved will take a long time, but is essential to both better drug and vaccine distribution. However, this author would argue that repayments of R&D costs to private sector firms for malaria vaccines are far more sensitive to improvements in the public sector under current proposals than is the case for drugs given these distribution systems.

<sup>866</sup> See below Nancy Birdsall’s comment to the Senate Committee on Foreign Relations that a malaria APC would be “simple yet powerful” when it is anything but either of these things.

Instead, after years of successfully building up PPP approaches, advocacy effort has been turned to push for poorly worked-out risky schemes that may well aggravate the PPPs (PPP, for example, work on very different IP and access arrangements to APCs). Indeed, those pushing for these poorly-worked out schemes never lose an opportunity to turn complaints about the failure to fully fund successful PPPs and treatment programs, against those who make the complaints.

### **Many components dropped**

In the early days, the APC subsidy proposal involved an auction mechanism to set the overall subsidy size, since it was realized that there was no other way to set an efficient size.<sup>867</sup> This was dropped. There were pre-sunk co-payments from eligible countries to force them to face a ‘market test’; a terrible idea.<sup>868</sup> These were dropped. There was said to be no need for money to be put aside even though the mechanism was very risky.<sup>869</sup> The introduction of the two stage contracts, tying *all* firms into the scheme, was admission that this did not hold either, and the solution just meant a whole new bag of problems were introduced to get around the first problem (though the Kerry-Lugar Bill is not clear on the status of these contracts within the proposal being put to the Senate, since the Kerry-Lugar Bill does not even mention them). Tremonti now reveals that even this may fail, and lists three funding options instead. Finally, Tremonti now reveals all the statist credentials of the APCs being promoted, perhaps inadvertently, by Kerry and Lugar.

The Kerry-Lugar Bill is as it is therefore, because, having removed other key features of the original proposal due to their underlying faults, to have removed the core idea of a sunk fixed subsidy pool and a (supposed) variable R&D subsidy attached to purchases, would have removed any remaining policy relevance and *raison d’être* of the whole APC project for early-stage vaccines such as malaria, HIV, and TB. The idea had to stay, even though this device gets most of its faults – problems in handling quality, incentives to rent-seek and corruption, lack of a price signal to create follow-on incentives, problems setting long-term price to cover costs without harming R&D incentives, too little competition to push production prices lower, time-inconsistency risk to firms, excess risk to biotechs, etc. – from the same route as the originally-proposed, sunk, eligible country co-payments: It is both sunk and it is not credible.

If APCs collapse down to mostly a price-fixed procurement scheme, it raises the issue of what the whole point is of devoting limited systems capacity and exhausting political capital on setting up the institutional and monitoring framework for such schemes *now* (given very much higher priorities), with all the inherent inefficiencies of fixing terms well in advance of the science and the costs being known, given that such schemes will

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<sup>867</sup> See Farlow, A.W.K., 2004, Section 11 for why this would not work in this case.

<sup>868</sup> See Farlow, A.W.K., 2004, Section 7 for the problems with these.

<sup>869</sup> Farlow, A.W.K., 2004, Section 9 pointed out that, in the absence of any other arrangement, the notion that money did not need to be put aside was wrong, principally because the commitment would lack financial credibility and open the system up to financial instability that might, like financial crisis in a financial system, cause the commitment to collapse in self-fulfilling fashion. Somehow, the system of contracts is supposed to prevent this.

do nothing *now*, yet create the dangers of the ‘law of unintended consequence’ of irreversible instruments. It also raises the question of how and why Kerry and Lugar have been conscripted into launching such schemes.

**Do not fight global imbalances – go with them in a novel way**

It is also not clear to this author why, with US deficits soaring and strong pressures to cut US government spending, all attention is on initiatives that require the US to pay pretty much everything anyway. China, Russia, and India will be major beneficiaries of HIV vaccines. With the state of global imbalances at extremes, China is running a balance of payments surplus of several hundred billion dollars a year and parking most of it – more than \$200bn per year – in low-paying US government debt (it has about \$800bn holdings already). Even Russia has swung to generating a surplus of \$100bn per year. Have the Chinese really got so few social and welfare enhancing programs that they are prepared to lose so heavily on holding US debt? Throw in the fact that when the dollar falls and/or the yuan revalues, China will make a large quasi-fiscal loss,<sup>870</sup> it does rather suggest that targeting schemes at the US Treasury and not at China, Russia, and India, is really rather misguided anyway. A PPP approach might be able to draw China, Russia, and India in, but it goes against the notion of creating large ex post APC subsidy pools. So, we do not go that way, and we lump everything on the US Treasury and US taxpayers instead. Why?

Instead of trying to run schemes through those running large deficits, why not try to encourage the Chinese (and others, such as the Russians) to park \$5billion to \$10billion in malaria/HIV/TB vaccine and neglected disease PPP research instead of US debt (paying only a few percent per year), then do a deal that exploits the fact that when the dollar falls and/or the yuan revalues, this parked sum will have avoided the quasi-fiscal loss, such that a large chunk of the cost to them will turn out to have been for free. Vaccine research becomes part of a global hedge.<sup>871</sup>

So, the Kerry-Lugar Bill is set up to disincentivize the many, especially non-US companies, even as it does nothing to change the real payoffs to US companies for malaria, HIV, TB and other vaccine R&D. At the same time, it encourages the notion that a powerful instrument is in place to incentivize malaria, HIV, and TB vaccine creation and, in turn, that shortfalls from cuts in other vaccine funding (or failures to expand funding) are fine. It achieves little that could not have been cracked otherwise with political will (for example for pneumococcal) and diverts attention from acting on any of the things the Bill finds are the most promising ways to act, destroying the useful things that could have been done instead. Is this what successful policy is all about? Who advised on the wording leading to such a document?

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<sup>870</sup> See Farlow, A.W.K., “UK House Prices, Consumption and GDP in a Global Context,” January 2005, Section 6.2 (and do not be put off by the title):

[www.economics.ox.ac.uk/members/andrew.farlow/Farlow%20Housing%20and%20Consumption.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/Farlow%20Housing%20and%20Consumption.pdf)

<sup>871</sup> This is just a playful idea, but it has serious intent. China and Russia are getting a lousy deal on their balance of payments surpluses. And China and Russia would eventually be a big beneficiary of HIV vaccines. It must be possible to exploit these two facts.

### **10.11. Who advised on this?**

Nobody could doubt the sincerity of Kerry and Lugar – individuals busy on many other things besides this – in their desire to tackle the problems of malaria, HIV and TB, and neglected infectious diseases. Indeed their Bill refers to various positive insights about how to do it. However, on the crucial new policy initiatives they propose, they can only frame the terms as well as they are advised, or as well as the current policy environment articulates the policy ideas. As a matter of public interest, we should be told who advised them.

CGD reports, as follows, the reaction of Senator Lugar to the testimony of CGD's President, Nancy Birdsall, before the U.S. Senate Foreign Relations Committee in May 2005 regarding the Commission for Africa report initiated by Tony Blair:

“She suggested the U.S. should prepare a package of Africa-related initiatives for the UK-hosted G-8 Summit in July covering areas such as peace and security, advance market commitments for vaccines; debt relief, trade, and aid delivery. Sen. Lugar praised the proposal for an advance market commitment for vaccines. “This is an extraordinary idea and I thank you for bringing it to our attention,” he said.”<sup>872</sup>

Barder<sup>873</sup> explains that CGD had no part at all in framing the proposed Kerry-Lugar legislation, and hence cannot take any blame for any subsequent poor legislation. However, this is against the background of CGD itself promoting the idea to Kerry and Lugar while recognizing the faults of a poorly-applied model. As Barder puts it on behalf of CGD in response to criticisms of the faults of APCs: “These are all valid criticisms of a winner-takes-all prize, or an Advance Purchase Fund. However, the Working Group is not proposing a prize or an Advance Purchase Fund. In fact, all these potential criticisms are explicitly taken into account in the design of the (rather different) Advanced Markets proposal.”<sup>874</sup> It is one thing to recognize the faults to be avoided, but another one altogether to make sure that legislators avoid them in practice.

#### **It lacks crucial credibility**

When we looked at precommitments in a previous chapter we found that we either needed costly acts to back up credibility (e.g. a firm invests in capacity to deter a rival) or costly potential penalties, that indeed usually showed up straight away even at the slightest hint of renegeing (e.g. higher interest rates to the US from even hinting at defaulting on its debt, including by inflating it way). With neither of these present here, the only thing to hold credibility in place for the 20 to 30 years that commercial players would need, would be very precise and extremely carefully worded legislation and a system of threats and punishments in the APC subsidy contracts. Then we discover that there has been complete lack of any thought (or effort) as to how to set up legislation to bear this weight. And we already found that the threats and punishments in the APC contracts proposed are confused and non-credible at the 20 to 30 year horizons at which

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<sup>872</sup> [www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf](http://www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf)

<sup>873</sup> Private correspondence.

<sup>874</sup> Barder, O., CIPIH Forum, 19 December 2004.

they would need to hold. The Kerry-Lugar Bill is badly written even with respect to the current APC proposal.

Indeed, contrary to the logic of APC schemes, politicians have been allowed – indeed openly encouraged, in spite of the dangers – to make off-the-cuff announcements of the use of such schemes for low efficacy malaria ‘vaccine’ candidates (see, in particular, Gordon Brown’s various announcements, discussed in the next chapter, about GSK’s RTS,S/AS02A candidate, including in front of CGD’s Nancy Birdsall, with Birdsall saying not a word about the dangers). How are a wide variety of private investors ever to believe in the sustainability and fairness of the system in giving them a return, when those involved in setting it up seem to think that it is not even an important issue?

**This follows a pattern – malaria vaccine and the G8**

Unfortunately, this follows a recent pattern. There is a tendency amongst those involved in advocating pre-set vaccine APC subsidy schemes to disassociate themselves from the challenging task of actually carrying through the policy even remotely efficiently. The APC idea was previously parachuted in to the UK Treasury by CGD who then had little involvement in seeing that the idea was actually worked through properly (more details of this in the ‘politics’ chapter below).

Challenged on the worries that the UK’s response to the GSK case might distort incentives and disincentivize better vaccines by failing to even remotely live up to the idealized ‘Making Markets’ approach, Barder said<sup>875</sup>: “I can’t speak for the UK Government, but I can tell you how the proposal in the Center for Global Development Working Group tries to address these issues.” This is a stunning statement.

First, and around the same time as the proposal is going through with the UK government, the WHO CIPIH Discussion Forum is filled with calls by Barder and others urging readers not to falsely misinterpret the proposal.<sup>876</sup> “James Love expressed skepticism about using a prize, or Advance Purchase Fund, as a way to create incentives for vaccine development, because of (a) the need to set the right incentives for the varied community of public and private researchers that collaborate on neglected diseases; (b) the difficulties of specifying the desired outcome; (c) uncertainty about the costs of development; (d) the need to reward both early movers and subsequent incremental improvements... *These are all valid criticisms of a winner-takes-all prize, or an Advance Purchase Fund.* However, the Working Group is not proposing a prize or an Advance Purchase Fund. In fact, *all these potential criticisms are explicitly taken into account in the design of the (rather different) Advanced Markets proposal* put forward by the Working Group... As expressed so far, they appear to be a critique of a different proposal from the one that is being put forward here... The particular proposal in the Working Group’s report is somewhat different from other proposed advance purchase arrangements.” (emphasis added).

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<sup>875</sup> Barder, O., CIPIH Forum, 27 November 2004.

<sup>876</sup> Barder, O., CIPIH Forum, 19 December 2004.

Of course, all of the above criticisms were, and remain valid.

Then, the CGD website boasts of the policy advice it has given to the UK Government and of the ‘great success’ of a malaria APC along the lines of the CGD proposal. Indeed, press releases claim that: “Strong Medicine argues that commitments to purchase vaccines, *of the type proposed by Brown*, can provide incentives for the private sector to develop these vaccines.”<sup>877</sup> (emphasis added)

Then, and in spite of agreeing with the list of ‘valid criticisms’ described above and arguing that the proposal is not for an ‘Advance Purchase Fund’, we discover that those involved in the CGD project have not got the foggiest idea whether the UK government is doing anything along the lines of the ‘rather different’ proposal and not just instigating a very large ‘pot’ of winner-takes-all funds or, even worse, specifically targeting GSK, and failing to put in place any of the parts of the ‘rather different’ proposal to avoid the potential dangers. It is not great encouragement to hear that the CGD “cannot speak for the UK government,” who are supposedly acting on their advice, but they can tell you what the latest tweaking to the model says.

#### **How did this all come about?**

Maybe this situation came about because most of these ‘design issues’ and problems were not in the 400+pages of material put on the No. 10 Policy Unit website, nor in the book *Strong Medicine*, nor, clearly, in any advice given to the British government. These design issues were raised in Farlow April 2004<sup>878</sup> not to indicate what needed to be “explicitly taken into account in the design” on paper (though the hope was that some fatal flaws could be avoided), but to indicate just how difficult it would be to instigate such design issues in practical applications.

If the APC mechanism is as good as its keenest proponents suggest, then why, when the first real chance arises to use it, is it not used? And if criticisms have genuinely been “explicitly taken into account in the design”, it does not say a great deal about those advising the first users of the mechanism that the advisors are not bothered to make sure that the first users take the criticisms into account in *their* design. The very things that the advisors criticize others for criticizing, the advisors then go and do anyway.

Now we see that, though CGD got feedback from many sources suggesting worries about key practical details of the policy, they have pushed ahead regardless, and failed to check that those building legislation on top of their advocacy effort do not badly enact the policy idea and even detract from and harm other initiatives in the process.<sup>879</sup>

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<sup>877</sup> Barder, O., CIPIH Forum, 19 December 2004.

<sup>878</sup> Farlow, A.W.K., 2004, *ibid*. Copies were given to key people at the Center for Global Development working on this project.

<sup>879</sup> Including by encouraging the cutting back of R&D funding: “Our belt is being tightened for us... the previous largess that was associated with all research, particularly HIV, is now not going to be a reality for the future.” Anthony Fauci, arguing that current budgetary tightening may well hit HIV vaccine research especially hard, in “U.S. Belt Tightening Could Hit AIDS Efforts-Official,” [www.medicinenet.com/script/main/art.asp?articlekey=43642](http://www.medicinenet.com/script/main/art.asp?articlekey=43642).

## **11. When Politics Drives Malaria Science and Not the Other Way Around**

There are at least four parts to the malaria vaccine puzzle: Science, economics, finance,<sup>880</sup> and, one increasingly realizes, politics. It might be convenient – and less controversial<sup>881</sup> – to ignore the politics, but if we do, we will fail to learn some extremely useful lessons, and we will fail to understand why policy has ended up the way it has. Politics, and not economics and finance, is a big driving force for *how* things get enacted in the real world and for how funding is directed. How do policy ideas surface and stubbornly persist in spite of intractable practical flaws and widespread skepticism? Politics is a key part of the explanation.

What has been the political context, especially of the push for APCs, of the last two years or so? This chapter tries to treat events in vaguely chronological order along with some assessment of the underlying general themes. Naturally, the following is colored by the author's involvement in, and understanding of, the policy process, and should not itself go without challenge. Furthermore, the author feels obliged to be discrete with some of the views expressed by a wide range of individuals. People have been prepared to be much more candid in private, sometimes to the extent of holding a completely different position to the one they present in public. So as not to harm confidences, this chapter does not list the identities of many of the individuals involved.<sup>882</sup> Many of the more sensitive observations are left out. Here are the salient features of the political components as understood by this author.

### **11.1. An interest in APCs, but CGD failed to evaluate those things it was asked to evaluate**

Two or three years ago there was a heightened interest to explore what an APC/AMC was, and what it could or could not be usefully applied to. After all, the concept had never been used for anything before, neither inside or outside of neglected diseases and vaccines. Potentially applied to vaccines, the idea had been around for many years, since at least the 1997 Denver G8. However, no thorough *critical* evaluation had been made of the idea. In particular, being an instrument based entirely on the confidence of financial markets, self-fulfilling features are very important, but especially so in complicated

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<sup>880</sup> Since “The Science, Economics, Finance, and Politics of Malaria Vaccine Policy” was too much of a mouthful for the title of this report, one term had to be left out, and this fell to the term ‘Finance’. However, it was always key to the underlying thinking; an APC is, above everything else, a financial instrument that has to attract ‘buyers’ on financial markets.

<sup>881</sup> I am aware, for example, that this chapter will make comments that will be negative on some of the players involved in this process whose motives, and hearts, are nevertheless in the right place, but whose analysis and advocacy, in the opinion of this author, are having some harmful consequences. Unfortunately, the effort to pull the politics in a different direction will involve a degree of discomfort and pain for all involved.

<sup>882</sup> Good records have been kept of everything.

applications such as that of the R&D of early-stage vaccines such as those for malaria, HIV, and TB. Good outcomes are self-fulfilling equilibria, as are bad outcomes.

The *only* principle for how to spend many billions of dollars on global health R&D should be the relative efficiency of the different approaches. There is always a budget constraint, and if one approach gets any new funds made available, other approaches do not. Yet, the main, and pretty much the only, work till recently on APCs was a large amount of material deposited at the UK's No 10 Policy Unit, almost entirely by one author, Michael Kremer of Harvard University, and this material put a great deal of emphasis on HIV, malaria, and TB. The one-sided nature of this material – that never seemed to see any problem with the concept of an APC – and the way it deliberately biased the power of APCs when comparing APC schemes to any other approach to funding vaccine R&D, was regularly commented upon in the global health policy community. To the astonishment of many, the No. 10 material generated figures alleging that PPPs for HIV were four to five times more expensive than a HIV vaccine APC, and that PPPs for malaria were three to four times more expensive than a malaria vaccine APC.<sup>883</sup> This material had sat for several years on the No. 10 Policy Unit without comment or reflection. Kremer subsequently became a key individual in the writing of the CGD report and other work on APCs.

The attitude of many (including the World Bank and CGD in Washington) and many others in the process less than even two years ago, was that, given the scientific complexities and the difficulties of setting terms and running the institutional arrangements, an APC would struggle to work for HIV, malaria or TB vaccines and that, perhaps, it (or more probably something not quite like it) could be used for other vaccines first, such as pneumococcal and rotavirus. There was, indeed, a feeling that the pressure to push for a HIV, malaria, and TB application was often overbearing and needed to be resisted.

The Gates Foundation probably did not have a policy on APCs and did not see itself as running any APCs. They just wanted to know how such schemes might work, and asked CGD in Washington to do the analysis. It is clear that some individuals inside Gates have been pushing an APC for 'a' malaria (and HIV and TB) vaccine regardless. Certain individuals at CGD gave the impression (to this author) of having a ready audience inside the Gates Foundation at a very high level. This author, however, prefers to believe (based on interactions at meetings and correspondences with and knowledge of some of the individuals involved) that others, maybe many others, inside the Gates Foundation are more open about possibilities, and that Gates himself, when the workings of such schemes for HIV, malaria, and TB vaccines are properly explained, will not want to be associated with them. One cannot escape the fact, however, that all of the lobbying effort is Gates funded, and that Kremer ended up playing a central role in the CGD and Tremonti endeavors.

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<sup>883</sup> See Kremer, M., No. 10 Policy Unit Summary p2 and tables on p4. The layers of distortions to drive these results are discussed in Farlow, A.W.K., 2004, Chapter 8.

One of the side-effects of an idea the results of which are many, many years off, is that there is no ‘market’ test of its validity. And potential bad results are very heavily discounted by politicians too. Policy ideas run the danger of becoming parodies of bad publicly-funded projects, that survive just because politicians have no desire for killing off inefficient projects and facing the political consequences.

When dealing with a difficult complex scientific problem, it pays to spread funding over alternative possibilities. The Gates foundation wisely spread funding to explore all options, including APCs, PPPs, the Global HIV Vaccine Enterprise, and so forth. One side-effect of this strategy however is that some people may have misread this and seen funding as an endorsement of their ideas.

**CGD fails to evaluate the things it was asked to evaluate**

The devil is always in the detail of policy proposals. In the case of a novel new instrument that has never been used before, an APC has the beauty of not having any *history* of problems. But this also means that it has no history of *tackling* problems either. There has been an unbelievable desire to avoid critically evaluating the power and practical difficulties of using these novel instruments for the cases of malaria, HIV, and TB.

In particular, the CGD Working Group was set a range of key issues to explore in its original briefing. These were<sup>884</sup> (with wording taken verbatim from that briefing<sup>885</sup>):

- a) Diseases and products on which to focus;
- b) Scale of incentives required to change firm investment behavior (for early- and late-stage products);
- c) Appropriate eligibility rules for products (efficacy, number of required doses, side effects);
- d) How such incentives could be made credible, including legal enforceability;
- e) Relationship between pull programs and existing push programs.

Not one of these issues was remotely resolved by the CGD process:

- a) A methodology for picking products was never formulated independent of the preferences of those advocating APCs. This would have required working out the impact and practical problems in each case – but that would have required identifying, and accepting, practical problems;
- b) Scale of rewards was determined in a way that, as we showed in Chapter 6 above, was methodologically wrong, especially with regard to the treatment of the probable costs of developing vaccines, finance costs, and how different generations of products would be handled. The impact of any scale of rewards on incentives was never explored, and no mechanisms (e.g. event studies) were ever suggested for testing impact and financial market sentiment towards APCs, though frequent mention was made of APCs as ‘potentially a powerful’ scheme (but never any mention of actual power);

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<sup>884</sup> [www.cgdev.org/globalhealth/proj\\_pull.cfm](http://www.cgdev.org/globalhealth/proj_pull.cfm)

<sup>885</sup> The five terms of reference are taken from an original hard copy.

- c) Eligibility rules were left a long way off complete (indeed left blank in many key places in the original contract term sheets, now also attached to the Tremonti Report). Over time, ever-lower malaria vaccine criteria were tolerated in discussions and papers on the topic, even though APC proposals explicitly rule out the possibility of setting higher criteria later and though even discussion along these lines is a risk to current investors. We will look at this in more detail in a section below. This asymmetric pressure (both before and after an APC is set up) is, as we showed, a risk to all developers other than the one getting the lower criteria;
- d) Contract terms sheets were suggested to tie all developers in from even before conducting trials, though the key role of punishments was left undetermined, along with a range of key contract terms like long-run price, rules for altering contracts, and the institutions running the contracts, etc. Nothing was said about the realism of every malaria, HIV, and TB vaccine initiative in the world being signed into such contracts. The Kerry-Lugar Bill implicitly visualizes this system of contracts being paid for by US taxpayers via the US Treasury and the President of the United States (though Kerry and Lugar do not seem to be aware of the details). The Tremonti Report backtracks on ‘credibility’ issues by now suggesting that funding may have to be more up-front than claimed just a few months previously, so as to shore up the lack of credibility in the face of problems with legal enforceability of such systems of contracts;
- e) *Nothing* was done to explore how push and APC pull would in practice fit together, other than to assert that APCs would be complementary to, and not a substitute for, other policies to promote R&D in neglected diseases – that they were an ‘additional tool’. We have seen that it is a very problematic issue, key to balance, fairness, and the non-distortion of incentives. Only now is this issue being looked into.

Failure to satisfy this original brief was partly because, as internal voices explained to this author, there was pressure to get a report launch in time for the key 2005 G8 meeting, and that this required an early April 2005 report launch. The report also had to be easily useable to lobby G8 leaders. Filling in difficult practical details would no doubt have taken too long, and would have revealed many awkward issues that still needed to be resolved. Instead, the released report repeatedly asserted that the idea was ‘practical’ and that terms ‘could be designed’ to make the scheme work.

### **Many issues ignored**

Of course, there are a huge range of other issues that were not even listed in the original brief. In particular, because an APC is a price-fixing instrument and because advocates for some reason have chosen to base everything on *revenue* streams only, it is no wonder that R&D and trial costs and manufacturing cost issues were not listed even as issues to be explored. The Pharmaceutical R&D Policy Project (PRPP)<sup>886</sup> at the LSE, under the direction of Mary Moran, has now been set the task of analyzing this for malaria vaccines.

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<sup>886</sup> [www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm](http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm)

Similarly, since we repeatedly hear that the target is ‘one or two’ firms, issues regarding the structure of the industry were also not listed, including issues about emerging developers and competition.

Since ‘size’ is everything, finance issues – including risk and cost of capital, and availability of finance to different players – are not listed as of interest either. An APC comes with all kinds of risks attached, yet is treated as if it is risk free, and it is imposed on a situation that is stuffed full of different risks already, and yet little thought has gone in to how to tackle *those* risks either.

And since the ‘high-tech fix’ part of the solution was deliberately separated out from the greater problem, there was no look at any evidence of practical distribution and health infrastructure problems. As Light puts it: “Almost no time was spent analyzing the organizational, regulatory, and financial causes of past delays in making new vaccines available in poor countries. Will a \$3bn buyout solve all the sources of delay? Learning from the past did not seem to be the point.”<sup>887</sup>

Finally, we earlier saw the key need to integrate vaccines into an overall control strategy. Not even lip-service was paid to this, so it was hardly going to make it on to the list (malaria drugs, for example, never get mentioned, except as mysteriously being totally replaced by vaccines).

But the list does not end here.

## **11.2. Just three of the problems left behind**

This failure to talk about key issues means that we can spin forward 6-12 months, and pick just a couple of issues (taken from a huge range) that alone would be capable of running the whole malaria vaccine APC project into the ground: Let’s try: Who will want to run a malaria vaccine APC, and how will funding commitments be treated in national accounts? Thinking much further ahead, we also review the way distribution issues and drugs and other interventions were ignored in the thought process.

### **11.2.1. Who will want to run a malaria vaccine APC?**

Who will be home to a malaria or HIV or TB vaccine APC?<sup>888</sup> The Gates Foundation will not want to. Some say they could be, but, in truth, it is too sensitive a role for them. There is already controversy, with claims of an overemphasis on ‘technological fixes’ and distorted funding flows, without making the Gates Foundation the financial back-up to the biggest ‘technological fix’ of all. We will see below how potentially controversial an APC would be for ‘big pharma’ too. Why would the Gates Foundation want to share the reputational consequences? The Gates Foundation really regards itself as a specialized push funder; if an APC is around of the sort proposed as an R&D instrument, it would be

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<sup>887</sup> Light, D., 2005, *ibid.*

<sup>888</sup> Again, we need to clarify that this is as an R&D instrument and not as a procurement fund only.

bad practice not to separate out the roles of each to a different institution. And, finally, once the risks of an APC are fully spelled out, the Gates lawyers would not let this one through for sure.

Nor will the World Bank want to run it. One only need think of the flak onto all their other activities if they ran it badly, or if it was simply doomed to fail from the start. Once they take a closer look at the amateurish nature of the terms-setting so far and quantify some of the risks, that alone will (or should) make the Bank baulk.

And given the heavy involvement of MVI, one suspects there would be problems (and protests from non-MVI vaccine groups and control/drug R&D groups) if MVI took control. Besides, purely from the perspective of good science and good decision making, MVI is only one of the players with vaccine candidates, and it would be best practice to separate the funder and eventual decision-maker from any of the players holding candidate leads.

Furthermore, Gates and MVI have already started to become concerned<sup>889</sup> at looking too much like tipping the playing field to MVI/GSK, and this also suggests a lack of desire to go ever further towards Gates/MVI running a malaria APC. We only need to think of the bad signal this would send to other investors otherwise. To avoid distortion and corruption of the process, the bureaucracy running an APC should also be separated completely from advocacy and other policy areas too, which suggests separation from the other activities of MVI.

Given the overwhelming evidence (and in many quarters) strong feeling against APCs for malaria, HIV or TB vaccines, if the WHO Commission on Intellectual Property Rights, Innovation and Public Health, CIPIH, do not report favorably on APCs for the big 3 killer diseases (there is a general feeling that they have not swallowed the heavy marketing of the idea, and, indeed, shortly after this report was written the report of the CIPIH Commission found against the idea of APCs for HIV, TB, and malaria vaccines<sup>890</sup>) this will not exactly encourage the WHO to become the home either for schemes for HIV, malaria, and TB vaccines. Besides, an early version of the CGD report stated that WHO would definitely not be considered as a home for the Adjudication Committee. As one correspondent put it: "Several donors have high antibody levels to WHO."

The G7/G8 leaders can make pronouncements, but they are not a permanent body capable of running such things either. And GAVI has a comparative advantage at what it already does, and would not, and should no, want to run risks on the rest of its portfolio of activities by taking such a problematical financial scheme on too. Of course, GAVI may see (or be persuaded to see) an APC as no more than a, fungible, procurement fund and not an R&D instrument for malaria, HIV, and TB vaccines anyway, suggesting that it can be added to its portfolio even if it does nothing to incentivize the creation of these vaccines. But the rest of this report provides plenty of evidence for why even just seeing

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<sup>889</sup> According to private correspondences.

<sup>890</sup> See Report at [www.who.int/intellectualproperty/en](http://www.who.int/intellectualproperty/en), pp 104-106.

it this way, is dangerous to GAVI; such an APC essentially achieves nothing positive (except to make politicians look good for a while), but creates plenty of risks of negative consequences.

So who does that leave to run an APC? Again, by avoiding such practical issues, we have no current answer. It may just turn out that all the interest in APCs, especially for malaria, HIV, and TB vaccines, got the G7 leaders off the hook in 2005, only to get them tangled up in 2006 and 2007.

### **11.2.2. How will APC liabilities be treated?**

Let us try a second issue: How exactly will APC financial promises be treated on the balance sheets of governments? It is still not yet clear whether a future liability of such a scheme would simply be allowed off-books until used. It is a form of borrowing (off future generations) after all, and represents an obligation to tax later. The case for the International Finance Facility for Immunization, IFFIm, (the immunization finance mechanism promoted in summer 2005) raised this issue. The ruling by the UK statistical office dealing with national accounts was that this was a one-off and would be allowed this time, but that each future case would need its own separate ruling. Tremonti reveals however that this has, in general, not been sorted: “Currently, discussions are taking place within DAC on the application of criteria for ODA scoring in relation to innovative financing mechanisms for development, such as the one underpinning the IFFIm. The result could have implications for the ODA scoring of donors’ support to the AMC framework.”<sup>891</sup> Could a pile of APC-type instruments be allowed without registering them as future liabilities, even as the private sector is supposed to be sinking all of the costs that need to be repaid via the APCs later?

Let us imagine what would happen if various G7/G8 governments are told that, indeed, any financial promises they make will have to be classified as liabilities on their books and that this raises government deficits. Governments could, after all, wheel out APCs to pay for all kinds of developing country programs and offset the costs to ten to twenty years hence (or never), yet this would not be allowed in most cases for sure without being counted as a liability. Suddenly the benefit of not having to pay anything is offset, and this will limit the mass run out of such schemes.

#### **Tremonti now recognizes the problem**

The Tremonti Report now recognizes that this is indeed a problematic issue, and that countries will face different constraints on funding, which means that some will have to pay something up-front. This had been clear all along (though the 2005 CGD report argued that the problem could be avoided via locking all developers into a system of contracts<sup>892</sup>). Tremonti now presents a range of payment options including (see Tremonti Report pp. 13-16):

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<sup>891</sup> Tremonti, G., 2005, *ibid.* p16.

<sup>892</sup> Farlow in April 2004 pointed out problems in the logic that said that there was no need for front payment under an APC [www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf), Section 9. Though, at that point in time I would never have believed that anyone would seriously have suggested

- d) Either ‘*Full frontloaded financing*’ at launch of an APC;
- e) Or ‘*Financing through periodic contributions*’. This option also requires a bridging facility to create extra funding in the case of earlier-than-expected licensure of a vaccine, and some, so-far unmodeled, mechanism to reassure initial developers that they will be fairly treated<sup>893</sup> and that follow-on innovators will not be disadvantaged.<sup>894</sup>
- f) Or ‘*Financing when disbursement is required*’.

The first two of these would seem also to require mechanisms to reallocate funds if no vaccine is ever developed. However, these would have to be designed to hold the deposited funds in, low-paying, Trust funds for the expected life of an APC (30 years or so, as suggested by Kremer and CGD) so as not to undermine incentives. The opportunity costs of financial options 1 and 2 are simply ignored by Tremonti. As is the conflict they pose with front-loading efforts to develop vaccines and other health products for the poor.

The third option requires all developers to be signed into contracts even before investing in vaccine R&D.

Tremonti also recognizes that there are a range of ‘*ODA scoring issues*’, with the fiscal scoring of option 3 funding in particular (and large chunks of option 2 funding) still an unresolved issue. These various options also require a complicated understanding of how different countries would fare in a mixed system, with some holding off funding till disbursement at the end and others constrained to periodic contributions or even up-front contributions to the fund, and the reactions of vaccine developers to this.

The revelations of the Tremonti Report are no doubt another reason why the G8 Finance Ministers are narrowing down to one disease chosen from six candidates as a ‘pilot’ project, and why they will almost certainly go for one that avoids these issues as much as possible, and indeed the one that represents the easiest application (and, therefore, the least test) of the scheme.

Yet again, here are issues that have not been fully, it at all, worked through – and again all because of the desire to avoid tackling issues, and because advocates seemed content with the easy parts of the ‘policy success’ rather than with the many difficult practical details. Maybe funders will get away with not counting APCs as liabilities; we just do not know yet. It is yet another future hurdle. And again, we see how opportunities have been wasted.

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locking in all developers, including all potential developers, to a system of contracts so as to make the mechanism credible; it would have seemed a bit ‘incredible’ at the time.

<sup>893</sup> Thinking of an APC as an R&D instrument, early developers will have spent a fraction of the potential APC fund. They may have ‘got lucky’ early. However, payment needs to be based on the ex ante probabilities, and not on the actual outcomes. If the bridging mechanism is not watertight, firms will have to push for extra funding to get a fair ex ante return even if their behavior looks ‘greedy’ ex post. These bridging arrangements have not even been sketched, and seem to be just another get-out clause from having to deal with an otherwise intractable practical problem.

<sup>894</sup> Try thinking how this would be made to work!

### **11.2.3. Why were health infrastructure issues, and other interventions ignored?**

Kaper et al. point out that “infrastructure to support disease surveillance and vaccine delivery is essential,”<sup>895</sup> but that “Infrastructure through which vaccine programs can be administered is often weak or nonexistent in the developing world, another factor that limits vaccine uptake [and hence vaccine R&D]. This deficiency can be found at all stages of program implementation, from a shortage of trained personnel at vaccination sites up to a shortage of qualified individuals in governmental agencies needed to design and administer vaccine programs.”<sup>896</sup> As Thaul puts it: “In many developing countries, inadequate public health infrastructure overshadows any question of access.”<sup>897</sup> Even when chloroquine *was* effective, about one million Africans – mainly children – died of malaria every year, because of lack of access to health care and inadequate preventive measures. Similarly, Richie and Saul observe that: “In the meantime there is much to do to ensure that when the vaccines are available, health infrastructures are in place to deliver integrated programmes that will use the vaccines effectively. That may be as much of a challenge as the vaccine itself.”<sup>898</sup>

Ignoring these issues might help an idea such as an APC subsidy scheme to survive in the political sphere, but it hardly makes for good ‘practical’ policy. Against this practical background, it is almost bizarre to see the way some think that long-term access problems can be handled by legalistic contractual threats set even before any R&D is done.

The notion of a *package* of measures *including* vaccines has also not featured in the APC proposals, on the reasoning that vaccines replaced treatments, and because it was felt that APCs should concentrate on vaccines alone.<sup>899</sup> Indeed, we saw above that to introduce thoughts about a package of measure would have made a malaria vaccine APC even more unmanageable. Delivery issues, basic research, and the role of PPPs were also kept largely in isolation from the APC analysis. Reference to these was boosted when some<sup>900</sup> argued heavily that an APC report could not go out with such little emphasis on them. As Light – a member of the CGD working group who declined to sign off on the report – puts it: “Ironically, complementary uses of pull mechanisms with push ones were little discussed by the Group over the months of deliberation. Criticisms of the Kremer draft led to softening the final report but not to substantive development of synergistic combinations. Those are still waiting to be done.”<sup>901 902</sup>

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<sup>895</sup> Kaper et al. 2005, *ibid.* p2.

<sup>896</sup> Kaper et al. 2005, *ibid.* p5.

<sup>897</sup> Thaul, S., “Vaccine Policy Issues.” Domestic Social Policy Division, *Congressional Research Service*, The Library of Congress. Updated May 19, 2005 <http://fas.org/sgp/crs/misc/RL31793.pdf>.

<sup>898</sup> Richie, T.L., and Saul, A., 2002, *ibid.* p700.

<sup>899</sup> Based on correspondences with several of those involved.

<sup>900</sup> Notably Don Light.

<sup>901</sup> Light, D, 2005, *ibid.*

<sup>902</sup> Indeed, as we saw, the CGD report largely feeds delivery failures on to firms through the requirement to allocate the APC subsidy by quantity of sales. It is as if delivery problems did not exist, and almost as if these are just trimmed down versions of developed economy drugs markets, just without the purchasing power (as was the case in Kremer App 3, which has no push, no delivery problems, no difficult science, etc.). Barder has regularly argued as if this is the case.

Indeed, *not one* of the five representatives from PAHO – an organization with a strong reputation for *delivery* – who had sat on the CGD Working Group, was around to sign off on the final report. The last PAHO member to leave, Jon Andrus, cited “concern about global approaches to support only countries with average annual per capita income of less than \$1,000, such as the approach taken by the Global Alliance for Vaccines and Immunization, thus limiting the scope of work and benefits that impoverished children and families could otherwise receive in the Americas.”<sup>903</sup> Andrus argued: “Future approaches that attempt to enhance practical markets for vaccines and that enhance the introduction of new and underutilized vaccines should consider prioritizing the following: access and equity for as much of the population as is possible, well-implemented accelerated disease-control and prevention strategies, and development of a public-health infrastructure.”

Setting the terms of a malaria vaccine APC would be extraordinarily difficult to do if these terms had to be set relative to all the other aspects of the problem. They would be even more unworkable than they currently are. Frankly, these delivery and health systems issues were ignored precisely because to have even begun to address them would have challenged the underlying practicality of the APC approach.

#### **No drugs or non-vaccine components to the package**

Neither could the notion of choosing between vaccines of different efficacy and their interplay with a package of measures, including drugs, vector control, etc. possibly surface in publications that had no notion of a budget constraint. Indeed, both the CGD report and the Tremonti report relied on a cost-effectiveness methodology that, as we saw in Chapter 6, was based on there being no budget constraint, and that was biased to picking up too little extra value from a higher efficacy vaccine when part of a package of measures, and hence biased towards overemphasizing low efficacy vaccines as goals. None of the scientific issues we saw in earlier chapters got a word in. Even as the UK pushes ahead with launching an APC for ‘a malaria vaccine’, the resolution (if it is even possible) of these issues is still in its infancy.

Indeed, much of the reasoning about a *package* of measures was much more prominent in the Malaria Vaccine Vision Meeting Summary Report. The Vision Meeting argued that “The public health impact should be quantified through cost-effective analysis *that also takes into account other control measures*,”<sup>904</sup> (i.e., completely unlike the Berndt et al. methodology). It was also pointed out that the “real costs of full scale development of multiple constructs” did not exist and “should be derived”. It argued that the malaria vaccine community should “Develop tools to analyze vaccine cost-effectiveness relative to other interventions (inc ‘developing detailed data and modeling tools for integrating vaccine with other strategies; establish working group to work on financing and sustainable procurement issues; establish group to develop policy guidance and support;

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<sup>903</sup> Andrus, J.K., and Fitzsimmons, J., “Introduction of New and Underutilized Vaccines: Sustaining Access, Control, and Infrastructure Development.” *PLoS Medicine*, 2005, Vol. 2, Issue 10, <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020286>.

<sup>904</sup> VMSR p21.

coordinate roles of multiple immunization, advocacy, and alternative control mechanisms group).<sup>905</sup> The Bethesda meeting urged an emphasis on ‘malaria researcher’s and not just ‘vaccine research’, “to avoid infighting between vaccines and other control techniques.”<sup>906</sup>

To this end, the Vision Meeting Summary Report advised the establishment of a committee “to link malaria vaccine development with immunization and malaria control and prevention programs,”<sup>907</sup> to help “in developing the evidence base for effectively integrating a malaria vaccine with other malaria control interventions.”<sup>908</sup> It argued that it was best to “Include a description of the total portfolio of malaria interventions – move from this down to the development of vaccines and how these fit into an overall plan for fighting malaria.”<sup>909</sup> The de-emphasizing of all of this in key policy circles was a direct result of the recent APC lobbying effort.

### **11.3. The Brown/GSK ‘understanding’**

Already complicated issues were massively exacerbated by the intervention of Gordon Brown, the British Chancellor of the Exchequer, and GSK, the UK’s largest pharmaceutical firm, in late 2004, at the time of the first Alonso et al. paper containing the 6 month GSK figures. Brown made several announcements regarding the GSK candidate vaccine. There are unconfirmed reports that it was Brown who made the offer to J.P. Garnier, head of GSK of an ‘APC’, and not the other way around, and that J.P. Garnier accepted without really understanding what an APC actually is, and in particular all the risk that GSK would be expected to take on as part of the deal (or maybe he interpreted it as merely a procurement fund). Others argued it was GSK having sway over Brown. Whichever way, since balance is everything in complicated R&D, and the risks of the science still extremely high, this behavior was short-sighted to say the least – some have argued that it was even ‘dangerous’ – and it showed no understanding of the underlying financial and economic issues.

We also saw above that, of the ‘big pharma’ companies, it is only GSK that has shown any support for an APC for early stage vaccines, and only for their one malaria project. When given the opportunity to list all those large pharmaceutical firms interested in pursuing an APC, all Kremer could come up with was that “GlaxoSmithKline has been amongst the most supportive.”<sup>910</sup> Recently, various sources have argued that GSK are now in “so deep” that though it would be best for them to draw back, they cannot. Many other ‘big pharma’ companies have either not settled their position, or are unhappy. One senior industry figure described to the author his/her view that an APC for HIV, malaria, or TB was an “impending crisis” for the whole industry. The author has heard similar concerns from various other senior industry figures in several of the ‘big pharma’

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<sup>905</sup> MVTR p33.

<sup>906</sup> RMSR p14.

<sup>907</sup> VMSR p27.

<sup>908</sup> MVTR p34.

<sup>909</sup> RMSR.

<sup>910</sup> <http://msnbc.msn.com/id/10206224/site/newsweek>, 19 November 2005.

companies, but who, for company reputational and PR reasons feel unable to speak out. The reasons are dotted all throughout this report, but they can be summed up relatively simply: An APC is a carrot but it is also a stick. And the amateur nature of the thinking that has gone into the design of the carrot, means firms will have little expectation that it will be anything other than mostly a stick.

### **11.3.1. A political low point**

This political process reached a low point at a CGD news teleconference on 25 April 2005,<sup>911</sup> with Nancy Birdsall of the CGD and Gordon Brown. Here is the section in the teleconference, when Gordon Brown gives his take on a malaria vaccine APC:

**Brown:** On the advanced purchase agreements: I've obviously not only talked to the Gates Foundation about this, but talked to Smith...

**Questioner:** GlaxoSmithKline, right?

**Brown:** Yes, GSK. And J.P. Garnier who is the head of the company – and they themselves acknowledged that if the next stage of development work, which is being held in Mozambique, proves to be successful, then the further agreement that would have to be made is for someone or some organization or some group of people to come in offering an advance purchase agreement to make possible the supply of this vaccine.

Now, we, Britain, are ready to come behind this. I believe there are other countries ready to do this, so there is, if you like, an understanding with the Gates Foundation and with the pharmaceutical company that the next stage would be an advance purchase agreement.

And we're very impressed by the original and initial findings of the research. It does seem to be possible that we have this breakthrough in medicine that perhaps people did not anticipate. The trials seem to have gone very well.

The next stage is not only that we encourage the trials to be completed, but that we say that we can bring other countries together in an advance purchase mechanism.”

Nancy Birdsall, at Brown's side, made no comment. GSK was mentioned in the CGD Report. Indeed, it was the only firm specifically mentioned as being targeted. It is also telling that the Brown meeting referred to in the statements is with J.P. Garnier and not with Jean Stéphenne, president and general manager of GSK Biologicals, the arm of GSK that actually works on malaria vaccines. But more on the implications of this below.

This 'deal' was also revealed in text inserted into a Gordon Brown speech of 16 November 2004, indicating that the deal had to have been within days of the first Alonso study containing only the six month data, and well before the data was even being worked on for the second Alonso paper:

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<sup>911</sup> Transcript details taken from LexisNexis.

“And let me just add. The recent breakthrough which for the first time *gives us a vaccination to prevent malaria* that could be ready *in three to four years time* is a revolution in our time. The challenge is in an area where there are insufficient purchasers with funds we need to ensure that *the vaccine* does go into commercial production and is available at affordable prices. And therefore I can announce that the British Government working with other Governments is ready to enter into agreements to purchase *these vaccines* in advance to ensure a secure market and that *the vaccines* are available more cheaply – and thus avoid many of the 1 million deaths from malaria each year.” (emphases added)<sup>912</sup> As any malaria vaccine expert would have told Brown, the notion that we now have “a vaccination to prevent malaria that could be ready in three to four years” is completely and utterly wrong on all counts.

Similarly, Brown wrote regarding the GSK vaccine in an op-ed in the British newspaper ‘The Observer’ in early June 2005: “The challenge is that in an area where there are insufficient purchasers with money we need to ensure that the vaccine, when developed, goes into commercial production and is available at affordable prices. That is why the British government is inviting other countries and companies to join us to explore a jointly agreed advance purchase scheme to underwrite the buying of millions of vaccines...”<sup>913</sup>

In January 2006 Brown, writing in the British newspaper The Guardian, repeated his intent to push the G8 to put in place an APC for this malaria vaccine at the forthcoming February meeting in Moscow, since “a life-saving vaccine could soon be available for malaria to save 1 million lives each year.”<sup>914</sup>

In the context of the chapter above detailing the much more nuanced situation with the GSK candidate vaccine RTS,S/AS02A, one correspondent talked of a “reductionist approach to statistics,” and wondered “how on earth something so positive” as the various Brown statements could have been got out of the GSK statistics. One correspondent (a senior malaria vaccine figure) even accused Gordon Brown of “sexing the figures up” in order to, as this correspondent argued, push for a G8 funding instrument biased towards GSK, and to generate a political ‘success’, even if this was damaging for the long-term development of malaria vaccines in general.

### **11.3.2. The emphasis on malaria**

The spin on malaria and HIV came on in particular force after Gordon Brown had reached his “understanding” with GSK and the Gates Foundation (or, more precisely with individuals at each). The emphasis in CGD lobbying efforts took particular advantage of this. One correspondent also observed that the recent upsurge of interest in APCs stemmed “from the earlier complete crisis in HIV vaccine research when all NIH and company efforts were faltering; an APC [for HIV] becomes suddenly a more attractive

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<sup>912</sup> Gordon Brown, speech, October 2004,

[www.hm-treasury.gov.uk/newsroom\\_and\\_speeches/press/2004/press\\_94\\_04.cfm](http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_94_04.cfm).

<sup>913</sup> The Observer 5 June 2005 [politics.guardian.co.uk/development/comment/0,15709,1499651,00.html](http://politics.guardian.co.uk/development/comment/0,15709,1499651,00.html).

<sup>914</sup> [www.guardian.co.uk/comment/story/0,3604,1683463,00.html](http://www.guardian.co.uk/comment/story/0,3604,1683463,00.html).

instrument if based on a vaccine model [malaria?] where some progress could be evidenced.”

It is not clear to what extent Brown was responding to CGD, or to what extent CGD were responding to Brown. But, when the CGD Report came out in the spring of 2005, it, and all the media reports surrounding its release, emphasized three diseases – malaria, HIV, and TB, with grand claims about a simple way of cracking the problem of each for ‘only \$3bn’ apiece. Just recently, the blurb for the latest rendition of the CGD proposal<sup>915</sup> came with the really quite outrageous line: “Why are millions dying of neglected diseases without vaccines, and is there a way to cheaply change that?” before suggesting that APCs would do this for HIV, malaria, and TB for \$3bn each. We saw above the huge problems that were swept under the carpet in order to make such bold claims, the poverty of the analysis justifying the \$3bn figure,<sup>916</sup> and why it was so dangerous to spread this utopian myth.

CGD later retracted the \$3bn figure describing it as only for illustrative purposes anyway. This claim is not entirely convincing, given all the press coverage, and given the dominance of the figure in the CGD Report (the reader might just take a look at the start of Chapter 5, and also read some of the strong claims made such as: “We recommend commitments worth about \$3 billion per disease for early-stage products such as malaria.”<sup>917</sup>). One would hardly make something so feeble so dominant, if one was aware of just how feeble it was. \$3bn was given so much dominance precisely because CGD thought that it was more than just ‘illustrative’. And CGD continues to promote the \$3bn figure, as we just saw even very recently arguing that this figure can “cheaply change” the situation.<sup>918</sup>

The back of the CGD Report, released in April 2005, featured praise from Professor Jagdish Bhagwati, Columbia University, Tony Blair, Prime Minister, UK, Richard Feachem, Executive Director, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Senator Richard Lugar, Chairman, U.S. Senate Foreign Relations Committee, Trevor Manuel, Minister of Finance, South Africa, Patty Stonesifer, Co-Chair and President, Bill and Melinda Gates Foundation, and Meles Zenawi, Prime Minister, Ethiopia. Richard Feachem has since voiced his concerns at the overemphasis on distant blue-sky solutions over current practical solutions. Many have pointed out that none, or very few, of these

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<sup>915</sup> Barder, O., 2006, *ibid*.

<sup>916</sup> It was reported to the author (correspondence on file) that the \$3bn figure was settled in a CGD meeting at which the \$4bn figure was chosen one minute and then \$3bn the next, and that \$3bn was settled on as about what those involved felt they could make fly politically. Remember that in earlier files it had been over \$6bn for a higher efficacy product (in the case of malaria, 80% for three or four years, etc.) before falling to \$3bn for much lower efficacy. Note the title of the chapter, “\$3bn per disease,” ([www.cgdev.org/doc/books/vaccine/MakingMarkets-chapter5.pdf](http://www.cgdev.org/doc/books/vaccine/MakingMarkets-chapter5.pdf)) and the strong claims made for this \$3bn figure in the Senate by Nancy Birdsall and in the Commission for Africa Report (see reference below). Yet, there really is no veracity to the figure at all.

<sup>917</sup> CGD, 2005, *ibid*. p49.

<sup>918</sup> See the Barder, Kremer and Williams article just quoted for the continued reliance on this \$3bn figure, and the way that critical observations made about the figure seem to have had no impact on reasoning.

individuals knew what they were signing up to beyond the clever marketing exercise they had been subjected to.

CGD awarded Gordon Brown their 2005 ‘statesmen of the year’ award after he took up and ran with their proposal.

### **11.3.3. Pneumococcal and rotavirus – no desire for ‘APC’ schemes**

This emphasis was also encouraged by the fact that at some point, many of those involved in pneumococcal and rotavirus realized that they were looking for something much more like successful instruments of the past, such as those used for hepatitis B, and not really the mechanism being proposed by CGD – i.e. none of the new layers of institutions and the two-stage contracts as proposed by CGD and attached to the Tremonti Report, not every potential player signed in from the start, not the heavy monitoring as described by CGD and Tremonti, and no expectation of pull (and monitoring) deep back into the research process.

Instead, they were looking for good-sized procurement funds fed through institutions the workings of which were well understood, with risks that were manageable. Besides, it has proved surprisingly difficult to get prices down on late-stage products, prompting doubts as to the veracity of the supposedly ‘absolutely crucial’ APC contract terms covering long-term prices. This is not to downplay the importance of ‘pull’ and demand stabilization instruments, but even late-stage products have turned out to be about a great deal more than simple APC proposals might suggest. This, in a sense, reduced the novelty of the ‘big’ idea of an APC if attached to these late-stage vaccines.

### **11.3.4. GSK Biologicals does not ‘need’ an APC**

Given that GSK was putting all the investments in place to bring this research forward, including from philanthropic, and British and European funding sources, given that the research was being pursued through a PPP with opportunity to invest in that PPP, and given that any eventual vaccine that might have resulted from this activity was already lined up to become part of the standard package of child vaccinations, the “insufficient purchasers” phrase of Brown is not a correct understanding of the underlying financing problem.<sup>919</sup> Nevertheless, Berndt et al. link the “gathering momentum” behind an APC (for ‘a’ malaria vaccine or even just ‘this’ malaria vaccine) to Brown’s announcements.<sup>920</sup>

Yet, nowhere on the GSK Biologicals or GSK websites is there the slightest hint of interest in an APC, something one might think highly unusual if GSK Biologicals or GSK were to regard the announcement of an APC as a financial breakthrough worth signaling to their investors and useful for positive PR purposes.

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<sup>919</sup> That is if the “250 million vaccine courses at \$15 per course, that would translate into a \$4bn guarantee,” later in the same op-ed has anything to do with this notion of “insufficient purchasers”. It is all a little vague.

<sup>920</sup> Berndt et al. 2005, *ibid.* p3.

Instead, all GSK and GSK Biologicals statements have emphasized an approach very different to that of an APC:

“Public-private partnership leads to scientific breakthrough in malaria vaccine development.” Headline, GSK Biologicals website.<sup>921</sup>

“This project demonstrates the power of collaboration between the public and private sectors.” Jean Stéphane, president and general manager of GSK Biologicals.<sup>922</sup>

“GSK Bio stressed how important public private partnerships were in the area of sustainable vaccine development and supply and how highly they valued their current working relationship with the European Commission.” GSK Press Release.<sup>923</sup>

“GSK believes a public/private partnership approach to drug discovery and development in diseases of the developing world is vital. GSK currently works in partnership with the National Institutes of Health, Medicine Malaria Venture, Global Alliance on tuberculosis and many others. Companies provide to the partnership technology in which they have invested for decades and their discovery, development and distribution expertise. The public sector partners help fund the development costs while also ensuring that the medicines and vaccines get to the people who need them. This has the double benefit of encouraging R&D and accelerating the product's use in the developing world.” GSK website.<sup>924</sup>

“Development of an effective malaria vaccine can be accelerated through international partnerships between private and public sectors, including scientific institutions in endemic countries. In combination with existing and other promising new malaria-control measures, malaria vaccines could greatly contribute to reducing the intolerable global burden of this disease.” Professor Pedro Alonso, University of Barcelona, who led the recent RTS,S/AS02A research.<sup>925</sup>

Several sources (very reliable, but nevertheless unconfirmed) argued that GSK Biologicals, who do all the neglected disease vaccine work under a PPP approach, is much less keen on APCs than the main GSK company. The PPP route has the advantage to GSK Biologicals (and GSK) of being good from a PR perspective, of having lower risk, and of avoiding worries that an APC would be a big negative factor in their multiple efforts to advance relationships with non-pharmaceutical researchers and others in malaria vaccine research. It is significant that it is J.P. Garnier and not J. Stéphane that gets mentioned in the Gordon Brown and Nancy Birdsall news conference. We will see

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<sup>921</sup> [www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10392](http://www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10392), 15 October 2004.

<sup>922</sup> GSK Biologicals website *ibid.* London, Friday 15 October 2004.

<sup>923</sup> “GSK in collaboration with European Union.”

[www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379](http://www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379).

<sup>924</sup> [science.gsk.com/about/disease.htm](http://science.gsk.com/about/disease.htm). The reader should dwell on what this is saying about the way R&D costs are being borne and the pricing structure achieved as a result, and then think how an APC is different from this.

<sup>925</sup> Alonso et al. 2004, *ibid.*

later that the overall impact on GSK of an APC for malaria is likely to be much more bad than good, since it forces them into a “dammed if they do, dammed if they don’t” corner.<sup>926</sup>

If a good, widely-applicable, vaccine was on the horizon, is it realistic to believe that the funds would not be created to procure it? The key issue is to create a good vaccine in the first place, whereas most of the recent literature seems to frame the problem as one of current lack of ability to procure the GSK product if it is ever licensed.

### **11.3.5. What is GSK getting?**

From what can be made out from the information released so far into the public domain, the apparent GSK ‘understanding’ is *not* along the lines of the recent CGD proposal anyway. *That* proposal in its purest application would be for, amongst many other things, a large fixed sum set at the start to cover *all* potential privately-funded malaria vaccine developers, and not just GSK. There would be rules about efficacy limiting players’ room for maneuver. There would be plenty of monitoring and the resetting of rewards later.

The firm would have to reveal details of all its sources of funding and its cost information, so that other developers could work out the value of the portion of APC likely to be ‘left over’ to them, and so that there could be correct removal of push payments not strictly motivated by the APC. There would be a huge disconnect between what GSK would get from the APC and what GSK had actually spent on R&D, but they would still *not* get the whole pot of APC subsidy.<sup>927</sup> Given all the public and foundation funding into GSK, a large chunk of any APC would be denied to GSK.

From the APC analysis, it is *required* that, for efficiency of an overall APC, the exact nature of the GSK contract, to the extent any exists, be placed – and indeed be policed – in the public domain so that *other* developers will know exactly how to respond optimally. The APC literature should not become just a veil to justify a deal that might have looked less open without the scaffolding of an APC. That is, an APC should not become a Rube Goldberg machine for a GSK ‘deal,’ and a secret set of terms. One correspondent argued that most malaria vaccine stakeholders are “always bargaining from a position of weakness vis a vis large pharmaceutical players” such that the terms of anything, and not just APCs, almost invariably reflect the interests of the latter and not those of the former. If an APC is to be an R&D instrument, this should not be the case this time.<sup>928</sup>

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<sup>926</sup> The (so far unconfirmed but probably reliable) information this author has been given suggests Brown himself, unexpectedly, volunteered the notion to Garnier in a private meeting in his office at the time of the first Lancet announcement, 16 October 2004, and that this was a Brown-inspired initiative. It was made public almost immediately by Brown.

<sup>927</sup> To restate the obvious – but to thus avoid caricature – this is the totally optimal result of such a mechanism and not in any way a ‘critique’.

<sup>928</sup> Indeed, in this case, this author would argue that this is good for GSK too.

### **11.3.6. What if an APC for GSK becomes just a procurement device and adds little or nothing to R&D incentives?**

One possibility is that any APC for malaria/HIV simply never gets set up but becomes instead a fix-price procurement device and not the precommitment R&D device envisaged (or claimed to be envisaged) by CGD and Tremonti, with all its pre-set terms and committees. Indeed, the above Brown quote (like the Kerry-Lugar Bill discussed in an earlier chapter) seems to indicate that the purchases would lock in for “the vaccine” only “when developed”. This contradicts the CGD notion that APCs are devices to cover the R&D costs of multiple parallel privately-funded developers, with most getting nothing, and with firms like GSK facing a great deal of entrepreneurial risk. The Brown notion seems to suggest that the heavy costs of vaccine development would be paid for from alternatives to those of an APC. If so, practically all of the APC analysis *as an R&D instrument* is largely irrelevant to this case, and the APC being promoted is just a “political stunt”<sup>929</sup> to look good while doing very little, or even nothing, to actually spur a high-quality malaria vaccine into existence.

If it isn't being used as claimed, then when APCs bite and the \$5-\$6bn for malaria and \$3.3bn for HIV are called upon, the money will be fungible.<sup>930</sup> It will simply be taken from other competing claims on fresh funding at that later time. The whole thing becomes a grand political gesture, that is all about shifting funding about later, and does nothing to create new funds globally now for R&D, and for incentivizing the creation of these (better) vaccines in the first place via multiple parallel developers. The key issue ought to be the precommitment-related benefits, but we already see from the way Kerry and Lugar were advised, that those doing the advising haven't grasped this key feature. Now we see that something pretty similar seems to be going on with the GSK candidate vaccine.

But it is worse. If all the subsidy pool goes on the (high) manufacturing costs of a ‘lower’ quality vaccine, and it does not get used as a true R&D instrument, that would just mean that a ‘poorer’ quality vaccine was given a huge competitive advantage over a ‘better’ quality vaccine that it displaced, and would also harm other parts of the overall malaria control package. Intuitively, thinking of the underlying R&D model, the losing ‘better’ vaccine needed the subsidy pool to go to one of multiple parallel vaccine candidates for it to stand a chance of being discovered and developed in the first place, but the ‘lower’ quality vaccine displaced this activity, and thereby the creation of the ‘better’ vaccine. One correspondent argued that the lost lives consequent on this would run into the hundreds of thousands.

The final possibility is that an APC is not paid out due to the fault of those setting it up. There are then three possibilities. Either, firms do not respond and it collapses in self-fulfilling fashion from the very start. Or, firms do respond, the scheme collapses, and they have a case to sue those setting the scheme up (Why ever not? They were mislead?).

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<sup>929</sup> Editorial in *Pharma Marketletter*, February 20, 2006.

<sup>930</sup> We ignore for the moment the reputational damage to the pharmaceutical industry for not investing in light of the APC, and we ignore the fact that a range of APC institutions will have to be set up and run meanwhile.

Or, they do respond, the scheme collapses down to paying for the least challenging, lowest quality outcome acceptable without having to declare that it has, to all intents and purposes, failed.

In this topsy-turvy world it is still possible to go from discussing six billion dollar funding proposals to reading pleas such as this:

*“An additional \$20 million per year could lead to several new products moving to clinical trials. Similarly, an additional \$20 million per year for the extramural program, which funds directed R&D as well as investigator-initiated grants, would greatly accelerate the development of new vaccine concepts.”* (“Malaria Vaccine R&D: The Case for Greater Resources”<sup>931</sup>)

### **What better impact could \$6bn have?**

It rather begs the question of what sort of vaccine leads we would have to work on by now had even a fraction of what is now being proposed was poured into finding more and better vaccine leads in the first place, and cracking some of the scientific and collaborative problems. That we are considering £6bn for one vaccine lead that has achieved, so far, ‘only’ 30% efficacy – and even that hotly debated – does rather suggest the potential expensiveness of *not* using more collaborative approaches to achieve the 90%+ effective vaccines we ultimately seek. \$6bn is *a century’s* worth of the entire public and private spending on malaria vaccine research at current rates of expenditure.

## **11.4. The ever-falling malaria vaccine goal**

Until very recently, the APC literature regularly discussed efficacy rates of 80%, 90%, or even 99%,<sup>932</sup> with protection lasting for five years, with emphasis on minimizing the number of vaccine doses.<sup>933</sup> As Kremer explained it: “Unnecessarily stringent specification would discourage pharmaceutical firms from following promising leads. For example, it would be a mistake to require a vaccine to be 90% against all strains of the disease, since this would discourage developers from pursuing a candidate vaccine likely to yield 99 percent protection against most strains, but only 85 percent protection against others.”

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<sup>931</sup> [www.malariavaccine.org/files/Two-page-funding.pdf](http://www.malariavaccine.org/files/Two-page-funding.pdf).

<sup>932</sup> [www.pm.gov.uk/files/pdf/Appendix%207.pdf](http://www.pm.gov.uk/files/pdf/Appendix%207.pdf), p10. See also Kremer, M., and Glennerster, R., 2004, *ibid.* p78, and Kremer, M., Appendix 4, No. 10 Policy Unit, p20, which also discusses 80%.

<sup>933</sup> Compared to one or two shot vaccines, there is much less point in having treatment that requires four vaccine shots, and a vaccine that has to be administered outside of the EPI, the standard childhood vaccine package, given the high distribution costs, and the low levels of health service personal and record keeping in some resource-poor settings, and the strains that already exist on health infrastructure and personnel. With low-efficacy vaccines, the opportunity cost of continuing drug treatments remains nearly as high as before. Who pays for the distribution and health-system costs? How do the costs of this approach compare to alternatives involving from the start better drugs and use of more preventative measures such as bednets? What happens in such situations to the cost-effectiveness arguments being made for such vaccines? And what happens after all the APC has gone on this vaccine? Is this a good deal for all the PPP funding absorbed and for the countries relying on this vaccine?

Berndt et al. set the base case for a malaria vaccine at 60% effective protection for five years from a three-dose course.<sup>934</sup> In late 2004 Barder, on behalf of CGD, argued the goal would be that “It should prevent at least 50% clinical episodes of *Plasmodium falciparum* malaria in infants and young children for at least 5 years, with no qualitative or quantitative exacerbation of subsequent disease; requiring 1 to a maximum of 4 immunizations; presented in multi-dose vials.”<sup>935</sup>

In mid 2005, the CGD contract term sheets stipulate no more than 50% efficacy for two years from up to four doses, with as few as four members of a committee having the discretion to “to grant waivers of, or make modifications to, the application of specific technical specifications or usability requirements”.<sup>936</sup>

In early Malaria Vaccine Technology Roadmap discussions, such as the Vision meeting of November 2004, there was no ultimate product-characteristic or region-specific goal. By the time of the Malaria Vaccine Technology Roadmap,<sup>937</sup> the goal was minimal efficacy of 50% against severe disease and death and minimal duration of one year,<sup>938</sup> the notion of minimal efficacy of 80% and minimal duration of four years<sup>939</sup> was pushed off to 2025. Similarly, the goal was narrowed down not to include pregnant women and *P. vivax*. The 20-plus year goal sounded remarkably like the original Kremer principle goal, now pushed off a full twenty years.

Berndt et al. observed that “Even a 30 percent effective vaccine would be highly cost-effective.”<sup>940</sup>

If it really is the case, as Berndt et al. claim, that “the promising results of the recent GSK trials suggest that developing a malaria vaccine may not be as technically difficult as many had previously thought,”<sup>941</sup> it does seem rather odd that this does not translate into sights being set higher, rather than sights actually being set much lower.

Similarly, CGD started off regularly using a quote of \$6.25 billion each for malaria and HIV, but ended up titling everything “\$3bn per disease”. This was later described by the report’s authors – after the report had been released with wide publicity of the \$3bn figure, and after the \$3bn had been argued as the right figure to set an APC in the US

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<sup>934</sup> Berndt, et al, 2005, *ibid.*

<sup>935</sup> Barder, O., CIPIH Forum, 27 November 2004.

<sup>936</sup> CGD, 2005, *ibid.* p94 (part of the contract term sheets).

<sup>937</sup> At the time these appeared in the Roadmap, GSK had produced 6 month efficacy figures, but not yet the 18 month efficacy figures (i.e. the 21 month figures).

<sup>938</sup> Number of doses unclear.

<sup>939</sup> Number of doses unclear.

<sup>940</sup> Berndt, et al. 2005, *ibid.* p19.

<sup>941</sup> Berndt et al. 2005, *ibid.* p9. Though in the same *Lancet* as the first Alonso study, Philippe van de Perre and Jean-Pierre Dedet, argued that there was no reason to think things will now get easier: “The road toward a safe and efficient malaria vaccine being available and usable on a large scale...will be long and chaotic.” I have no idea on whose behalf Berndt et al. believed themselves to be speaking. This author has found no malaria vaccine experts willing to take the Berndt et al. line. Chapter 3 above illustrates the huge challenges that still lie ahead.

Senate, and after Farlow et al. had pointed out the ever-lowering standard – as “merely illustrative”<sup>942</sup> anyway, and we were reassured that “the requirements haven’t been set at all” either.<sup>943</sup>

The ‘only’ thing that happened since the early CGD statements was the GSK result. However, a rationally set ‘efficient’ goal, or set of goals, must stand independent of any single study, and be set relative to a greater package of measures. The only thing that happened since the early statements was a hasty political announcement about willingness to heavily subsidize purchases of a low efficacy vaccine, and the need to create a goal that could supply that political announcement with a product within a time frame that might be politically useful. Indeed, grand announcements were made suggesting the goal would be achieved in 4 years,<sup>944</sup> just about soon enough to be politically useful.

The author has been told<sup>945</sup> that the Malaria Vaccine Technology Roadmap 50% target one year goal was not set with reference to the GSK Mozambique results, but that it emerged as a general consensus of the sort of effect that might be considered useful by Ministries of Health, and that it matched the efficacy of insecticide-treated nets. It was based on a ‘guesstimate’ of cost-effectiveness, with no strong claim to being especially ‘scientific’. The problem, however, is what happens when a, perhaps useful, *aspirational* goal becomes treated as an *operational* goal to drive the allocation of large amounts of funding, when the overall level of funding is very tight. In the policy circles this author found himself circulating in, the absolute<sup>946</sup> 50% one-year goal<sup>947</sup> rapidly became conventional wisdom; certainly it seemed to be taken at face value as a ‘good’ goal in the UK Treasury and DFID and helped also to feed the push for an APC.

### **An example of dynamic inconsistency?**

This is another form of dynamic inconsistency. Recent vaccine criteria would not have been even considered, let alone vocalized as operational goals, before the recent GSK case. One of the criticisms of APCs is that they encourage incentives to push towards absorbing all funds on a low-efficacy outcome. In fact, it is almost impossible to politically resist ‘blowing’ all APC funds on the least challenging outcome. Now, we see that even before APCs exist, this sort of pressure goes on too.<sup>948</sup> perhaps these ex post

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<sup>942</sup> IAVI also discusses ‘illustrative scenarios’: “After subtracting out \$0.7 billion in revenue that a company would likely recoup from sales in developed countries, the AMC market would be \$3.3 billion. In one of the illustrative scenarios developed by IAVI this would be achieved by guaranteeing a price of \$15 per course for 250 million people. Since it will likely take a number of years to get the vaccine to everyone who would benefit from it, IAVI’s proposal is based on the expectation that the commitment would last about ten years.” [www.iavireport.org/Issues/Issue9-3/apc](http://www.iavireport.org/Issues/Issue9-3/apc).

<sup>943</sup> Barder et al. 2005, *ibid.* p8.

<sup>944</sup> Gordon Brown, speech, October 2004, *ibid.*

<sup>945</sup> Correspondence with senior highly respected malaria figure present at that meeting.

<sup>946</sup> I.e. not the marginal improvement that a vaccine adds to a malaria control package.

<sup>947</sup> At the time, two year, and also with ability to set terms lower.

<sup>948</sup> Try a few thought processes. The ability to lower the ‘quality’ bar is a risk to other privately-funded developers, a risk to GSK (should other developers come along later), and a risk to eventual users. Imagine the problems if another ‘better’ vaccine candidate comes along. Is it set a target of 50% efficacy so as not to be treated ‘worse’ than GSK? Even if it is capable of 90%? If it is set at 90%, would the developer not

rationalizations for lower requirements demonstrate some of the difficulties of efficiently setting terms far in advance for such schemes?

**How would GSK have fared?**

GSK would have probably fared badly had a pre-existent APC been in place for the past five to ten years. Had the terms of *that* contract been categorically set to require a *minimum* of 80% to 99% of permanent protection against attacks for four years in children bestowed by one or two malaria vaccine shots in a low resource setting, then any current GSK vaccine would have had to be categorically denied any APC funding at all. If GSK was offered a contract breaking this original contract, then all other firms would have had to be compensated (perhaps after litigation), since this would be very risky for them. Even the knowledge of breaking the stipulated requirement would be so damaging to investors that it ought to have been legally ruled out from the start (even if few investors respond).

It is highly unlikely that the British government would have encouraged the renegeing, since it would have put developers off from ever trusting such contracts again, and these costs would have weighed heavily against the possible gains from breaching the terms of the original contract. Even the *ex ante* possibility that GSK might be given APC funding ‘against the rules’ would damage the value of the investments of other developers. At the same time, firms other than GSK would worry *ex ante* about the PR disaster of having to litigate for a fair deal (in the *ex ante* sense) and would *ex ante* simply refuse to invest in the first place.

Incidentally, breaking the ‘implicit contract’ of a high efficacy vaccine by setting a low efficacy APC for GSK *now*, also imposes risk on all current developers, but it is harder to visualize, and there is nothing to legally prevent it. Observe therefore how the threat of use of an APC at first sign of any positive result, is itself risky for developers.

Had a malaria APC been set five to ten years ago, is some of this recent advocacy literature suggesting that the terms of that would have turned out to be very wrong? It may be that the only reason this particular vaccine candidate might *now* be able to view itself as a potential candidate for a large APC payment, is precisely because there was no early-stage APC of the CGD-Tremonti variety in place in the first place?

**Advocates argue for lower efficacy**

We also are increasingly aware that one of the biggest dangers of an APC for malaria is that it would contain self-fulfilling pressures towards acceptance of lower quality. Advocates have sought to argue that this is not so, and that a committee, and pre-set rules, would ensure that this would not happen, even as they have pushed the required efficacy and duration criteria ever lower, and exaggerated the value (compared to alternatives) of devoting a sizeable chunk of the limited funding to lower quality. Ironically, they demonstrate the very fault they say does not exist, that it bites even

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object to the ‘tougher conditions’ when the earlier vaccine of GSK has been set ‘only’ 50% or so (and may yet be allowed at something lower) and may have taken most of the APC subsidy pool? Why should the 40% or 50% product get *anything*? Even more so when we consider the marginal, and not just the absolute, efficacy of a vaccine, thus taking these percentages much lower.

before an APC is set up, and that they are even quite happy to become the principle agents for driving it.

### **11.5. Wider constraints revealed in G8 choices**

The summer of 2005 also illustrated some of the wider political and financial constraints. We saw huge struggles to put together a \$25bn per-year extra aid package for Africa, and some write-off of debts (this is mentioned without taking a position as to whether or not these were the best policies). The debt ‘written off’ was \$40bn, but the yearly cost is at most only about \$1-\$1.5bn to rich nations. Some argue that even this is an overestimate given the low likelihood of getting repaid anyway. The aid package was less than half what was asked for, and the debt right-off was a close call too and nearly did not make it. Brown and other politicians know this, and they must want to resist such a close call in the future, including the consequences of finally having to face up to the up-front resource requirements of APCs as revealed in the Tremonti Report. As with the aid package, the debt package was only a portion of what was lobbied for previously.

Why the debt right offs and why the \$25bn aid package, and why not something else? The reason was, partly, because politicians genuinely thought that these initiatives might help (again, the author is not taking a position here), but also partly because these are ideas that politicians involved in them (especially the British, who were chairing the G8) could ‘claim’ as their own initiatives. Reforming the global system of farm subsidies – running at \$1bn a day in Europe and the US, distorting markets for African exporters and numbing the ability of African and other poor countries to grow through trade – or dealing with trade issues in general, is much less rewarding because these are much more difficult for politicians to claim as ‘their’ own novel ideas; many others have worked on them before and have more claim to the credit of any successful initiative, and the issues are tough and involve long slog and political risk and the sinking of political capital, over long periods of time. Politicians in a hurry look for more immediate gratification. The message is simple: Certain ideas grab politicians and others do not.

One further thing that tends to limit possibilities at G7/G8 meetings is that each country wants to have success on its ‘own’ novel idea, such that making big financial commitments to someone else’s ‘big idea’ is not always welcome. For example, Gordon Brown’s ‘big idea’ of an international aid facility, the International Financing Facility, IFF, fell flat at the UK-headed G8 meeting in July 2005,<sup>949</sup> partly because of its own problems but also because other G8 members have their own novel financial instruments for helping the poor (though many have done little to advance action on their chosen instrument). Other G7/G8 leaders may yet defer committing to another big financial promise (such as an APC for a malaria, HIV, or TB vaccine) to avoid having to commit to an initiative that gives them little credit. But, then again, they may have swallowed all the stuff about the power of malaria, HIV, and TB vaccine APCs, and the notion that it

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<sup>949</sup> This author discussed the IFF issues in Farlow, A.W.K., March 2005, Section 3.5, and Farlow, A.W.K., July 2005.

will do what it says it will do for ‘only’ \$3bn, and that it will get them off the hook of doing something much more practically useful?

### **Tough fiscal conditions of G7 countries**

Most of the countries in the G7<sup>950</sup> (especially the UK and US, but others too) are facing tough fiscal positions and also balance of payments problems, and this will get worse. Indeed, this is a fairly widely held view amongst G7 finance ministers. One correspondent even described the G7/G8 as a “broken financial system”, already unable to finance its commitments. By pitching at those with deficits and not at those with surpluses, a wide range of options are deliberately excluded. In particular, APCs look to be a great way to avoid having to pay anything on the watch of current finance ministers, even better if they are not likely ever to be disbursed. In a sense, the long-off HIV or malaria commitment is heavily discounted in the minds of politicians, and, in fact, may never be paid. This was an argument repeatedly put by APC advocates, as if it were a positive virtue. This ‘benefit’ is no ‘benefit’ at all if an APC fails; private investors (i.e. taxpayers) still have to pay the real resource costs of firms engaged in activity based on APCs, they just don’t do it through their up-front taxes. The Tremonti Report now reveals that even the notion of avoiding early payments into APCs is not going to be achieved. G8 leaders were never told this in July 2005.

If firms read the writing on the wall and do not respond to APCs by investing their own resources, the G8 leaders can get away with a grand gesture, pay not a penny, and then not be around when the initiative does not work anyway, and terrible suffering persists.

### **11.6. The poorly-worded Kerry-Lugar Bill**

When the Kerry-Lugar Vaccine Bill was announced in late summer of 2005, it was, as we saw above, riddled with poor wording, and showed that the authors of it had been poorly advised on how APCs were actually supposed to work. Barder has confirmed<sup>951</sup> that CGD did not advise on any of the wording. Kerry and Lugar did not seem to know anything about the contract structure of an APC, or the monitoring issues and the role of a committee determining returns to investors via readjusting subsidy allocations at the end, or the statist credentials of such schemes.

In Chapter 10, we found a proposal that was very risky and lacking in credibility to investors. To credibly sustain a precommitment – over very long stretches of time – requires either a costly action (for example, when a firm invests in excess capacity to deter rivals) or a costly punishment for reneging (for example, interest rates that rapidly rise if a country shows any sign of defaulting on its debt). With neither of these available for vaccine precommitments, the wording of the legislation is everything, and, in this case, we found it seriously deficient. This makes it a very high chance that any Kerry-Lugar supported APCs would not act as R&D instruments at all encouraging multiple developers into vaccine R&D. This increases the chance of poor outcomes. Indeed,

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<sup>950</sup> Russia, the last member making up the G8, is running a decent-sized balance of payments trade surplus.

<sup>951</sup> Private correspondence.

Chapter 10 suggested that if the APCs described in the Kerry-Lugar Bill turned out to be ‘just’ procurement schemes, they might even do nothing to generate HIV, malaria and TB vaccines in the first place, whilst still giving the appearance of something being done, while harming other activities and many investors.

On closer inspection, the Bill is also found to limit itself to malaria, HIV, TB, and pneumococcal disease, missing out huge areas of infectious and other diseases. This was partly as a cap dictated by the – to politicians – high impact diseases, and desire not to commit too much, or spend too soon, and because more kudos comes from seeming to ‘tackle’ high profile diseases, even if there are swathes of lower profile diseases where impact would be much quicker, but that would cost more now. Since the Bill will have no impact on malaria, HIV or TB vaccine R&D, one concern is that, even if the Bill gets through, it would only in reality be used to try to achieve a result on pneumococcal disease – itself a useful outcome, though a useful discussion can be had about relative cost-effectiveness of the outcome compared to others that are foregone – even if this could have been achieved with less delay by other means, while misleadingly suggesting a solution for the other three vaccine problems. If the Bill fails, it would even harm the pneumococcal disease outcome.

The Bill also excludes all but the poorest of countries, even if countries like Russia, China and India are likely to be (or should be) major sources of trials and technology leading to the creation of vaccines for HIV, TB, and even malaria, and are likely to have major need for such vaccines. It also sets up potential tensions between European (and other) malaria vaccine efforts and the US Treasury, since it would require all developers to be signed in to contracts, the purse strings of which would run through the US Treasury and the President of the United States of America. The Bill also places conditions on the countries deemed ‘eligible’ and ‘non-eligible’ for subsidies, and this would create later tensions between the US and Russia, China, India, Latin America, and middle-low income countries with regard to HIV vaccines, and possibly even malaria vaccines, since the scheme is set up to deny subsidies to them, leaving them to face (tiered) monopoly prices instead.

The wording of the Bill goes out of its way to avoid action to bolster malaria control programs now, and on funding, especially of PPPs and of basic science, which might actually have a genuine impact on malaria, HIV, and TB and other vaccines in five to ten years time. This suggests political *unwillingness* to fund a multitude of global health needs (not just products and not just vaccines).

At the time the Bill was being formulated, politicians – at the level of the US Senate indeed – were being sold the myth of the huge value of a \$3bn APC for malaria and HIV, as if \$3bn gets malaria and HIV cracked for ever (thus generating fantastic looking cost-effectiveness figures, even if such figures mean nothing). This encouraged politicians to think that such a Bill was a ‘powerful’ instrument when it wasn’t.

### **11.7. Emerging and middle-income countries left out**

One of the distortions of the last few years has been the emphasis on instruments to tackle global diseases but aimed only at certain groups and countries. HIV will be a major issue for China, India and Russia, but by the time a HIV vaccine is ready (if ever one is ready) it will probably have long passed the time when other solutions for Africa will have been much more useful. Meanwhile, APC proposals for HIV just leave China, Russia, India, and Latin America written out.

These countries have been ignored partly because an APC could not remotely work if these countries were included in the group of eligible countries, and because of the current US and G8-centric view of the world amongst certain influential policy advocates. To this author, this is a strategic failure, since tackling these diseases will need the heavy cooperation and technology of these countries in the future, such that ignoring them in thinking about incentive structures is to show a lack of vision as to where the technology of vaccines may come from in years to come. We end in the paradoxical situation of targeting R&D funding schemes at deficit countries, rather than exploring alternative schemes that might benefit surplus countries and can also be targeted for payment at the very same surplus countries.

This is also an international relations failure, given the way that such schemes set up Russia, China, India, Latin America and many others for HIV vaccine price debacles reminiscent of previous such price debacles over HIV drugs in Africa, but this time with the US government even more one of the key players. When the last PAHO representative switched the light out and left the CGD Working Group, a warning light should have gone on in the heads of those leading the APC effort.

### **11.8. The faulty financial reasoning in the Tremonti Report**

The next milestone in the PR exercise was the Tremonti Report published in December 2005 along with the G7 announcement about a ‘pilot APC’ to pay for an outcome that would have and could have happened anyway, but now dressed in the guise of an APC. Tremonti argues that “Developing a new vaccine presents huge scientific challenges, can take up to twenty years and requires large investments,”<sup>952</sup> but then proceeds to calculate the net present value (NPV) of the sums being offered for HIV, malaria and TB vaccines by using an astonishingly generous<sup>953</sup> (and really rather ridiculous) 6%.<sup>954</sup> Tremonti does not even say whether the 6% (already way too small) is real or nominal, but seems to treat it as nominal (and therefore even less adequate). 6% seems to reflect the notion that firms will not actually have to bear any entrepreneurial risk, and it also ignores any option pricing components in their required rates of return.

Similarly, Tremonti discounts at extremely generously-set horizons, such as 11 years for malaria, including all follow-on innovations. There is nothing incorporated for delays in

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<sup>952</sup> Tremonti, G. Background Papers, 2005, *ibid.* p14.

<sup>953</sup> In terms of therefore making the NPV much higher than it would in truth be.

<sup>954</sup> See Tremonti, G., 2005, *ibid.* p10.

setting up the mechanism (in spite of the delay needed for the pilot project, and the fact that it would take years to fix APCs for HIV, malaria, and TB), and no incorporation for uncertainties regarding this horizon either, and no incorporation for the risks and faults of APCs.

The Tremonti Report outlines three ways for funders to pay for a malaria vaccine APC (see above) with a range of financial impacts on the costings (generally making the APC scheme much more expensive) that are then promptly ignored in all calculations, even though knowing these figures is important for calculating priorities, and given that one side-effect of the APC lobbying effort is that it deflects attention from other approaches. This part of the Tremonti Report even contradicts the Kerry-Lugar Bill.

To have used discount rates and horizons even marginally nearer to the truth, and to have costed for delays and the use of these different funding approaches would have revealed just how low-value the impact of APCs would be for malaria, HIV, and TB. So, it was not done.

Furthermore, since the cost of a vaccine will only be a fraction of the cost of programs for administering it, one correspondent argued: “In terms of covering vaccination program costs on a long term basis, APCs in the way they are formulated by Tremonti are not sustainable and can add additional harm as they distract limited resources.”

#### **Why no sensible set of figures for malaria, HIV, or TB vaccines?**

Had Tremonti used a discount rate similar to that used by the sort of firms being targeted by APCs (large pharmaceutical firms with access to equity finance), one can only conclude it would have revealed a figure for NPV too shockingly small to have kept the APC ship afloat as an R&D instrument for malaria, HIV, and TB vaccines. Being very rough with figures,<sup>955</sup> the HIV figure of \$5.5bn discounted at 11% (say 8%-9% for capital costs and 2%-3% for inflation) for 15 years would have given a NPV of \$950m (well under half of Tremonti’s \$2.3bn). Discounted at 15% (as done by Grabowski et al.) would have generated a NPV of \$480m, 20% of Tremonti’s figure. Even a 15% discount rate is still a rate too low for most biotechs and venture capitalists, who would be key to HIV vaccine success via an APC. Throw in the possibility that the 15 year horizon is overly-generous anyway (especially given delays in setting the program up, and should the APC fail) and allowing for sensitivity for a longer horizon – and the NPV figures collapse even further. On very rough calculations we get a 20 year NPV of \$530m and \$210m respectively, a tiny proportion of what Tremonti reports.

In addition, the payment would – unlike in Tremonti – not all be paid out at the 15 year (or 20 year) horizon. A five-year spread chips about a quarter to a third off even these extremely low NPV figures.<sup>956</sup>

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<sup>955</sup> Since investments sunk to try to win an APC are spread over time. These figures just indicate what the value would be of putting all investments in *now* to get the APC payback in 15 or 20 years. The point is to demonstrate just how misleading the Tremonti figures are.

<sup>956</sup> Worked out on the basis of a constant rate of disbursement of the APC funds over five years.

Tremonti should also have thrown in extra discount rates for the riskiness of the APC mechanism itself, for the extra required rates of return on account of ‘option price’ components of required rates of return (which would be especially large for early R&D), and he should have accounted for the extra costs of the three financial funding methods he proposes, several of which would be very costly.

A few simple calculations immediately reveal the deception being perpetrated in the Tremonti malaria, HIV, and TB vaccine figures – hardly encouraging for private investors.

One correspondent, close to what was going on, observed that Tremonti seemed to have simply halved the size of the deemed overall push and pull funding package before it got presented to other G7/8 ministers, and saw fit to halve the discount factor too! If he did the former, then the halving of the discount rate was still wrong, since the Tremonti billions are to repay the private sector billions spent on R&D, and these get discounted at the full private-sector discount rate, and not Tremonti’s 6%.

#### **Paying for APCs partly from the start, and not just at the end**

The figures also pale in expected value compared to levels of push funding into alternative approaches, and even compared to the value of the funds being deposited into some of the financial payment mechanisms proposed by Tremonti. Would there honestly be much point at all in “full financing at the time of the launch of the APC” (Tremonti’s option 1)<sup>957</sup> or “building up the necessary resources through periodic contributions” (Tremonti’s option 2) if the true figures look anything like those above? Could funders really arrange to pay funds into an APC via these funding routes till vaccines would be ready, even as treatment and prevention options and alternative vaccine push approaches are crying out for funding?

Tremonti argues that the figures have been “cross-checked with the ones presented in several other studies and obtained through different methodologies,” and that: “It is reassuring to note that the results are all roughly comparable (when compared in common units).”<sup>958</sup> However Tremonti provides little detail of these independent studies, referring only in specific detail, in the background papers, to the calculations in the previous CGD study<sup>959</sup> and to the Boston Consulting Group analysis for MVI.<sup>960</sup> This is not sufficient independent verification. CGD (with the help of several key Tremonti Report authors) had earlier admitted that these figures were “only illustrative”. And we saw in chapter 6 above just how badly worked out these figures are anyway (especially devoid of any notion of costs, and hence not based on required investor returns). Independent

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<sup>957</sup> See Tremonti, G., 2005, *ibid.* p14 for all three financing options.

<sup>958</sup> Tremonti, G., 2005, *ibid.* p10.

<sup>959</sup> Tremonti, G. Backup Papers p19: “These estimates have been cross-checked with other estimates available, including those obtained following different approaches, such as the estimate by the Centre for Global Development (CGD), which was based on the analysis of a sample of successful pharmaceutical innovations,” (that sounds remarkably similar to the Tremonti methodology itself). No reference is made to any other estimates or methodologies.

<sup>960</sup> Tremonti, G. background Papers, 2005, *ibid.* p25.

verification of bad figures is not nearly as reassuring as independent agreement over right figures.

### **Tremonti wrong to lump all conditions together**

Tremonti also repeats the fault of others by constantly lumping all vaccine problems together,<sup>961</sup> even though there are dangers of suggesting simplistic solutions to malaria, HIV, and TB vaccine problems because of a link to a very different set of scientific issues. One correspondent put it: “The Tremonti Report puts vaccines that are in the very early stages of clinical development and for which no proof of concept exists together with others, such as pneumococcal, whose level of development is close to reaching the market/distribution. The barriers are also very different. Since pneumococcal is a frequent complication of HIV in children, the challenge to a pneumococcal vaccine are considerably different than for a malaria vaccine in achieving reduced mortality. Other vaccines are efficient because they built up herd immunity (pneumococcal, Hib, Pertussis). It is *not correct* to naïvely put all these difficult-to-do vaccines in one box.” Many correspondents alleged a policy of muddying the waters by mixing different scientific problems together. It has certainly made nuance (in media coverage for example) extremely difficult to achieve.

### **Tremonti’s dereliction of duty**

The problem would seem to be that Tremonti did not write the Tremonti Report. The extent of this dereliction of duty is seen in the uncritical and lax way some quite extraordinary analysis of costings, that have no basis in sound finance, are accepted at face value. APCs are a financial instrument; if they do not appeal to investors and financial markets, then, no matter how much politicians might swallow this sort of analysis – APCs will not work. Tremonti is a finance minister; he should know this.

One correspondent observed that Italy is one of the “lousiest spenders” on development issues and neglected diseases, and a country desperate to shore up its finances after “mega deficit spending”. APCs are, according to this correspondent, ideal to play to such “stinginess” whilst still wanting to appear to be doing something. Rather than emanating from a high moral position, to this correspondent, the Tremonti Report is an elaborate deception, a case of “the pot calling the kettle black”, and deeply morally reprehensible.

Another correspondent, heavily involved in the process leading up to the December G8 announcement, explained, somewhat disillusioned with the whole process: “The World Bank effort to support the Italians was more rigorous than the CGD process but still was under a lot of time pressures. The papers that the bank developed internally and from consultants were ultimately stripped of the caveats (about whether it would work and for what) by the Italian MoEF...I am no longer involved, (possibly because I was not a full ‘convert’, especially for early stage vaccines).” One day, perhaps, somebody will explain why a short-term temporary political appointee, only in place to fix an internal political problem in Italy, with no apparent relevant economic or financial skills, was allowed to

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<sup>961</sup> Right back to this author’s first interactions with CGD and the World Bank over this issue, he urged this not be done. Tremonti now places them all in the same table and applies a similar approach to them all.

manipulate evidence and strip key caveats out of policy papers designed to tackle a 20-30 year problem on which millions of lives depend?

### **11.9. How the institutions of UK policymaking feed policy failure: The 'O-ring' principle**

To a degree, the institutional aspects of policy making can work against critical perspectives and the avoidance of failure. Let us call this the 'O-ring'<sup>962</sup> principle after the 1986 Challenger disaster. That disaster was caused by a failure of the O-ring in the right solid rocket booster of the Challenger space shuttle, even though the O-ring engineers had tried desperately the night before to get the launch cancelled. This was the coldest ever launch of a Shuttle; most of the night before temperatures were well below zero at the launch site. The rubber O-ring seal only worked at much higher temperatures when it would have the flexibility to seal the joint so that fuel would not leak out. The engineers had performed insufficient low-temperature testing of the O-ring material, and argued in emergency meetings with NASA managers the night before the launch that they had no evidence that the Challenger would be safe. The engineers' requests were overridden by the managers who thought they knew better, and who were anxious to launch the Challenger for various reasons, including economic considerations, political pressures, and scheduling backlogs. They took a gamble – and it failed.

In his closing address of the commission enquiring into the disaster, Richard Feynman famously placed a piece of the rubber from a Shuttle O-ring into a glass of iced water and put a clamp on it. After suitable cross-examination of NASA officials, he removed it from the glass of iced water. At 0 degrees Centigrade the rubber became like lead and the clamped part of the rubber stayed squashed flat for all to see, demonstrating that it could not have operated as a seal at the time of the launch. An incredibly simple scientific experiment demonstrated that the shuttle was doomed to perish.

One sees the hallmarks of this failure gripping the UK policymaking process as it works its way towards the launch of APCs for malaria, HIV, and TB. For example, over a period of just a few years, this author's interactions with the UK Treasury and DFID over these issues involved three waves of officials. The first wave of key officials were never more than email names, overlapping with the second wave. By the time issues had progressed enough for the author to have face to face interactions, the second wave was in place. Now there is a third wave, and several of the key officials this author dealt with have since moved on too. Even the Tremonti Report was not supposed to be the Tremonti Report, but rather the 'Siniscalco' Report, Siniscalco having himself been replaced after the July 2005 G8 meeting. Tremonti, in turn, left by April 2006. So, he has already gone before this reaches any serious G8 decision. This reflects how casual policy making is on these issues.

The lack of consistency and stability of involvement has various consequences:

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<sup>962</sup> <http://en.wikipedia.org/wiki/O-ring>.

- 1) It makes it very difficult to maintain consistency of mutual understanding between officials and those interacting with them, with the latter having to repeat over and over again their efforts to ‘educate’ the officials as to the nuances and complications of policy. Many of the civil servants involved have insufficient specialist knowledge to be able to formulate policy without the input of economic, financial, science, or global health expertise from outside.
- 2) This means that certain advocacy groups have a natural advantage. Rigorous logic has a disadvantage against consistently spun, simplistic one-liners, and large lobbying efforts. In the end, the Tremonti Report pretty much repeats, at least with respect to malaria, HIV, and TB, the same literature of the same few key individuals as went before under various other guises.
- 3) It means that those with more privileged access to politicians are much more able to influence the setting of policy, and indeed the allocation of huge sums of public funding. In particular, J.P. Garnier, head of GSK, with high access to Gordon Brown was able to get a ‘deal’ out of Gordon Brown.<sup>963</sup> This is not a criticism of such industry individuals; it is their job to defend the interests of their companies. Nor is it a criticism of industry in general (the reader should know this by now, even if some advocates tend to put an ‘ideological’ spin on critical observations, to suit a purpose). But, given the dangers of creating a non-level playing field – of creating worries in the minds of *other* investors and thus reducing the number of parallel scientific leads, of reducing much-needed competition, and of forcing lower quality outcomes out on average – politicians need to have much more distance from any especially powerful interests.

As Light observes regarding the GSK candidate malaria vaccine “Ironically, this is the only candidate mentioned in the [CGD] report...Why is GSK's marginally effective vaccine candidate mentioned by name in the report – and why are the terms of contract then made loose enough so that a small, hand-picked committee is permitted to lower (but not to raise!) the minimal thresholds for a vaccine to be acceptable?”<sup>964</sup>

Advocates do not help either. Nancy Birdsall sat at Brown’s side when he made his teleconference revelations of a personal ‘understanding’ to

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<sup>963</sup> When this author (a ‘leading critic’) managed to get a short policy briefing through to the Prime Minister’s Private Secretary, he received a perfectly polite letter explaining that it was being forwarded to the official in charge of these matters, even though that official was in the process of moving on (and, indeed, out of the civil service). A short policy briefing, with Richard Mahoney, to Paul Wolfowitz, President of the World Bank was, apparently, more successful in getting through (but only because *we* had someone in a privileged position).

<sup>964</sup> Light, D., 2005, *ibid.* Many others have worried about the closeness of GSK to MVI, and the closeness in turn of MVI to the Gates Foundation, but I leave that to others to more fully explore this. Again, the issue is that of balance and investor perceptions.

provide GSK with an APC deal, but she did nothing to remind him of the dangers of destroying higher quality outcomes by distorting the vaccine and malaria control playing fields.

- 4) Consultation processes becomes a simple rubber-stamping exercises:
- i. The call for submissions to the recent DFID consultation process and the announcement of DFID stakeholder meetings suggested that whether or not an APC would be suitable for malaria was not even up for discussion.
  - ii. All recommended reading material posted by DFID to the consultation process was from one side of the debate only, with nothing of a growing critical literature presented.<sup>965</sup>
  - iii. It was announced that the DFID consultation process was due to finish taking submissions on 31 December 2005. Yet Gordon Brown and G7 ministers were already making announcements about the conclusions of the DFID process in early December 2005, as if the outcome of the consultation process meant nothing.
  - iv. The subsequent wording of the minutes of the November DFID stakeholder consultation meetings suggested that there were dissenting voices and that pharmaceutical interest was much more lukewarm than originally claimed by CGD, if not non-existent. In a case of ex post reinterpretation of the facts, the minutes of those DFID meetings start by suggesting that the use of APCs *was* still up for debate: “The aim was to solicit views on whether the AMC concept is a good thing in general? Should we be supporting it?”<sup>966</sup> It then goes on to reveal the concerns of many about the proposal. One of the world’s leading industrial economists, F.M. Scherer,<sup>967</sup> challenged a number of the underlying assumptions of the CGD modeling, suggesting it was inappropriate for technological problems needing multiple research routes to get a high-quality solution.<sup>968</sup>
  - v. Nevertheless, in mid-January 2006 – and two days before the extended deadline for the DFID consultation process was due to expire<sup>969</sup> – yet again Gordon Brown wrote in a British newspaper

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<sup>965</sup> This author did not change his US travel plans to go, reasoning it was just another rubber-stamping exercise.

<sup>966</sup> [www.dfid.gov.uk/consultations/amc-consultation-note.pdf](http://www.dfid.gov.uk/consultations/amc-consultation-note.pdf), p1.

<sup>967</sup> The presence of Scherer was reassurance that CIPIH and the WHO were not going to come down on the side of APCs for malaria, HIV, or TB. I leave the explanation of the cryptic meaning of this to another time. CIPIH subsequently supported the Farlow et al. line against the CGD line for HIV, malaria, and TB.

<sup>968</sup> [www.dfid.gov.uk/consultations/amc-consultation-note.pdf](http://www.dfid.gov.uk/consultations/amc-consultation-note.pdf), p3.

<sup>969</sup> Following the release of the Tremonti Report, the deadline for DFID consultation was extended to 13 January 2006. Brown’s statement of intent was printed on 11 January.

of his intent to push through an APC for malaria at the G8 meeting in February, almost as if the DFID consultation process had not taken place: “So next month, I will ask the G8 to...create the first mechanism whereby rich countries underwrite the research, development and bulk production of affordable vaccines and treatments.”<sup>970</sup> On the one hand, his civil servants are sitting down with stakeholders asking “whether the AMC concept is a good thing in general? Should we be supporting it?”<sup>971</sup> On the other, Brown is doing what he has long since decided he wants to do anyway, and acting as if the consultation process does not even exist.

In late January we hear that: “The World Economic Forum in Davos, Switzerland included a number of sessions and announcements related to vaccines. Britain and Italy [based on the Tremonti Report? Surely not?] voiced support for Advance Market Commitment (AMC) approaches to ‘stimulate pharmaceutical companies to develop drugs and vaccines for diseases of the developing world.’ [at last someone knows to put these things in quote marks] The AMC approach will reportedly be discussed at next month’s G8 meeting in Moscow for approval as part of a broader package designed to raise funding to tackle disease in the developing world, including further talks on pledges made last year to support broad access to HIV/AIDS medication by 2010. AMCs, sometimes termed advance market mechanisms or advance purchase contracts, would offer significant, up-front sums from donors and others to create a guaranteed market for the successful development of a treatment for a disease such as malaria.”<sup>972</sup>

Given some of the dangers, it also seemed very odd in the middle of a DFID consultation process supposedly to determine *whether* APCs are even the right way to proceed, and in the middle of a robust Roadmap debate, in part funded by the Gates Foundation and under the auspices of MVI – taking place on the understanding that nothing has yet been fixed in stone and everything is open to the ‘whole’ malaria vaccine community to decide – to hear that “there is, if you like, an understanding with the Gates Foundation and with the pharmaceutical company that the next stage would be an advance purchase agreement.”<sup>973</sup>

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<sup>970</sup> [www.guardian.co.uk/comment/story/0,3604,1683463,00.html](http://www.guardian.co.uk/comment/story/0,3604,1683463,00.html).

<sup>971</sup> [www.dfid.gov.uk/consultations/amc-consultation-note.pdf](http://www.dfid.gov.uk/consultations/amc-consultation-note.pdf), *ibid.* p1.

<sup>972</sup> [www.bioethics.upenn.edu/vaccines/?pageId=2&subpage=213](http://www.bioethics.upenn.edu/vaccines/?pageId=2&subpage=213).

<sup>973</sup> Kremer, referring to the APC model, also argues that “British Chancellor of the Exchequer Gordon Brown has said he’d press for this sort of model,” in Kremer, M., 19 November 2005, *ibid.*

- vi. In early February 2006 it was being alleged that pressure was being put on the WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH), who looked to be forming too negative an opinion of APCs. One correspondent, with insight into the workings of DFID and the UK Treasury argued that DFID viewed this as something to “push Brown” and to enable Brown to “take credit for big ideas.”<sup>974</sup> The correspondent observed that Brown would not take a stand “unless it could be pushed through.” Going back and losing face was not on the cards, and having CIPIH out of line with DFID and Brown policy was not conceivable. In the end CIPIH found against the use of APCs for malaria, HIV, and TB vaccines.
- vii. Another argued that APCs had an almost cathartic purpose: “Some circles in DFID and the UK Treasury are pursuing a chimera in order to signal their non-responsibility for a funding short fall; The UK is indeed far away from reaching the agreed ODA level of 0.7% of GNP and, despite the rethorics, far behind the Nordic Donors.” This was backed up by arguing that the “Treasury seems little interested in gathering support for its ideas in the G8 finance context apart from asking Professor Tremonti to report. I really wonder what the point is in consulting with a bioethicist, such as Ruth Levine, and none of the health sector/development economists of G8 countries such as Prof. Buse in Germany, Fleury in France etc. These will be in turn be consulted by their governments hence the sense of involving them now.” This author had previously argued that APCs are largely a way to put off doing anything, whilst still looking to be doing something.<sup>975</sup>
- viii. As part of the same casual and reckless approach to policy, there is no evidence that Tremonti had much input into the Tremonti Report, or spent much, if any, time checking the financial and economic logic, apart from stripping important caveats out, and, possibly, even himself manipulating the figures to make them more palatable. But then, Tremonti was temporarily in post for just a few months to achieve political compromise in Italy. He was the Northern League appointment that Silvio Berlusconi had to make to hold things together till the April elections. One might well ask why the British, with the whole of the EU to look to, are looking for allies amongst those who are short-term political appointments of countries with a very poor record on development and related issues?

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<sup>974</sup> There is something of a fight back against this. The FCO has close ties with ‘Chatham House,’ i.e. the Royal Institute for International Affairs ([www.riia.org](http://www.riia.org)), a think tank, to (as it was put to this author) “deal with all the problems created by DFID that the FCO then has to shoulder.”

<sup>975</sup> Farlow, A.W.K., March 2005, *ibid.*, and July 2005, *ibid.*

- 5) It means that when those pushing a policy have no evidence to justify what they propose, or have distorted the evidence to make their case, the officials dealing with the matter have no inclination to challenge this.
- 6) It mitigates against responsibility. The notion is that civil servants should *not* themselves become the face of policy. Carrying the can is not their job; they are vessels for others who make the policy 'higher up'. The problem is that those higher up do not carry the can for failure either.
- 7) It means that policy is increasingly set in a 'dictatorial fashion'. As various correspondents observe, it is always possible to find those ready and willing to act as apologists to give credibility to any decision made at the top of such a decision process. It has been quite shocking for this author to see politicians lauding certain groups and individuals on the one hand, whilst, on the other hand, there is a wide swathe of discontent across the malaria, vaccine, and global health communities, with equally low regard for these "policy experts/hacks" and anger at the way they have been allowed to "hijack" the policy and funding process in an area of science that they "do not understand and that they have never bothered to understand" (this is not easy to report, but it is a regular refrain, and is even toned down here). Other pharmaceutical players will think twice before risking being in a similar situation to GSK in the future, if this is what happens when a large pharmaceutical firm goes out of its way to work on neglected disease products.

**Why the policy of never discussing the negative possibilities, and the setting up instead of a straw man argument to get out of responding to specific arguments?**

Why has there been no desire to stress-test ideas? And why has there been a complete disregard for the inherent risk of major new policy initiatives? An International Relations colleague of the author explained that the US State Department deliberately did not plan for post-Saddam Iraq scenarios in order not to have to plan for bad scenarios, because they realized that sooner or later the fact that they were planning for bad outcomes (as well as for good outcomes) would get leaked to the press. So – no plan for *any* outcomes! Something similar has gone on in the processes being run to promote APCs. By not looking at potential problems, advocates of such schemes have been able to avoid having to reveal any possible problems to the politicians. However, it is not clear how one encourages private investors to invest in a new untried initiative that is still so full of unresolved issues and problems, the details of which no-one has even fully laid down yet (or bothered to investigate).

When it does surface, there has been no attempt to pick on the specifics of any critique directed at the APC logic, to try to disprove the logic being used in the critique. Nor has the response been to critically analyze the awkward practical issues being raised. As David Dobbs put it in an article in Slate: "Kremer's response to this critique is incomplete and unsatisfying. He and his co-authors attribute the Farlow group's criticisms to

ideological differences over whether market incentives have a place in public-health initiatives. In response to Farlow's practical beefs, Kremer says little... Kremer asserts that AMCs 'can ... be designed to create incentives for new products and competition.' But he doesn't say how. Instead, he simply restates criticisms he has made of the existing system for vaccine production that AMCs are supposed to address... At first glance, the AMC looks like the alphabet-soup option of choice. But its problems have proved terribly stubborn."<sup>976</sup> Maybe it is telling that Farlow and Farlow et al. have never received a single email or any correspondence complaining about the logic of the critique. The general approach has not been to set about exposing the faults in the logic of the critique (so, I dare say we will see no complaints about the logic in the chapters above about long-term supply problems, or the tradeoffs between goals 1 and 2, and nor will we see the cost effectiveness critique in Chapter 6 carefully picked apart), but to simply become more strident about the logic of APCs for malaria, HIV, and TB vaccines.<sup>977</sup>

Indeed, the response has been to repeatedly create a straw man argument out of the critique. When David Dobbs, wrote his negative assessment of the CGD proposal in his article in *Slate*, within a day or two Barder et al. had fired back a response, principally refreshing the straw man argument, previously (and regularly) used by Barder et al, that Farlow et al. had set up a straw man argument.<sup>978</sup> As Barder et al. put it: "Mr Dobbs suggests that the Advance Market Commitment proposal may be difficult to implement in practice... But the criticisms he cites are the result of a misunderstanding of what is proposed... the criticisms are of a proposal that nobody is making... a straw man." Once the straw man argument is knocked down, it allows Barder to declare, with no apparent sense of irony, that it "isn't what is proposed in the report of the CGD Working Group, so the criticisms [of Dobbs and of 'the Farlow group'] are well wide of the mark."<sup>979</sup> The straw man argument of the straw man argument allows Barder et al. to effortlessly avoid responding to the observation that their proposal would be "difficult to implement in

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<sup>976</sup> Dobbs, D., "Run-AMC: The latest idea in vaccine funding won't cure AIDS and malaria." *Slate Magazine*, 29 December 2005, [www.slate.com/id/2133355/?nav=fo](http://www.slate.com/id/2133355/?nav=fo).

<sup>977</sup> Light has revealed (see his forthcoming article) this reluctance to deal with awkward critiques. Light reveals that the extensive April 2004 Farlow paper (Farlow, A.W.K., 2004, *ibid.*) delivered to a few key individuals at CGD and the World Bank, was not circulated to any of the Working Group (including to Light himself) nor its presence revealed, for them to make up their own minds about it. However, Kremer and Glennerster's letter in the *Lancet* in December 2004 in response to this author's review (Farlow, A.W.K., "Over the rainbow: the pot of gold for neglected diseases." *The Lancet*, 2004, Vol. 364, pp. 2011–2012.) of their book *Strong Medicine* contained references to things only in the paper of the previous April – comments and ideas that had since been removed as the paper had been updated in light of feedback received. It seemed Kremer had been passed the April paper, even if none of the Working Group had. Enough of the 'this is not like a market' critique stuck to get the APC scheme – in self-defense perhaps – renamed an 'advance market commitment' in place of an 'advance purchase commitment,' even if most of the practical reasons that made an APC not like a market were ignored.<sup>977</sup> Incidentally, the Farlow review of Kremer, N., and Glennerster, R., 2004, began with the line: "Over a hundred people in developing countries will have died of infectious or parasitic diseases by the time you have finished reading this article."

[www.economics.ox.ac.uk/members/andrew.farlow/The%20Lancet%20%20December%20pdf%20version.pdf](http://www.economics.ox.ac.uk/members/andrew.farlow/The%20Lancet%20%20December%20pdf%20version.pdf). This subsequently appeared as the first line of the CGD report.

<sup>978</sup> See the Barder et al. 2005 response to the Farlow et al. critique.

<sup>979</sup> [http://blogs.cgdev.org/vaccine/archive/2006/01/slate\\_on\\_advanc.php#more](http://blogs.cgdev.org/vaccine/archive/2006/01/slate_on_advanc.php#more)

practice” referred to by Dobbs (and Farlow et al.) and it relieves them of any need to explain *how* a set of market-like incentives could ever, in practical reality rather than in simplistic models on paper, be created by an APC for malaria, HIV, or TB vaccines.<sup>980 981</sup>

This is even said while no attempt is made to check that “a proposal that nobody is making” is not in fact the only proposal actually being carried out. This happened, we saw above, with the Kerry-Lugar Bill, and with Gordon Brown’s interventions on behalf of GSK, and throughout much of the G8 process.<sup>982</sup> Incidentally, nobody has yet apologized for creating the myth, and repeating it several times in the media, that Farlow et al. deliberately “misunderstood” what CGD have been promoting in order to make their critique.<sup>983</sup>

### **The role of Brown**

The author has many times been told that Brown – these days the leading instigator of APCs – does not easily take advice from advisors when it goes against what he wants to do; he just ignores them, and this limits both their ability and their inclination to provide corrective advice in the first place. Certainly, there have been plenty of potential critical voices around Brown, if he would only listen to them.<sup>984</sup> Various correspondents observe

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<sup>980</sup> Farlow et al. *ibid.* simply had not had the time and resources of CGD to respond to the original straw man argument of Barder et al. – nor to the claim of “ideological differences” made simply to wiggle out of the Farlow et al. criticisms. I leave the reader to judge from this report what ideological position is being taken. If ‘ideological’ refers to a desire to have a workable mechanism and to avoid mechanisms that will fail and meanwhile waste a lot of time, then the author is very happy to be accused of “ideological differences”.

<sup>981</sup> Interestingly, at the most recent check (25 February 2006) the CGD report, *Making Markets for Vaccines*, was ranked 465,166<sup>th</sup> in Amazon.com books, but it has the highest, 5 star, average rating possible. This rating was based on one reviewer – from CGD itself – using the statements of Meles Zenawi, Prime Minister of Ethiopia, Tony Blair, Prime Minister of the United Kingdom, Senator Richard G. Lugar, Chairman of the U.S. Senate Foreign Relations Committee, and filling in the five star rating.

<sup>982</sup> One surreal instance (to this author anyway) of this non-involvement in the face of press releases suggesting otherwise, happened in the run up to the 2005 G8. Having discussed face-to-face with Treasury and DFID officials in London what was going on in the run-up to the G8, and arguing not to lock in the wording of any APC deal in any G8 announcements, and hearing them say that CGD’s idea was just one point on a spectrum of ideas under consideration, I found myself discussing with Owen Barder of CGD what our impressions were about what was ‘going down’ in thinking at the Treasury and DFID and what might happen at the G8, since Owen had himself had no contact with the officials involved for some while. Days later I was surprised to see CGD’s vaccine blog quoting what I had told Owen about what was going on, but as what officials in London had told him, with a suitable spin in favor of APCs.

<sup>983</sup> The day after *this* report was posted in its first preview version and the British newspaper the Times covered it release, it was highlighted on the Private Sector Development Blog of the World Bank as containing “valid objections”

([http://psdblog.worldbank.org/psdblog/2006/02/advance\\_market\\_.html#comment-13949526](http://psdblog.worldbank.org/psdblog/2006/02/advance_market_.html#comment-13949526))

Hours later, the *same day*, Owen Barder shot back, having not read the report, that “On the basis of the article in the Times, I am not sure how [name of another blogger] concludes that the objections are ‘valid’. Andrew Farlow’s previous objections have not been at all persuasive.” End of argument. Maybe one day Barder will apologize for alleging, in the mass media, that I had “misunderstood”, i.e. deliberately misinterpreted, the CGD argument, unfairly set up straw men arguments against it, and, now, it seems, written piles of ‘invalid’ arguments against what is being promoted.

<sup>984</sup> A copy of a Farlow paper, trying to put more balance into the debate, was delivered to Gordon Brown’s office via one of his closest advisors early in the process, before the chances for big errors might arise.

what a small circle Brown takes any advice from. Or maybe he has listened, but he knows that most of the public will not understand the intricacies of the problems of APCs and only see the simple underlying idea, and that even if pushing ahead will result in much inferior outcomes (or no outcome at all) compared to alternative approaches, it is a political winner and worth the risk?

One correspondent argued in Brown's favor, and blamed this outcome on the policy advisors: "Brown has probably got correct intentions but is wrongly briefed by some of his hacks, and they have been winning so much ground that even GSK cannot retract anymore." Another senior figure in global health likened policy consultants to a sectarian cult: "So why all this hype? It appears that the policy consultants have discovered a new market opportunity for themselves. It is the same as the one created by sectarian cults. They create a big artificial debate on an issue where the science is inconclusive and trap profile-hungry politicians." It could be argued, however, that if one does not want to be trapped and badly advised, one might just set up the institutions and processes of one's own advising so as to make it not happen in the first place.

### **11.10. Neglected funding for neglected diseases**

There have been various recent analyses pointing to the shortfall in funding for neglected disease drug and vaccine research and the need to boost it, with a figure of \$1.5bn-\$2bn over a few years suggested in various policy papers. It is rather telling that the PPPs that have done so much to revive work on neglected diseases have been heavily funded by, and are still surprisingly dependent on, philanthropic foundations and especially the Gates Foundation, but that now, challenged to take the baton, political leaders look for ways to avoid any financial obligation.

In the summer of 2005, CGD hung a case against Farlow et al. on the basis that they were unrealistic to believe that this \$1.5bn-\$2bn could ever be forthcoming. \$1.5bn-\$2bn seems a lot, but is well short of any APC figures being banded about, with the increased financial demands of CGD far outstripping the \$1.5bn-\$2bn. Recent G7 announcements suggest malaria, HIV, and TB APCs in the region of \$5bn-\$6bn *each*, even if they are ineffectual as R&D instruments, and on top of what the G7 Ministers now recognize will be a huge amount of additional push funding.

In light of these failures, Farlow<sup>985</sup> accused key policy advocates of undermining efforts to do something much more practically useful with the 2005 G8 opportunity. Practical action is not just about money either. It is also about the way we *do* things, given the amount of money available. Paradoxically, APC advocates have spent less time arguing about *how* we do things, than about how much we spend, even as they criticize others for unrealistic expectations of funds available.

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Apparently, at the time, it was received well, was "widely read," and it was felt that it might help policy makers to be a little less starry-eyed. It had no effect on Brown.

<sup>985</sup> Farlow, A.W.K., July 2005, *ibid*.

Imagine if the idea of APCs for HIV, malaria, and TB had not been available during 2005 – on the understanding that it will do nothing to help crack malaria, HIV and TB vaccines – and if, instead, politicians and finance ministers had been unable to use them as excuses to get themselves off the hook? With so much emphasis on Africa and poverty, politicians would have been bare without some way to deflect attention from their inaction. APCs were the ideal fig leaf. Political demand arose for them. Certain advocates were only too happy to oblige, rather than challenge what was going on. We ended 2005 with just the very notion of APCs for HIV, malaria, and TB holding up progress on real practical and financial action. Some recent advocacy efforts seem to have acted almost as political shock absorbers, neutralizing more challenging demands for practical and financial progress.

Indeed, there is a crying need to invest in a wide range of neglected diseases R&D (including malaria drugs R&D), well-implemented accelerated disease-control and prevention strategies, and public-health infrastructure, and much disquiet about the huge emphasis on spending fictitious billions on non-existent vaccines, when we have masses of underused products for all kinds of diseases.<sup>986</sup> Why the reverse priorities? Frankly, politicians should be judged by what they do and not what they promise, and we have seen very little progress on real practical measures.

At all turns, CGD have used none of their influence to argue strongly against the insufficient levels of PPP funding, nor helped to put legislation in place to help overcome this failure, nor challenged the plethora of other failures that lead to products going unused in developing countries. Indeed, those times when others railed against this failure, CGD used the complaint against them:

*“Yet Farlow et al. say, ‘previous promises from policymakers on funding for many of the components of the current mechanism have been betrayed.’ They say that ‘the public-private partnerships are estimated to need an additional \$1-2 billion over the next 2-3 years alone’... resources which do not seem to be likely to be available even on the most optimistic assumptions.”<sup>987</sup> (Observe how this quote indicates that CGD regarded APCs as substituting for PPPs and not, as they now claim, complementing them).*

Latest figures (released as this goes to press) show that over the recent 2-3 years, the US alone (so add to this the figures of other countries) spent \$226bn on Iraq. Yet \$1-\$2bn over 2-3 years for neglected disease R&D is deemed not “likely to be available even on the most optimistic assumptions”? Why have CGD not joined in complaining against this failure in priorities? It is almost as if to push too much for this failure to be rectified would have taken away too much from the novelty of the APC proposal and have gotten in the way of that particular ‘policy success’.

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<sup>986</sup> See Molyneux, D.H., Hotez, P.J., and Fenwick, A., “‘Rapid-Impact Interventions’: How a Policy of Integrated Control for Africa’s Neglected Tropical Diseases Could Benefit the Poor.” *PLoS Medicine*, 2(11): e336, <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10%2E1371%2Fjournal%2Epmmed%2E0020336>

<sup>987</sup> Barder et al. p3, referring to Farlow et al. April 2005.

### **11.11. The contrast with pandemic flu**

In late 2005 and early 2006, this reluctance to actually make ‘public’ funds available for neglected diseases (and to tackle faults that are not just financial, there being many other reasons for products being unavailable or undeveloped<sup>988</sup>) contrasted sharply with the quick creation of funds for pandemic vaccine preparedness – \$7bn by the US alone, with over a third of that being push-funding for pandemic vaccine R&D (well exceeding the neglected disease funding demands that CGD argued did “not seem to be likely to be available even on the most optimistic assumptions”). As this was going to press, the UN’s call for global funding for pandemic flu initiatives exceeded its \$1.5bn expectations by more than \$400m.

Outside of the Gates Foundation giving more money for neglected disease research, yet again the minimal \$1.5-\$2bn has still not been placed on the table by politicians. The willingness to entertain large APCs and to spend on pandemic flu push-funding but not to put these (relatively trivial) sums on a regular basis into PPPs for neglected disease research is telling. Instead of fighting this, it suited key APC advocates to feed the notion that similar such funding could not be created for neglected disease research, increasing the market niche for the APC idea instead.

### **11.12. The logic, but the dangers, of riding inappropriate policy instruments**

In December 2005, in the run up to the UK-chaired meeting of G7 Finance Ministers, several PPPs, including those for pneumococcal, rotavirus, HIV, malaria, and TB, were encouraged to sign a letter lobbying the G7 finance leaders to support APCs. One way to interpret this is that the term ‘APC/AMC’ has become so generic (and vague) that it can be used on several different levels, including as just a useful hook on which to hang a demand for more of successful strategies from the past. The author has also been told by some of those involved that it is really difficult *not* to go with such ‘stunts’ (as one correspondent described it) especially if all involved are the targets themselves of policy spin, and if there is a lot of mutual ‘getting-in-line’, leaving those who do not do so vulnerable to criticism. Others observe that any initiative, if surrounded by plenty of publicity that raises the profile of the issues – however bad the underlying idea – is treated as a good thing. The problem for PPPs, however, was that the Kerry-Lugar Bill had already ruled out many products from getting funding anyway, and the G7 Finance Ministers then proposed a ‘pilot’ APC that ruled out most of the rest of them for many years to come. Indeed there is already talk of ‘compromise’ such that most PPPs get nothing.

The July and December G8/G7 announcements, instigated no APCs for HIV, malaria, or TB, and Tremonti announced a pilot APC, with disease or diseases, supposedly, yet to be

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<sup>988</sup> This author is known for complaining about failures to prioritize funding for neglected disease R&D, but this runs the risk of creating the presumption that the answer is just about funding, when, in fact, there are a huge range of failures that are not just about more public funding.

selected (only ‘supposedly,’ since Brown has recently been heavily pushing malaria as a target for an APC, though it is increasingly less clear that he is getting his way).

**A ‘test’ case that is not a test case**

The February 2006 result was that: “Finance ministers from the G8 major industrialized powers, who met in Moscow over the weekend, expect to green-light a pilot project when they next get together, in Washington in April. Advised by the World Bank and other outside experts, G8 negotiators are working through the details, including which one of six developing-world killers should be the test case: HIV/AIDS; malaria; tuberculosis; pneumococcus, a source of pneumonia and meningitis; rotavirus, which causes fatal diarrhea in children; or human papillomavirus, a cause of cervical cancer.”<sup>989</sup>

If this author had to hazard a guess, he would suggest that the most likely result is that the G8 will go for either pneumococcal or HPV, initiating a financial instrument that will look nothing like what is being proposed for malaria, HIV, or TB vaccines, and an instrument that could have anyway been initiated without linking to the APC models being proposed for malaria, HIV, or TB vaccines. Several correspondents argued that this was the intent all along, and wondered why there had been a need to muddle-up procurement for pneumococcal and HPV (and rotavirus) vaccines with R&D for malaria, HIV and TB vaccines, given the dangers it created for the latter, and given that progress on procurement funding for pneumococcal or HPV could have been achieved without creating these dangers, divisions in the malaria community, delays for action on malaria, and general mess for malaria policy.

One of the core observations of the ‘Farlow literature’ however is that APC payments do not tend to go to the most challenging R&D outcomes. The latest twist of this logic would be if the first ‘APC’ attached itself to the disease problem of those available to it that faced it with the least challenge, with that disease then used to promote the notion of an APC ‘success’. As one correspondent put it: “I think we can safely assume that they’ll pick one of the existing vaccines that just needs a simple strain adaptation. Any lobbyist worth their salt would do this if they wanted to prove their idea ‘worked’ without really putting it to the test.” Indeed, nobody involved has articulated what would make a good ‘test’, or how to judge an application against a set of clear criteria, as if testing an APC was the last thing on anyone’s mind.

The author used to think that rotavirus would be a leading candidate for a ‘pilot APC’, but given the recent problems and high price of the two new rotavirus vaccines, politicians might veer away from this. Forced to make a choice between pneumococcal or HPV, one would hazard that the choice would be pneumococcal, the most probable target all along. However, this author was also advised by those involved in decision-making running up to the April 2006 G8 meeting to think what would be the ‘politically’ most appropriate ‘pilot’ project, and to stop thinking of R&D as the key issue. This, observed several correspondents, may make HPV the target for the pilot, with something non-APC

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<sup>989</sup> <http://web.worldbank.org/WBSITE/EXTERNAL/NEWS/0,,date:2006-02-13~menuPK:34461~pagePK:34392~piPK:64256810~theSitePK:4607,00.html>.

done for one of the early-stage products, probably malaria, on the understanding that HPV could not be targeted without anything being done for malaria. Given how much two companies had been fighting it out to develop the first HPV vaccine (GSK with Cervarix and Merck with Gardasil, and indeed submitting to the European Medicines Agency within weeks of the G8 making its April decision) this would prove nothing about the power of an APC as an R&D instrument for malaria, HIV, and TB vaccines.

Clearly most PPPs are going to get nothing quick out of this effort. One wonders what will happen as it dawns on some that they have been manipulated to push something that benefited others (including, in particular, politicians and policy advocates), when they themselves got nothing out of it, and when the effort has even dislodged genuine progress for their initiatives at a time of unusually high opportunity. The creation and use of this large policy hammer to crack what should have been a manageable policy nut, was all pretty transparent and predictable from a long way out.<sup>990</sup> Indeed, the complete predictability of the result from a year or two out at least, lead one senior figure to quip: “Too bad Federico Fellini had the bad taste to die. He could make a movie out of this.”

#### **A use for pneumococcal and rotavirus?**

One other possibility for explaining this PPP support is that some of those lobbying for pneumococcal, rotavirus, and HPV – maybe realizing that this particular bandwagon was going to run and run – came at some point to understand that, nevertheless, it might be possible to go along with the push for APCs for HIV, malaria, and TB as a tool for launching something for diseases of more immediate interest to them, if not of much interest to politicians. Some policy advocates (including within UK institutions working on policy for the 2005 G8) openly explained to this author that they were riding the push for malaria and HIV APCs in the hope of repositioning for late-stage vaccines instead. The reasoning was (in words used to the author) that “politicians have no interest in most diseases of the poor,” but they all know about and “seek kudos” from “apparently tackling” HIV and malaria. So, a scheme is launched to ‘pilot an AMC/APC’ for a late-stage product that already exists, when the ‘AMC’ scheme is actually a large procurement fund for a product that already exists, with none of the features specific to AMCs/APCs as discussed extensively in this file, and with the ‘easiest’ late-stage product picked off.

In many ways, going with the flow is quite a rational strategy. A similar strategy happened with IFFIm. There was no particular need to use an IFF mechanism (which failed in all other respects to attract interest) for immunizations – it is just one of several possible funding mechanisms, separate from immunization issues, with the funds having to be paid back later from overseas aid budgets or even just rolled over to future tax payers – but the political constraints dictated that it was possible. In particular, the UK Treasury had spent a lot of time working on the IFF. It was failing to attract support. The ability to link the IFF to immunizations in part helped to save political face. At least this was a worthy use of an otherwise failing proposal, with the caveat that politicians do not then use immunizations to serve the greater IFF push, and not the other way around – a

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<sup>990</sup> See Section III of Farlow et al. April 2005, though we still await which of the three possibilities suggested there get picked.

danger that is already becoming apparent in political pronouncements about the IFFIm. The saving face of an APC should not involve something much less worthy than the saving face of the IFF, namely the pushing through of a low efficacy malaria outcome just to get a ‘success’.<sup>991</sup>

Both the IFFIm and an AMC/APC for a late-stage product also share the same danger that critical analysis of the underlying idea is harder to make and more difficult to get on target. In particular, it is very difficult to criticize the IFF without it now harming immunizations, or to criticize the logic of an APC/AMC without it now generating seeming criticism on to the late-stage vaccine endeavor. This is a silly way to set things up in a world that is already fractious enough as it is.

### **Stopping the policy bandwagon at the right moment**

Given the ease with which the APC notion can be used to mean ‘all things to all people’, it can be used for various aims so long as details are not too heavily spelled out to politicians, and so long as advocates can time the stopping of the bandwagon before it is too late. A common intent amongst a lot of critics (including this one) was not to upset things too soon, given that sometimes – on account of the recalcitrance of politicians or simply the reality of the political constraints on politicians – something genuinely good can come out of exploiting interest in something that is not so good or may not actually be used, even if there would have been other and better ways of bringing about the same result.

Nevertheless, given the big dangers to malaria, HIV, and TB, there will at some point come a need to switch back to more sensible policy on malaria, HIV, and TB vaccines. There is a political balancing act, a careful timing issue, that requires not getting too locked in, but leaving enough room to reposition policy in a saner direction at the right moment and before it is too late. This strategy<sup>992</sup> can be based on four observations:

- 1) There is no point fighting an idea with a huge amount of momentum, and where the temporary political ‘need’ to have the idea as a ‘political fix’ is very strong. Critical observations simply end up looking as if they are lost as the idea continues to march ahead.<sup>993</sup> Many who are otherwise highly critical, will (perfectly altruistically perhaps) ride the idea anyway just in case they can get something out of it;
- 2) Good outcomes can still come out of misinformed ideas. If pneumococcal and rotavirus initiatives, for example, can use the push for an APC for malaria, HIV, and TB, to their advantage – even if pneumococcal and rotavirus do not use an APC themselves – then this outcome should also be taken into account in a

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<sup>991</sup> Observe, yet again, that this is an investment issue. This must not even be entertained as a possibility. Constant allusions to the acceptability of even just 30% efficacy is bad for investors in general.

<sup>992</sup> Certainly the strategy of this critic.

<sup>993</sup> There are also limited resources too. When Barder et al. responded to the Farlow et al. critique of the CGD report, Farlow et al. simply did not have the time and energy to respond.

- critical response, and in timing of that response. The point is not to win an argument, but to get a practical result;
- 3) At some point, momentum will be lost, and then the critical arguments can be brought to the fore. When most PPPs realize just how little *they* are going to get out of the APC effort (and how much they have been manipulated by a tiny handful of individuals) they will also think more carefully about what an APC actually is, and be more receptive to critical ideas, and alternative solutions. As the problems in the original idea become ever more apparent, the environment will become much more receptive to exploration. The only offsetting danger is that a lot of time, and effort is diverted away from other more useful activities, and one-off opportunities (such as various G8 meetings) are lost;
  - 4) The “danger of a bad outcome” can itself be used to get good outcomes. An HIV APC that is damaging to ‘big pharma’ and Russia, China, India, and Latin America can be used to encourage these companies and countries into exploring and practically supporting better alternatives.

### **11.13. GSK: Dammed if they do, dammed if they don't**

We saw earlier that there is a rather complicated debate about RTS,S that is tough to adjudicate. Indeed, this is what one might expect at what is still a very early stage of development. Is the effect that seems to have been picked up mainly an aspecific immune stimulation because of the very potent adjuvant? To what degree does this matter anyway? Might any eventual product still be useful? Are the Alonso et al. studies suggesting that the vaccine permitted the more rapid onset of naturally acquired immunity, such that this would explain the 21 month efficacy figures? Or are children being denied some longer-term benefit? Will efficacy be high enough in very young children in less-idealized settings than those of the trial? Was the study well done, as some say, or faulty as others claim? Are the claims made on the basis of the data robust, or are they much less well backed-up by the data than originally claimed? Can something useful be built off this, or will nothing come out of it in the end?

There is disagreement about what the statistics are saying too (on top of already wide confidence intervals). While Alonso et al. suggest that the “observed vaccine efficacy results from an interplay between cellular and humoral immune responses induced by the vaccine,” (though they did not measure it) even some of those who support the 18 month findings suggest that the Alonso et al. explanation is possible but highly unlikely – and several correspondents complain that Alonso et al. made no attempt to measure this anyway, and do not have the evidence to make any such claim.<sup>994</sup> Certainly more

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<sup>994</sup> Given the contentious nature of some of the evidence and the way it has been used heavily to lobby for certain financial instruments to be put in place, it is interesting to note Alonso et al. state (2005, *ibid.*) that: “The sponsors of the study were involved in study design, data analysis, data interpretation, and writing of the report.” Several correspondents responded to this, especially given that it relates to involvement that took place after GSK had negotiated an APC arrangement with Brown and the Gates Foundation. One commented that: “This is quite alright. Sponsor will normally be involved in design, analysis, interpretation

research will show. Till then the evidence so far is very uncertain and tells several possible stories. Perhaps, in more sober times, the results would have been treated as still provisional, subject to wide and open debate that would not be seen as threatening to policy objectives, instead of being the stuff of dramatic political pronouncements?

The issue now for GSK is the likelihood of getting much more than 20%-30% impact in the field, in the relevant populations of interest, and as part of the EPI, such that – given the need to have practically all the same non-vaccine interventions in place as before – the marginal impact of using a vaccine based on RTS,S/AS02A in the field is not way too low to justify distorting funding in its favor? What if the vaccine cannot be fitted into the standard childhood package of vaccinations? What if the adjuvant is maxing out already?

If there is some positive marginal benefit from using RTS,S/AS02A, the judgment call will then be how to trade off near-term and far-term mortality. What if RTS,S/AS02A can save lives (but maybe at high costs if it is supposed to be superseded and capacity is therefore too small to drive low average production costs), but the investment to make it happen would use up a large chunk of limited resources and delay development of a much better vaccine that could save more lives? There is already wide-ranging disquiet, in spite of increased levels of activity over the past five years, at the underfunding of a wide array of alternative vaccine proposals, and the poor take-up of current interventions.<sup>995</sup> There seems general astonishment in the drugs R&D and health communities that certain policymakers seem willing to jump in with multibillion dollar promises for products showing marginal but still highly uncertain impact, while continuing to starve known and proven products of decent levels of funding.

Finding the formula that will save the most lives cumulatively will be a tough job. That is why, knowing the scientific possibilities *has to* interact with the economic instruments used. In the circumstances, one should be very careful that the use of instruments (including to satisfy political ambitions and credibility already put on the line by past promises to use certain instruments) do not bias this solution. In particular, if 25%-30% absolute affect is too low to generate much of a marginal impact given that all other control measures have to be in place, how does one hold off on what turns out to be the low efficacy product – and, for the sake of other investors and funders, how does one communicate this to investors in advance? A *pre-sunk subsidy* fund does not seem the most obvious solution to have in place.

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and writing.” Another pointed out that the design of these studies is tough, so, within reason, the wider the input, the better; but that “despite this, the design was not perfect and they are open to criticism.” Another argued: “I would say this is unusual but not rare...it’s a good thing to have funders who are competent to participate and are engaged. Of course, one could argue that there could be a conflict of interest. I understand that some elements at NIH take this view.” One more skeptical voice observed that: “Sponsors being identified as having had a role in the design and results production of a study is a better way to inform readers that the study is likely to be biased towards the interests of a group with interests other than merely science than not disclosing this, as was the case for a long time [in earlier reported findings].”

<sup>995</sup> One can pick up some of the debate at: <http://allafrica.com/stories/200511180757.html>.

### **So what about GSK**

So what about GSK and an APC? The whole point of an APC is to encourage (indeed, to force) private developers to use their own private sources of finance to do vaccine R&D. Yet GSK must know that if the efficacy of their current lead candidate ends up even as high as 25%-30% – indeed, an intermediate range might be especially awkward for GSK – the best global strategy of funders is to invest much more in vaccine candidates that seek to destroy the market for the GSK vaccine. Yet, by accepting an APC early, GSK would be forced to ramp up private funding into the RTS,S/AS02A vaccine given the extant APC.

Indeed, if a malaria APC was as powerful as proponents claim, GSK would by now be using their own finances. Knowing the amount of APC that would have to be removed to account for push funding (a large *multiple* of anything GSK now gets from the Gates Foundation) there would even be very strong incentives to refuse any further Gates push funding. GSK would have viewed the APC as great news and wanted to respond by investing its own money. So why did GSK take another big chunk of Gates money instead? And why has GSK not taken on the entrepreneurial risk that it should have in the light of an impending APC? MVI even states that the Gates money is to “to complete development of the RTS,S vaccine.”<sup>996</sup> This hardly suggests that an APC is being used to force GSK to take the entrepreneurial risk. Is the Gates Foundation going to contribute the same level of funding for every vaccine lead that reaches a similar level of efficacy/duration, so as to maintain the integrity of the APC and keep all private firms on an equal footing? One can only presume that if the APC contract is set up badly enough, GSK could be incentivized to continue using large chunks of PPP funding, then (in the expected sense) to claim APC funding, even if this harms all *other* vaccine players, the overall vaccine endeavor, and the expected quality of any vaccines generated.

### **GSK are dammed if they do, dammed if they don't**

GSK is alone amongst big pharmaceutical companies in supporting the notion of an APC for malaria, HIV, or TB vaccines. This author has come to conclude that, once it actually comes to understand what an APC actually is, GSK will come to regret being dragged in to promoting it.<sup>997</sup> In truth, for large pharmaceutical firms like GSK, there is a dammed if they do, dammed if they don't mentality to APC schemes.<sup>998</sup> If this were a true market and not a committee-run subsidy scheme, firms could choose whether or not to respond. If they thought the market was too risky, or distribution systems too inadequate, or if they thought their product was too poor, they would not invest their own resources. But firms know that they will be dammed if they do not respond to the dangling of what the public will see as highly 'generous' malaria, HIV or TB vaccine APCs, even if these are never-before used, badly set up, and poorly run and very risky schemes, and may even be set too small purely for political expediency.<sup>999</sup> Yet private firms are supposed to respond in

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<sup>996</sup> [www.malariavaccine.org/files/060124-Benin-Decision-Making-Meeting.htm](http://www.malariavaccine.org/files/060124-Benin-Decision-Making-Meeting.htm).

<sup>997</sup> Of course, it may be that what is enacted looks nothing like the APC being promoted. But that, in fact, will also be bad for GSK.

<sup>998</sup> Though probably much more so for malaria and HIV than some other situations, and much less so for products closer to market.

<sup>999</sup> IAVI has been proposing an APC for HIV vaccine(s) with present discounted value of \$3bn (supposedly to cover all needed HIV vaccines too), with even this worked out on the basis of very low financing costs,

large numbers, sign on and be monitored,<sup>1000</sup> and use large amounts of their own money (see the latest IAVI briefing describing all of this for HIV<sup>1001</sup>) by a scheme that will punish them if they do not “invest enough”. If firms do not respond, how will that look?

And yet firms stand to be equally dammed if they do respond, by being forced to rent-seek the committee running the scheme in order to get a fair outcome, or risk being damaged if the scheme collapses down to supporting one firm at most, or even just collapsing after a few years, with no mechanism in place to compensate them for this failure.

### **Think of the financial risk**

Even in the case of a firm with a potential product like GSK, all that any GSK finance person would see, when trying to get their head around what is being proposed, is very high risk. The global ‘solution’ is seeking to remove the market for their product if efficacy after the next few rounds of trials indicate struggles to get the efficacy rate higher. So, they have a product that may never take up the offer of the APC if it proves unable to achieve useful efficacy, yet they will look as if they only bothered when a \$5bn-\$6bn APC was dangled their way on top of the further \$107.6m Gates gave to push it forward – losing all reputational advantage of their neglected disease research. They also run the risk of being linked to a political process that is being heavily manipulated in their favor, to the detriment of other vaccine developers and, indeed, non-vaccine alternatives, even if they ultimately get nothing out of it. Or they get backed into a corner, forced into either privately funding further work and even supplying a low-efficacy vaccine against their better judgment (and suffering for doing so), with most of the APC payment possibly going on high costs. Or they refuse to do any further work or to supply in the face of advocates pushing to go ahead on the basis of the ‘generous’ extant APC.

GSK may still fall short of a vaccine fit for the intended target of, mostly, very poor infants. The nightmare scenario would be that GSK still come up with a useful product for military purposes (perhaps a product based on the adjuvant, given that malaria is a very good environment for testing platform technologies), and somehow will have to resist pressure to pay for further development work for infants so as not to ‘look too bad’. But this runs just as much reputational risk.

### **Tarnishing better applications**

Since the devil is in the detail, and things can be set up good and bad, and be applied to inappropriate cases as well as more appropriate cases, there are possibilities also that bad publicity and failure on bad applications come to tarnish better applications. For example, if APCs go through just for malaria and HIV in the near future, what happens if the HIV

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and ignoring all costs of product development. If HIV developmental costs are fantastically higher than typical, the IAVI figure is way too low.

<sup>1000</sup> Though, in reality, would not large companies like GSK avoid most of the monitoring required of an APC?

<sup>1001</sup> IAVI even make grand claims about the analysis they ‘did’ even though they rely heavily on the same people working on the CGD endeavor.

one motivates trivial (if any) private investment, and becomes a complete institutional mess? Or really difficult issues start at last to get proper attention (and even media coverage) and this leads to problems? What happens if all the presence of a malaria APC does is force a distorting subsidy to a low-efficacy malaria vaccine, to cover the high manufacturing costs but doing nothing to draw private finance into malaria vaccine R&D, and all the malaria drugs people moan at the way it is distorting away from better solutions such as combination drugs for mass use in Africa (a couple of hundred million dollars maximum per year, and yet \$6bn promises for low-efficacy vaccines), and other malaria vaccine developers complain at their funding problems.

Worst of all, if after all GSK's efforts (and risks) in getting involved in neglected disease research, should GSK come off badly from this kind of behavior, it will generate long-term damage and harm any desire of other firms to engage in such efforts, and to take such risks, themselves. Why did GSK alone decide that this was a suitable way to proceed for them?

One correspondent observed that the interest in APCs stems in part "from the earlier complete crisis in HIV vaccine research when all NIH and company efforts were faltering; an APC [for HIV] becomes suddenly a more attractive instrument if based on a vaccine model where some progress could be evidenced." If so, what kind of impact would an over-hyped but failed APC for malaria have on the goal of HIV vaccine development? And what problems has GSK brought on for other companies?

Given all these looming issues, GSK would have done better to have gone with the PPP format. In a later section we will see that GSK largely fell in to the trap of agreeing to support the notion of an APC instead, persuaded by Gordon Brown that it would be a good idea, and bounced into sticking with it once Brown had made several very public announcements about the arrangement before they even had a chance to properly think it through, but that Gordon Brown in turn was a victim of the policy process.<sup>1002</sup> One of the main authors of the CGD Report, having expressed strong reservations about the idea of applying an APC to malaria, HIV, or TB, nevertheless also explained in detail the need to appeal to Bill Gates<sup>1003</sup> *personally*, and that this author needed to understand this. In the end, when Brown locked in a big-gesture announcement for malaria, the key APC

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<sup>1002</sup> Others tell the author that senior GSK figures only have themselves to blame because they regularly use the threat of their ability to relocate pharmaceutical activity abroad to extract favorable treatment from politicians.

<sup>1003</sup> Incidentally, before the reader gets the wrong impression, I do not wish to cast any aspersions on Bill Gates personally who has done far more than *any* politician to spur work on vaccines and health products for the poor, and who I regard as simply being badly advised and lobbied on certain issues. And the person in question may well have been working towards their *interpretation* of what they *thought* Bill Gates would like, whether or not they had understood that correctly (The reader will guess that I do not think Gates would want this particular policy initiative, if it were ever properly explained to him, rather than wrapped up in a big sugary marketing exercise). The discussion painted a vision of very intimate hands-on decision making over funding flows by Gates personally. But, again, one does not know if this is true or simply to impress the listener (namely this author). Of course, what a person such as Bill Gates needs to be told and what others think he or she needs to be told are two different things. Sometimes being a true friend involves saying something that the other does not want to hear or something that is less serving of one's own interests. Bill Gates is probably just as much a victim of advocacy efforts and spin as anyone else.

advocates recognized that instead of warn of the dangers, they could provide what was needed to support it.

#### **11.14. Detailed malaria vaccine R&D analysis on the horizon: Why the rush?**

There is a great deal of work on the horizon analyzing real-world evidence on the progress on malaria vaccines, and ways to improve finance to speed their progress. For example, the Pharmaceutical R&D Policy Project (PRPP)<sup>1004</sup> at the LSE, under the direction of Mary Moran, has recently been given a large grant to run a malaria clinical trials project to:

- 1) Quantify the funding needed to conduct clinical trials of new anti-malarial products, including trial capacity building and project costs for Phase I-IV trials (e.g. trial size, duration, epidemiological spread, etc.), and industry inputs needed to support malaria product trials (e.g. CMC, process development, manufacturing capacity etc.);
- 2) Look into the efficiency of clinical trials of neglected disease products (public, private and partnered);
- 3) Determine how resources for these trials should best be allocated;
- 4) Develop a coordinated mechanism/s to deliver these resources; assist with implementation of the chosen mechanisms; look at regulatory options, and so forth.

Yet, there seems undue haste by some to push to permanently lock in approaches even before much more of this evidence is revealed, and before even those seeking to lock in such mechanisms have any evidence of their own on how to set the terms. We should all be urging policy thinkers to take note and act on the PRPP evidence when it is eventually available (and be critical of it too, where appropriate).

At a time of maximal political possibility – with a G8 emphasizing the problems of Africa, UN meetings emphasizing development goals for the poor, bills such as the Kerry-Lugar being presented to the US Senate – hardly a fresh cent of public (as opposed to philanthropic) funding has been made on boosting the one thing that has been doing most to progress vaccine development, the various vaccine PPPs. And not a great deal of thinking has been devoted to the potential successes and failures of these approaches either. These approaches have been operating on a shoe string, and yet, the first time any seriously large sum of money is proposed, the strongest lobbying effort is absorbed in ‘potential’ instruments like APCs.

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<sup>1004</sup> [www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm](http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/researchProjects/pharmaceuticalrandd.htm).

### **11.15. The overuse of the word ‘potential’ and other verbal obfuscations**

This paper has shown plenty of economic reasons to doubt that APC subsidy schemes in the cases of malaria, HIV, or TB, would be as powerful as claimed, and hence a cost-effective way to incentivize R&D into these vaccines. We find repeatedly that little evidence has been presented that such schemes are capable of generating sufficient competition between developers and manufacturers or sufficient willing private capital into R&D. Neither is it obvious, when used as R&D devices, that they are particularly good for the one or two firms who may, if ever, find themselves subject to them, given the reputational and other risks.

Given the high stakes, there is some onus on those promoting the ‘power’ of such schemes to at least attempt to quantify and justify the claims of industry response. Instead, concrete evidence of ‘strength’ has been replaced with allusions to ‘potential strength’. Here is a selection:

The G8 Finance Ministers said: “We recognise also that advance purchase commitments (APCs) are *potentially a powerful mechanism* to incentivise research, development and the production of vaccines for HIV, malaria and other diseases.”<sup>1005</sup> Why did they need the word “potentially”?

CGD argues “A guaranteed market enhancement like advance contracting *could* unlock innovation today...”<sup>1006</sup>

Berndt et al. observe that “under a large range of values, a vaccine commitment *may be sufficient* to stimulate substantial research *towards* a malaria vaccine,”<sup>1007</sup> (though Berndt et al. also admit that “it is difficult to know how much a vaccine commitment would speed up vaccine development”<sup>1008</sup>).

Kremer says that: “*Potentially*, advance purchase commitments could be used to encourage research not only on vaccines, but also on other techniques for fighting disease,”<sup>1009</sup> and that, “*if successful*, millions of lives will be saved at very low cost.”<sup>1010</sup>

Barder et al. state that “there is no single ‘correct’ value for the market size, but rather a range of values within which an advance market commitment would be *likely to accelerate* the development of new vaccines.”<sup>1011</sup>

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<sup>1005</sup> [www.hm-treasury.gov.uk/otherhmtsites/g7/news/conclusions\\_on\\_development\\_110605.cfm](http://www.hm-treasury.gov.uk/otherhmtsites/g7/news/conclusions_on_development_110605.cfm). Part of point 6.

<sup>1006</sup> CGD, April 2005, *ibid.* p94. With respect to the ‘market enhancement’ phrase, see also sections above on ‘crowding out’ and long-term supply issues.

<sup>1007</sup> Berndt et al. 2005, *ibid.* p25.

<sup>1008</sup> Berndt et al. 2005, *ibid.* pp. 23-24.

<sup>1009</sup> Appendix 7, p39, No. 10 Policy Unit website, [www.pm.gov.uk/output/Page3704.asp](http://www.pm.gov.uk/output/Page3704.asp). The financial community might like to think what CAPM might say about a range of uses of such a mechanism all at once (there are both reputational advantages and disadvantages).

<sup>1010</sup> Kremer, M., *The Lancet*, 2005, Vol. 365, p753.

Tremonti claims that APCs “have the *potential* to dramatically accelerate the development of and access to life-saving vaccines,” though he provides no evidence of even likely response in the cases of HIV, malaria or TB (or any other vaccine), and even argues that “it is not known when, and possibly *even if*, the commitment... will become effective,”<sup>1012</sup> and uses phrases like “*if it succeeds...*”<sup>1013</sup>

Zandonella says that “AMCs *might help* vaccines reach developing countries sooner,”<sup>1014</sup> and that “AMCs *might help* vaccines reach developing countries sooner...”<sup>1015</sup>

Regarding what we already saw was a pretty meaningless way to set overall size of APC subsidy, Berndt et al. all state that “the mean sales revenue *may provide* a more reliable estimate of what level of expected revenues *may be effective in spurring industry investment*,”<sup>1016</sup> via an ‘advance market commitment’ that would be “*likely to* accelerate the development of new vaccines.”<sup>1017</sup>

The Tremonti Report (that we know has large sections written by the same authors as all previous material on this) claims that work done so far “shows that a viable legal framework to implement the APC approach *can be devised* [since it hasn’t been yet] to accommodate delegation arrangements between donors and entities acting on their behalf,”<sup>1018</sup> and that AMCs are “*likely to* increase R&D.”<sup>1019</sup>

Alonso et al. adopt a similar technique, by suggesting that: “Our results *indicate the feasibility* of development of an effective vaccine against malaria,”<sup>1020</sup> and not that in fact it could be done.

A DFID briefing note (though there is no evidence who wrote it) says: “The work undertaken by the Centre for Global Development has established that, *in principle*, APCs *could* work.”<sup>1021</sup>

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<sup>1011</sup> Barder et al. 2005, *ibid.* p8.

<sup>1012</sup> Tremonti, G., 2005, *ibid.* p13.

<sup>1013</sup> Tremonti, G., 2005, *ibid.* p13.

<sup>1014</sup> Zandonella, C., 2005, *ibid.* p19.

<sup>1015</sup> Zandonella, C., 2005, *ibid.* p19.

<sup>1016</sup> Berndt et al. 2005, *ibid.* p7.

<sup>1017</sup> Barder et al. 2005, *ibid.* p8.

<sup>1018</sup> Tremonti, G., 2005, *ibid.* p17.

<sup>1019</sup> Tremonti, G., Background Papers, 2005, p1.

<sup>1020</sup> Alonso et al. 2004, p1419.

<sup>1021</sup> DFID, June 2005, *ibid.* p3. What sort of a claim is: “In principle, X *could* work”? Later, the briefing note asks: “Are there any risks to the use of APCs and who bears them?” to which the answer is: “In principle these are issues that can be resolved with the efforts of all,” p5. It asks “Will APCs benefit developing country manufacturers and biotech as well as big pharma?” A very serious question. Amazingly, to numb a potential criticism of a ‘bias’ in the way the scheme would work, it answers: “Market pull benefits everyone who can take advantage of it. Most of all it benefits the children who receive vaccines sooner.” p4.

The Tremonti Report gets around every potential problem with suitably obfuscatious language – such as ‘by designing the AMC terms appropriately,’<sup>1022</sup> and the “terms would have to be designed”<sup>1023</sup> and “can be designed”<sup>1024</sup> to deal with each problem – without ever actually giving any examples of how, in practice, it *would be* designed to deal with each problem.

Some journalists too have gotten into the habit of simply repeating what they have been told, rather than doing the investigative journalistic thing and challenging for facts: “A novel incentive called an Advance Market Commitment *could help* spur private sector investment in AIDS vaccine research and development...[It] *could provide* the motivation that industry needs...”<sup>1025</sup> And try: “Advance commitments to purchase *may create* the incentives that inventors need to pursue active research.”<sup>1026</sup>

The use of the words and phrases like ‘potential’, ‘potentially’, ‘promising’, ‘indicate the feasibility of’, ‘in principle’, ‘could work’, ‘if successful’, ‘likely to’, ‘might help’, ‘may provide’, ‘may be effective’, ‘may be sufficient’, ‘a breakthrough...that...might be possible’, ‘could unlock’, and ‘could help’ allows for the illusion of a very strong claim to hide behind what is actually a very weak claim, and allows those promoting the claim to get away with providing little evidence to back up the claim.

What evidence did the leaders of the G8 see before making their “potentially a powerful mechanism” claim? And why did Russia agree to support something harmful to its own interests? Or did the word ‘potentially’ let G8 leaders off the hook of having to back the claim up? Read the G8 statement without the word ‘potentially’ for the stunning claim they avoided making.

Not all were quite so obfuscatious however. Nancy Birdsall, testified to the Senate Committee on Foreign Relations that an APC subsidy scheme for malaria and AIDS was

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<sup>1022</sup> Tremonti, G., 2005, *ibid.* p8.

<sup>1023</sup> Tremonti, G., 2005, *ibid.* p7.

<sup>1024</sup> Tremonti, G., 2005, *ibid.* p8. Observe how these three quotes were gathered within a page of each other.

<sup>1025</sup> Zandonella, C., 2005, *ibid.* Subtitle of article and line in text.

<sup>1026</sup> Comment, *The Guardian*, “Not just for profit, or not just?” Friday November 4, 2005, [www.guardian.co.uk/birdflu/story/0,,1627785,00.html](http://www.guardian.co.uk/birdflu/story/0,,1627785,00.html). This is yet another article in which ideas and concepts are completely mixed up, confused, and trivialized: “The idea behind advance purchases is deceptively simple. Governments use their bargaining power to secure bulk discounts from manufacturers and sell or distribute the drugs later to needy countries at prices those countries can bear...Advance commitments to purchase may create the incentives that inventors need to pursue active research. Thomas Schelling, who won the Nobel Prize for Economics this year, wrote about the value of precommitment. The idea has been fleshed out by Harvard's Michael Kremer and by economists at the Centre for Global Development in Washington. Kremer's research has shown that even at \$40 per immunized person, vaccines against malaria and HIV would be cost-effective in poor countries. But because private firms don't expect to receive even a tenth of that amount in the form of revenue from those countries, they have no incentive to develop vaccines. Kremer argues that governments or private foundations can step in, make an advance commitment to purchase a certain quantity at a particular price, if it were invented...‘This is highly cost-effective relative to other health programmes,’ Kremer writes in an academic paper clarifying his concept. Such a purchase commitment ‘would be highly cost-effective even if it covered vaccines that departed significantly from the ideal,’ he adds.” If this sort of reporting does not depress you, nothing will.

“simple yet powerful.”<sup>1027</sup> For an untried instrument, riddled with problems, this is a strong claim.

**Hiding behind weak language suggesting something much stronger**

The word ‘potential’ could be used to describe just about all malaria treatment and control options. Its use here avoids facing the huge problems and costs of turning ‘potential’ into a reality, and ignores any need to consider any underlying budget constraint (there always is a budget constraint when trying to improve the lot of the poor).

This report is studded with a series of remarkable claims taken from the recent literature – too many to repeat here – yet descriptions of deep faults in much of the analysis, especially the economic and financial analysis. We really must start to at least try to more honestly quantify some of this, especially if, meanwhile, such exaggerated claims run the very real risk of encouraging the current heavy budgetary pressures to cut vaccine and other R&D or to redirect funding to other vaccines (such as for bioterrorism projects) or to fail to increase funding to currently more powerful vaccine R&D approaches.

Perhaps the most brilliant verbal obfuscation of all was to re-brand ‘Advance Purchase Commitments’ as ‘Advance Market Commitments’, at a stroke commandeering all the intellectual kudos and psychological weight of the ‘market’ to an essentially statist instrument.

**Hiding behind non-experts who make ‘expert’ claims**

Another part of this obfuscation has involved encouraging non-experts to make expert claims, that a proper expert in the underlying economics or finance would never have dared to make. We saw, above, the way Zandonella was encouraged to make all kinds of uncritical remarks in support of the CGD/Berdt et al. cost-effectiveness methodology. Zandonella completely avoided facing up to the way CGD/Berndt et al. had ignored the costs of developing vaccines, and she treated their ignorance of risk and capital costs as if it was a virtue. Above, we extensively explored the claim, made by John Hurvitz, a lawyer, that “manufacturing costs will not be an issue,” and showed using simple economic logic that it was wrong. Why was Zandonella asked to write about finance and economics by IAVI? Why was Hurvitz put forward to make unsustainable economic claims on behalf of CGD? Why was Nancy Birdsall allowed to inform the US Senate that long-term malaria, HIV, and TB vaccine price would be \$1 per course, when we know that we have not the slightest shred of evidence that this is true, and given that this price is, as we saw in Chapter 6, itself a huge practical issue in its own right (and within months, long-term price was \$6 in policy papers anyway)?

Indeed, there is no evidence that even one properly trained finance expert has gone through the proposal, a proposal that is essentially of a large and complex financial instrument pitched at financial markets. If financial experts had been more involved instead, the very notion of ignoring capital (i.e. finance) costs, option-pricing based

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<sup>1027</sup> Nancy Birdsall, Reflections on “Our Common Interest,” The Report of the Commission on Africa Testimony for the Senate Committee on Foreign Relations, [www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf](http://www.cgdev.org/doc/commentary/BirdsallTestimony050517.pdf), p5.

finance costs, and any analysis of the ‘mechanism risk’ and hence financial risk, of the APC scheme itself (not to mention R&D costs) would never have got through.

**A few for the reader to try**

Hopefully, by now, when the reader sees something like the following: “The commitment creates incentives for firms to produce vaccines quickly and at the highest possible level of efficacy, and also encourages subsequent innovations which can enter the market and earn a return on their investment, by allowing demand to switch to those products as soon as they are available,”<sup>1028</sup> they will be able to spot at least 7 unfounded claims. Then they can try: “By selecting carefully the combination of price and quantity (which make up the market revenue guaranteed by the commitment), the sponsors can decide the extent to which they wish to focus the incentives on early discovery of a new vaccine, and the extent to which they want to use the commitment to reward the developers of subsequent improvements,”<sup>1029</sup> for a few more. And how about these: “The AMC replicates the incentives that produced almost all the drugs on the shelves in one’s local pharmacy;”<sup>1030</sup> and “it unleashes the *same* combination of *market incentives* and public investment that creates medicines for diseases that afflict us [i.e. the rich].”<sup>1031</sup>

Maybe, after reading the cost-effectiveness chapter above, the reader can spot the similar vacuity of the logic contained in the following too (this time in the case of HIV, with emphasis added, and notice the way a HIV vaccine is seamlessly equated with an APC/AMC): “If AMCs can pull research and accelerate development of a vaccine they will prove their worth. Over the next ten years, the \$3 billion price tag for stimulating the AIDS vaccine market will look like a bargain in comparison to the cost of providing antiretroviral (ARV) therapy to infected persons in developing countries...IAVI calculates [using CGD figures] the cost-effectiveness of an AMC [of \$3bn] to be between \$21 and \$67 per saved disability-adjusted life year (DALY)...At this rate, investing in a vaccine [AMC] would be more cost-effective than spending on most other means to fight AIDS or to otherwise improve the health of people in poor countries of Africa, Asia, and Latin America [though observe that an APC would give no subsidies to most of these].”<sup>1032</sup> Indeed, given that “UNAIDS estimates the cost of ARV programs at \$3-9 billion in 2007 and \$8-\$20 billion in 2015,” it would be “a bargain.”<sup>1033</sup> Indeed it would

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<sup>1028</sup> Barder et al. 2005, *ibid.* p9. Something similar repeated (with equally as many dubious claims) in Tremonti, G., 2005, *ibid.* p2: “Because AMCs establish competitive markets for vaccines, rather than a prize for the first developer, they can be designed to encourage private firms not only to accelerate the development of new and effective vaccines, but also to develop second and third generation products that improve on the first, to invest in large volume production with reduced unit costs, thus providing vaccines at low prices in the long term.”

<sup>1029</sup> Barder et al. 2005, *ibid.* p9.

<sup>1030</sup> IAVI quotes that Owen Barder said this, even if it is stretching imagination to believe that he actually did. Zandonella, C., 2005, *ibid.*

<sup>1031</sup> [www.cgdev.org/section/initiatives/active/vaccinedevelopment/overview](http://www.cgdev.org/section/initiatives/active/vaccinedevelopment/overview).

<sup>1032</sup> Zandonella, C., 2005, *ibid.* Incidentally, what is the logic of a \$3bn AMC spread over ten years?

<sup>1033</sup> Zandonella, C., 2005, *ibid.* p21, and also see [www.cgdev.org/doc/books/vaccine/MakingMarkets-policyhighlights.pdf](http://www.cgdev.org/doc/books/vaccine/MakingMarkets-policyhighlights.pdf), px.

be “a way to cheaply”<sup>1034</sup> save millions of lives by creating malaria, HIV and TB vaccines.

When one sees a fantastic bargain, one normally stocks up on it. This journalist simply cannot spot the cruel absurdity of an argument that a proposal is extraordinarily fantastic value for money but then hardly spends anything on it. It is worth rereading the authoritative statements of the last paragraph again, since they are astonishing statements of complete nonsense – and therefore a very dangerous form of journalism too.

And spot the deception in these: “As a final point, it should be mentioned that it could be possible to increase the size of an AMC commitment at a later stage if the initial commitment turned out to be insufficient to stimulate adequate industry response,”<sup>1035</sup> and “AMC funding that result(s) in effective vaccines that are able to prevent millions of deaths in countries with high disease burden are likely to provide outstanding value for money for donors and may prove to be one of the most cost-effective forms of development assistance.”<sup>1036</sup>

### **Some Capital Hill and other spin**

For an indication of how dangerous these things can get when this sort of approach gets out of hand, there is wide agreement that we have not got a clue at what level to set an APC for malaria (or HIV or TB or any other vaccine), never mind any evidence that it would have any ‘power’ as an R&D device. Nevertheless, we hear, at the highest places in the land (Nancy Birdsall, Testimony, Capital Hill, House Financial Services Subcommittee on Domestic Monetary Policy, Technology and Economic Growth at around the time of the release of the CGD report) such things as: “The financial and legal outline of this kind of advance market mechanism, at an estimated cost of \$3 billion, has recently been developed for the case of a malaria vaccine. It is *entirely feasible* within current budgetary and legal systems, and *would provide an adequate incentive* to both biotech firms and large pharmaceutical manufacturers.”<sup>1037</sup> (emphasis added). Yet no evidence at all has ever been provided to suggest that any of this is even remotely true.

These false claims are then picked up and repeated. The ‘Africa Report’ of the ‘Commission for Africa’ confidently asserted that “For Malaria, the market size needed to deliver the malaria vaccine is \$3 billion (CGD, 2004).”<sup>1038</sup>

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<sup>1034</sup> Blurb attached to Barder, O., et al. 2006, *ibid*.

<sup>1035</sup> Tremonti, G., 2005, *ibid*. p10. Apparently, this would be based on the results of monitoring of industry’s response by the committee running the scheme. Remember that this quote largely flows from the same sources as the CGD literature.

<sup>1036</sup> Tremonti, G. Background Papers, 2005, *ibid*. p14. Remember the way that Berndt et al. standardize all this to the moment of vaccine discovery; even if that moment never comes this claim can still be made.

<sup>1037</sup> Nancy Birdsall, Capital Hill Hearing Testimony, House Financial Services Subcommittee on Domestic Monetary Policy, Technology and Economic Growth. June 8, 2005. Federal Document Clearing House Congressional Testimony, p8. <http://financialservices.house.gov/media/pdf/060805nb.pdf>.

<sup>1038</sup> [www.commissionforafrica.org/english/report/introduction.html](http://www.commissionforafrica.org/english/report/introduction.html) page 409, Chapter 6, Footnote 92. Observe the notion of ‘the malaria vaccine’.

This was then repeated by the UNDP, with the claim picked up in the British newspaper *The Independent* (though not meaning it was endorsing it) as: “An advance commitment by rich countries to buy \$3bn (£1.7bn) worth of vaccines would be enough to encourage pharmaceutical giants to invest in finding medicines that would eliminate these pandemics [malaria, tuberculosis and HIV/Aids, as well as other pandemics].”<sup>1039</sup> If only it was that easy.

Economists worldwide were then told that an APC is “a way to cheaply change”<sup>1040</sup> the lack of malaria, HIV, and TB vaccines, and to save millions of lives, before the \$3bn figure for malaria, HIV, and TB vaccines was yet again promoted.

### **Why not target 80% if size is all that matters? Why short-change the poor?**

Incidentally, if the APC methodology had any veracity, one might well ask what is the ‘additional market size’ needed to generate a malaria vaccine that has protective efficacy of more than 80% against severe disease and death and lasts longer than four years, and is ready by 2015, instead of the current proposal for a 50% efficacious one-year duration by the same date with the better vaccine even pushed further off to make room? If the APC method is “powerful”, and amazingly cost-effective, and if it really is the case that “research has shown that *the major obstacle* to the development of vaccines for these diseases is the absence of a market...”<sup>1041</sup> (emphasis added) and that the only real problem is “insufficient purchasers with funds,”<sup>1042</sup> and that a bigger APC would speed up the day of vaccine development and increase the quality of vaccines, why should the poor be fobbed off with an inferior proposal of only \$3bn towards a 50% one-year vaccine and \$12bn losses per year in Africa alone and masses of continued human suffering, when the solution is simple – make the ‘additional market size’ bigger, by making the APC bigger. An argument that the science limits this, contradicts all the claims of the ‘powerfulness’ of APCs just described, and exposes the hypocrisy of the claim.

### **11.16. An overall conclusion based on these observations**

What is the point of all of these observations and what is the overall conclusion? Well, that there is much less of a desire to tackle global health issues than there is instead a desire to be looking as if there is a desire to tackle global health issues. Policies that might<sup>1043</sup> defer payment are favored – even more so if they may never be spent – over ones that might involve expense now, such as an APC for a genuinely existing product, or funding for PPPs. Combine this with policy advocates who, rather than protest the

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<sup>1039</sup> Thornton, P., *The Independent*, 30 January 2006, “UN unveils plan to release untapped wealth of...\$7 trillion (and solve the world's problems at a stroke).”

<http://news.independent.co.uk/world/politics/article341967.ece>.

<sup>1040</sup> Line promoting Barder, O, Kremer, M, and Williams, H, “Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases.” *The Economists' Voice*, 2006, Vol. 3, No. 3, Article 1. [www.bepress.com/ev/vol3/iss3/art1](http://www.bepress.com/ev/vol3/iss3/art1).

<sup>1041</sup> Kerry, Congressional Record, *ibid*.

<sup>1042</sup> Brown, G, [www.hm-treasury.gov.uk/newsroom\\_and\\_speeches/press/2004/press\\_94\\_04.cfm](http://www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_94_04.cfm).

<sup>1043</sup> Only ‘might’ since, as Tremonti reveals, even this is not yet clear.

unwillingness of politicians, exaggerate what they are promoting, and fail to rigorously think through what they are pushing for, and we end up with a narrow focus on dreamlike blue-sky solutions, and most practical issues overlooked.

CGD was set the task of analyzing if and how APC subsidies attached to early purchases of vaccines might work to stimulate R&D into the discovery of those vaccines. This was a useful exercise in its own right, something that needed to be done to help clarify the role of such instruments. CGD were vested with the responsibility of gathering the appropriate skills, of understanding issues that much of the scientific community would not have had the skills (or time) to understand, and then of communicating to the scientific community and political community their unbiased assessment of the findings. Instead they took advantage of the scientific and political community's lack of appropriate skills, and badly let them down. CGD *should* be criticized for this.

### **Carrying the can: The buck stops somewhere**

In such an emotive, scientifically challenging, and ethically complicated situation, there is the constant need to guard against short-term politically-driven rather than long-term scientifically-driven policy. In truth, politicians should worry about the law of unintended consequences:

- 1) Either, that in spite of good intentions, the proposed APC subsidy scheme may not be set up right;
- 2) Or, that such a scheme may not be set up well, perfectly deliberately – for example if policy makers are advised to act on the most simplistic thinking about the underlying proposal (see Kerry-Lugar Bill above) and they pitch to the lowest expected efficacy;
- 3) Or, that such a scheme was set up as intended, but it was never going to work anyway;
- 4) Or that such a scheme simply becomes the ‘front’, the Rube Goldberg justification, for a policy that would otherwise be unsupportable – the heavy distortion of funding flows to favor one firm over all other firms and all other players.

In all three cases, politicians, and those who advise them, carry full responsibility for the consequences. In the first case they should have checked the robustness of the idea to imperfect application. In the second case, they should have resisted simplistic lobbying and hype. In the third case, they should have analyzed the idea better, stress-testing it for faults.

Much is at stake. This is a major and extraordinarily complicated public health problem, with limited funding flows that need to be targeted efficiently. The big imperfect application here is that longer term ‘better’ vaccines are disadvantaged over more salient shorter-term vaccines, and the whole package of measures required to tackle the problem

is distorted, wasting resources, risking delay and even bringing about collapse, leading to more not fewer deaths, and more and not less suffering.

If investors feel that policy has been driven by political expediency, and is a mess, they will not respond. With growing fiscal pressures across a wide range of countries pushing in the direction of a collapse in vaccine funding, we find ourselves with an essentially politically-driven process now largely divorced from the science, economics, and finance, never mind from the needs of the poor. The poor deserve better than this.

## **12. Recommendations and Closing Thoughts**

A sense of what is going on can be had from reading the following two quotes through several times:

*“If scientific complexity means that R&D costs are much higher for an HIV vaccine than for other medicines, then \$3bn [based not on costs of developing HIV vaccines but on the costs of developing other medicines] may be too low to stimulate sufficient investment... Note that, if the commitment is too small to stimulate industry investment, and therefore does not succeed, there is no cost to sponsors.”*

CGD ‘FAQ’ sheet, April 2005<sup>1044</sup>

*“If thirty years pass and no substantial progress has been made on the product of interest, a vaccine commitment may not be the most useful approach, and the policy would be worth reevaluating.”*

“Strong Medicine” Kremer, M., and Glennerster, R., and ‘Making Markets’ CGD, March 2005<sup>1045</sup>

Incidentally, we really *would* have to wait thirty years to abandon the approach even if it was not working. We would have to commit to wait that long, so as not to harm incentives and cause self-fulfilling collapse from the start.

### **12.1. Possible outcomes of current policy**

At least these sorts of quotes admit that there are a range of possible outcomes including failure.<sup>1046</sup>

Malaria Vaccine Technology Roadmap participants in particular need to clue themselves up to the consequences of mixing the Roadmap process with an APC, and to work through whether it is better for them to have or not to have an APC *fixed* in place. These outcomes roughly, include:

- 1) There is no progress. We do not get even a highly imperfect malaria vaccine, but, meanwhile, the longer term goal is disincentivized.

If an APC for malaria is pushed, it could be that firms worry that rent-seeking and crowding out in the end market will not be handled well and insufficient funds are therefore invested to generate multiple parallel developers using private finance to fund vaccine development. Private finance is the whole point of an APC, though one might not think so from some recent coverage.

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<sup>1044</sup> Remember it is a, supposedly, an irreversible instrument.

<sup>1045</sup> Kremer, M., and Glennerster, R., 2004, *ibid.* p84, and CGD, April 2005, *ibid.* p46.

<sup>1046</sup> It is surprising to see such quotes getting through a consultation process.

Or firms worry that parts of the overall plan, in particular the ex post APC scheme, will simply be executed very poorly and, instead of encouraging multiple parallel developers, it collapses down to a procurement scheme at pre-set prices lined up for one firm at most, draining resources that might have gone on other vaccines. Hence, few private firms invest their own private funds. Indeed, fearing that poor response to the promise of an APC subsidy scheme will lead to it being withdrawn, collapse of the scheme and efforts based on the scheme become a self-fulfilling outcome.

The expected signal of an ‘early’ successful imperfect vaccine does not materialize, and the political fallout from the over-hyped possibilities either sober policymakers up or harm long-term responses as they get disillusioned with the whole idea of funding malaria vaccine R&D. This has happened before. Early clinical trial results for SPf66, a synthetic vaccine using antigens from two parasite stages, were encouraging, but Phase III trials demonstrated no efficacy. Recently, the ‘promising’ CSP-based ICC-1132 vaccine failed to show protection and Apovia, the firm developing it, collapsed.<sup>1047</sup>

Or firms come to expect the scheme will ‘sit-around’ being badly run and eventually be used very poorly many years from now. Meanwhile, there is the wasted opportunity and loss of momentum of other initiatives, including lack of collaboration harmed by the side effects of the APC subsidy scheme. There is huge absorption of ‘systems capacity’ of MVI, the Vaccine Fund and others, and of political capital, diverting human resources away from activities that are more certain to provide immediate benefit and experience in general. In 10 or 20 years time (though, surely much sooner?) we are back having to rethink, either with the APC scheme gone, or stuck with it even if it is not working (c.f. Kremer and Glennerster quote above).

There is reputational damage all round: GSK; MVI; CGD; Gates Foundation; British government; Gordon Brown; Kerry; Lugar, etc.

- 2) There is progress, but only on a highly imperfect vaccine. Firms do not trust the APC subsidy scheme to reward them properly (e.g. worries about time-inconsistency, reputational damage from a forced bad outcome, problems with follow-on, rent-seeking, excessive risk borne by biotechs, etc.) and not many firms invest, narrowing down the search. Progress is slow, and the chances of accepting a less than optimal vaccine high.

Firms come to expect that, based on recent evidence of the politicization of the APC process, politicians will drive a poor quality result out anyway to satisfy an APC. Given that the subsidy fund is sunk and that even low-efficacy vaccines are heavily subsidized, the use of such vaccines is ‘forced’ on the poor, and all the fund is exhausted on the imperfect vaccine. Politicians declare a success.

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<sup>1047</sup> *Vaccine* 2005, 23, 857.

- If the low efficacy goal is not particularly efficient, would firms en masse even want to try responding to it? Even they may suspect that policy makers will wake up to this fact eventually?
- 3) We get a very imperfect vaccine, but the costs of integrating with other parts of a package of measures is high, not many use it, or they are forced to use it by a large unbalanced subsidy in its favor, and/or the cost of production is too high, with lack of manufacturing competition aggravating this. If, for example, the GSK vaccine candidate is looking efficacious at 30%, or so, and is forced through, are GSK forced to scale up private funding as stipulated by the APC? Cost-effectiveness methodologies of the sort described in chapter 6 above will still be telling us what fantastic value the vaccine is.
  - 4) We get a very imperfect vaccine, there is big take up (maybe self-fulfilling if there is no other vaccine on the horizon), but it has short-lived value, and all the APC is gone. What do we do next? Is there claw back from firms? But firms did what they claimed they would do; it is not their fault that others failed to develop follow-on products. Since it is difficult to make sure that funds are left over to compensate for the R&D costs of later arrivals, this works by backwards induction to remove incentives to work on more difficult vaccines with private finance from the start. There is yet more delay. The waste of resources makes it even more difficult to encourage funding for the ultimate 'best' goal-2 vaccine.
  - 5) We get a very imperfect vaccine but it cannot be used on the intended target of mostly very poor infants (this includes cases of the use of the technology of this vaccine to produce other vaccines). This would be the nightmare scenario for GSK. On the one hand, there is potential heavy reputation damage of having a vaccine that is not found useful on infants even though it was heavily tested on children and infants, but it (or something based on it) is found very useful for military and other purposes. On the other hand, if somehow use of the vaccine is forced on infants or children so as not to 'look too bad', this runs just as much reputational risk. GSK only looks to have bothered since a big financial carrot was dangled their way, and they look to have abandoned the poor market.
  - 6) Or the notion of an APC might simply collapse, after a lot of wasted effort. Either all the problems listed earlier (but swept under the carpet by the recent policy process) mean that an APC never gets set up because it takes too long to sort out the mess. Or, as it becomes clear that APCs are going to be put in place for malaria, HIV or TB, large vaccine firms rebel and the initiative collapses. Various correspondents have pointed out to this author that large pharmaceutical firms simply cannot speak out against HIV, malaria, and TB APCs because of the reputational damage it would do to them. Their hope is that the idea simply dies in the G8 process and avoids them all the hassle and damage of protesting. Of course, some also hope to pick up contracts for late-stage vaccines they already have, without the use of APC-style early-stage R&D contracts.

If this were a true market and not a committee-run subsidy scheme, firms could choose whether or not to respond by investing their own funds. If they thought a market was too risky and not worth it, or if their product was too poor, they would not respond. Now, under an APC, they face the added problem that they would be forced to rent-seek the committee running the scheme in order to get a fair return, or risk being damaged if the scheme collapses down to supporting one firm at most, or even just collapsing after a few years with no mechanism in place to compensate them. They would be damned if they do respond.

But, firms also know that they will be damned if they do not respond to the dangling of what the public will see as highly ‘generous’ malaria, HIV or TB vaccine APCs, even if they will be never-before used, badly set up, and almost certain to be poorly-run and very risky instruments, and may even be set too small purely for political expediency. Looking at the extraordinarily amateurish nature of some of the analysis, it would be easy for firms to form a very pessimistic view of the likely outcome, and simply not invest.

There is even a notion that APCs will be wheeled out across the board. Yet, this is completely contrary to the logic in the head of internal financial officers of large pharmaceutical firms, who should conclude that the scheme is riddled with mechanism and reputational risk that cannot be hedged away and, unlike *real* markets, these risks will be correlated across APCs (it is a notable deficiency that CGD never got a financial person in to even think this through, never mind quantify it).

Why worry? If the scheme fails, “there is no cost to sponsors.” But there are costs – to companies and to their shareholders and to the reputations of policymakers, foundations, initiatives such as MVI, and politicians. If vaccine firms wake up to this at the start, they may simply (rightly) protest that the instrument will not work, and work to kill it off. Even GSK finance people, once they finally get their heads around what is being proposed, will come to realize the risk GSK are being forced to take on. Even potentially good uses may suffer in the fall-out. Meanwhile other malaria vaccine researchers will be complaining that their ‘better’ approaches continue to be underfunded.

Similarly, the notion of an APC/AMC for malaria could simply collapse because no institution is prepared to run it, once they realize what they have to do, and the way that running it could backfire on themselves.

The current figures being suggested for the size of the APC subsidy scheme for malaria are a century’s worth of anything we have ever spent on malaria vaccine R&D. The expenditure of such funds could achieve something, even if highly inefficient. What systems are going to be in place to judge effectiveness, and to indicate whether what we get is because of and not in spite of such schemes, and that such schemes have not simply arisen to be parasitical on successes that could and would have taken place anyway, in

order to feed the appearance of a policy success? The Berndt et al. methodology should have warned us: Even a failing APC was deemed highly cost-effective.

### **12.2. 50 key recommendations**

All alternative approaches include the involvement of commercial players. Indeed, one of the overriding concerns in this report has been to find out what are the commercial incentives of the two goal set-up and the matching APC subsidy scheme. Underlying all concerns here are worries that an APC for malaria makes poor commercial sense and that therefore, for a given (very large) sum of public spending, it will incentivize too few firms to take part, generate too low a quality of vaccine, with too little competition to drive R&D and to push production costs lower, and that this will slow vaccine discovery and access *compared* to alternatives.

Most of this fear stems, after closer inspection of such schemes, from their Soviet-style central planning credentials and the way they encourage capture and corruption, with the severe complication that developers spend their own money, building up large sunk investments, en route to the committee-run outcome. We have also seen how vulnerable such schemes are to interference and manipulation for short-term political gain – even before we start to use them – by politicians who do not understand even the basic economic, finance, or science principles at work.

This paper argues that there are far higher priorities on the agenda that should be absorbing the limited global systems and political capital. The solution involves many small things done well, not blue-sky heroic-sounding schemes. Before the political process gets even more out of hand, this paper recommends the following priorities:

- 1) Set a global malaria target, with all technologies and interventions put on an equal footing, since this will help to make better funding decisions about malaria vaccine R&D too. Stop singling out approaches that emphasize a narrow one-dimensional technology fix to a problem that is a complex package of failures and potential solutions.
- 2) Get rid of the two-goal approach. We already see it becoming a de facto one goal approach,<sup>1048</sup> with this exaggerating the highly risky gamble that is already inherent in the science. Instead, consider a policy that massively emphasizes control and prevention now with increased funding flows towards a greater number of vaccine candidates targeting more efficacious vaccines from the very start, with less efficacious vaccines treated as optional, with decision about their use determined at a later time, dependent on the progress of the greater goal at that time. The ever-falling required efficacy of the first goal in all APC discussions over the last two years is too startling to believe that the outcome will ever be based on any methodology other than one that is highly politicized.

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<sup>1048</sup> [www.malariavaccine.org/files/060124-Benin-Decision-Making-Meeting.htm](http://www.malariavaccine.org/files/060124-Benin-Decision-Making-Meeting.htm)

- 3) Do not try to do too much decades in advance. Make the mechanism as complexity free as possible. If we cannot work out a methodology for even working out the optimality of efficacy and duration at this point, why should we even be trying to permanently fix any particular (low) efficacy or (short) duration at this time as an *operational*, and therefore *legally binding*, goal? If we cannot even work out the size of the non-eligible market on the basis of current data (and hence determine the size of the ‘eligible’ market for the APC), why should we be trying to do it now in order to work out the terms of an APC? If we have no data at all on R&D and manufacturing costs, how are we ever going to know how to set up the distribution rules for sharing out the subsidy pool across developers to generate fair returns to investors? If we cannot even do this, how are we supposed to work out the even more challenging re-distribution of subsidy over products over time?
- 4) In spite of the claims to the contrary, an APC, if it is ever used as an R&D instrument, is an extremely statist mechanism, with very top-down control, and great dependence on its efficient management. Such institutional mechanisms have always proved unwieldy, inefficient, and prone to failure in the past. In this case, the problem is heavily compounded by the build-up of large private sunk costs and the creation of incentives towards rent-seeking behavior and corruption. The mechanism needs to be as light on statist credentials as possible, with less build-up of sunk costs at each decision point.
- 5) Create more *process* goals, to take away from these unrealistic notions of what is a ‘goal’. The success of process goals can at least be confirmed en route, whereas the goals currently being suggested never truly face a market test anyway.
- 6) If a malaria APC is forced through regardless, create goals for number of privately financed developers, and amounts of private finance to be sunk at given points in time – to avoid the APC collapsing down to an inefficient price-fixed procurement mechanism for one firm.
- 7) If a malaria APC is forced through anyway, do not make countries face co-payments. Face them instead with the full budget constraint and ask them to choose between the vaccine and alternatives such as drugs and prevention, and to face the full vaccine cost (including full R&D costs) at point of use. If spending \$25 or \$50 (depending on how much the vaccine development and production costs are) on the vaccine is poor value compared to alternatives, they will use the better-value alternatives. This will give incentives for firms to produce vaccines that countries will want to use, and create incentives to also push production costs lower. The argument that offering \$25 or \$50 for non-vaccine alternatives faces problems because there is ‘no budget available’ for all potential uses of funds, is not a valid excuse. It simply reiterates the point that pre-sinking the budget for the vaccines that eventually get pushed through would turn out to have been poor value for money, if countries would otherwise not have *voluntarily* spent the

- budget on the vaccine in place of the alternatives if they had been presented with the choice, and with the option to hold out for better vaccines too.
- 8) Follow through on the Arrow et al. report of 2004, and fully back and prioritize efforts to make ACT malaria drugs drive out malaria monotherapies globally. This will increase the impact of recent breakthroughs in developing cheaper ACTs.
  - 9) Create more goals based on ‘risk’ reduction. This will, of course, require us to understand a great deal more about the nature of risk.
  - 10) Production issues, especially costs, are a key variable, but cannot be known years, even decades in advance. Wherever possible, it is always better to use markets – and not long-ago fixed legal contracts – to extract information, to compete to make prices affordable and to give incentives to develop cost-cutting technologies, and to ensure long-term access. It is always better to use markets to avoid schemes based on lots of guesswork and pre-set rules. Consider ways to increase competition towards the end of the process and to avoid ‘sole supplier’ scenarios. To avoid capture and time inconsistency, acceptable behavior at the end of the process needs to be fully articulated in the framework of ‘rules of play’ set at the start. Consider ‘APC’ as mostly being about procurement and competition and less a complicated ex post subsidy device to repay decades of privately sunk R&D costs.
  - 11) Change funding arrangements so that UNICEF and others can negotiate long-term contracts.
  - 12) Avoid fudging long-term issues by throwing into the debate a supposed line here and there in a contract. If the line is not going to be legally credible in practice, then it should not be a part of the policy debate either, and should certainly not be in the contracts. The notion that contractual threats can carry the weight of long-term supply and price at ten to twenty year horizons is absurd. It should not be entertained as a serious answer to a major practical issue.
  - 13) Move away from an approach that has some aspects open to the many but others acted on by just a few. The less democratic, less open, and more predetermined processes will act as a constraint on the more democratic, open, and flexible processes. Take key decisions out of the hands of a tiny number of individuals. The Malaria Vaccine Technology Roadmap is potentially a useful move in this direction.
  - 14) Establish truly robust, independent, cost-effectiveness methodologies, taking into consideration some of the dynamic problems discussed above and the complete range of malaria options, and not just vaccines. Clarify all assumptions being made about the budget constraint. Make all cost-effectiveness evidence open to challenge at all times. Put an end to the biased cost-effectiveness evidence

- infiltrating all the policy papers fed to politicians and government leaders. Stop advocates from using this highly misleading cost-effectiveness ‘evidence’ to lobby and not instead to critically evaluate all potential solutions.
- 15) Stop generating genuinely nonsensical figures. To generate the NPV of malaria, HIV, and TB vaccine APCs, the Tremonti Report discounts the nominal value of the subsidy fund for each disease at just 6%, and at very optimistic and generously set horizons. Discounting is also done on the basis of the “assumption that the funds are available at the time of vaccine availability”<sup>1049</sup> even though actual disbursements would take place over many years (if the scheme is supposedly to incentivize follow-on vaccines). Such figures are meaningless to vaccine developers (indeed, they add to the meaninglessness of previous figures such as the \$3bn heavily promoted by CGD 6 months previous to the Tremonti Report), and destroy any sense of confidence that industry needs to have in such proposals to bother investing in the first place.
  - 16) Separate out in the mind of policymakers the notion of commercial players and the method of finance. It *is* possible to have commercial players involved without trying to badly replicate ‘blockbuster finance’ and create pseudo-markets that are really just committee-based schemes. Stop the travesty of saying that if anyone thinks APCs are a bad idea for malaria, that they must be suggesting no role for commercial players, and must be “ideologically”<sup>1050</sup> motivated.
  - 17) After just 5-7 or so years, PPPs are doing well (much better than many ever hoped<sup>1051</sup>) but they continue to be under-funded, relying mostly on philanthropic funds. It is still early to be prejudging their outcome. Therefore, make up the current funding shortfalls (including by involving Russia, China, India and others in funding arrangement). But also – since it is not just about money – encourage much greater openness, self-criticism, and democracy amongst PPP and vaccine initiatives. Procurement (not APCs) at the end of such initiatives can be used to enforce competitive pressure on outcomes and to discipline costs (compared to APCs that create too many sole suppliers and price-fix in ways that reduce this pressure).
  - 18) Remove highly-politicized decision making from what is a very scientific and complex process. This is policy-setting for the next twenty to thirty years, not the next two or three to serve a political goal. Stop politicians distorting towards the first low-efficacy outcome that comes along. The recent encouragement, even before any subsidy scheme takes off, of political interference hardly sets a good precedence, and is hardly likely to reassure investors that it is wise to take tough long-term decisions. There is a lot of disquiet (in some quarters, even anger) in the malaria community that politicians are able to do ‘deals’ with selected

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<sup>1049</sup> Tremonti, G., 2005, *ibid.* p10.

<sup>1050</sup> Barder et al. 2005, *ibid.*

<sup>1051</sup> See Moran et al. 2005 *ibid.*

- companies, without thinking through at all the implications for the greater scientific community.
- 19) Explore how safety and liability issues may differ for malaria, HIV, and TB compared to, say, flu, especially according to efficacy of vaccines.
  - 20) Make firms face risk, but only risk that will motivate them and that they have some control over. All other risk is wasteful. In particular, initiatives for currently-existing vaccines and late-stage vaccines are all about achieving lower prices by taking market risk away. Use mechanisms with R&D payment related to market risk only to the extent that this risk is controllable by firms, and will have a useful incentivizing effect. Avoid putting ‘market risk’ in just for the sake of ‘appearance’ and to create the pretense of a ‘market-based’ scheme.
  - 21) Think about more novel financial instruments – mainly to handle risks and the cost of sunk investments, and to encourage a wider range of active firms, including emerging developers, etc.
  - 22) Have more of an emphasis on the science and an understanding of the extreme scientific challenge. Educate politicians away from simplistic and over-optimistic models of the problem. Stop them from exaggerating the available evidence.
  - 23) Incorporate a more ethical element. Avoid encouraging trials that may not lead to anything and may even deter others from a greater goal.
  - 24) Work out much more precisely the dilemma of ‘sharing’ versus ‘commercial incentive’ before locking in any financial instrument that prematurely imposes an interpretation of this on all players, in particular locking in processes that presume no need for ‘sharing’ or ‘collaboration’. How does the need for ‘information’ sharing in very complex scientific challenges affect our understanding of equity-financed malaria vaccine R&D (implicitly, the financial structure underlying an APC)?
  - 25) We need lots of firms responding in parallel, not the few. Investors will not respond to policy that they see being pushed on the back of poor-quality analysis and poor-quality legislation. Investors need to believe in the competence of the policy process.
  - 26) Avoid forcing reputational damage onto players. It feeds back to undermine R&D. Especially, do not set up firms for a repeat of the AIDS drugs pricing and access debacles of the past.
  - 27) There is not a bottomless pit of funding. Budget constraints matter. Relative efficacy of approaches matter. Do not allow any analysis through that does not spell out its assumptions about the budget constraint and its true relative cost-

- effectiveness. The analysis of CGD, Berndt et al., and Kremer, etc. all ignore the budget constraint binding over the entire malaria solution.
- 28) There is need for more funding on basic science. However, it is not as straightforward as that for malaria, since one also can only learn certain things about malaria through field trials. HIV, malaria and TB vaccines are a long way still from licensure, and as broad a hunt as possible will be necessary to ensure success, with the need to encourage collaboration, a collaboration that is already proving hard enough to achieve.
  - 29) Hence, also intensify efforts to expand field trial capacity in developing and emerging countries, and encourage its efficient use.
  - 30) Explore a wider range of ways to increase productive capacity, and not just the use of one or so major players.
  - 31) Spend more time analyzing the differential impact of proposals on biotechs, 'big pharma' and others.
  - 32) Locate and explore all the 'option value' components to the R&D problem, and the implications for possible outcomes towards the end of the development process. In particular, locate bad outcomes that might be triggered by a hidden option value, and set up mechanisms *now* to avoid these outcomes later.
  - 33) Explore cost of finance issues. Does competition help to drive financing costs lower?
  - 34) Work out the positive value of procurement (as well as be aware of the problems) and exploit it. For example: disciplining of prices and production costs; disciplining of anti-corruption; positive impact on information revelation; etc.
  - 35) Work out if there are any 'good' impacts that 'lack of a market' might have, as well as the bad impacts. For example, are systems that are in need of heavy collaboration run better with less build-up of required sunk cost to be repaid to a 'winner' at the end? Can this lack of pressure be exploited to achieve more collaboration and 'sharing' when the science is especially challenging?
  - 36) Subsidies suffer crowding out. How? Explore the differential positioning and use of subsidies.
  - 37) Stop relying on unreliable evidence of firm interest. Make firm-level respondents face some cost to their 'revealed' preference. Only one big pharma company has publicly said anything vaguely positive about malaria, HIV, or TB APCs and even then very much as a second-best option, driven, as far as one can make out, by only a few individuals in that firm, and only relative to one malaria vaccine. Even

- then, it is increasingly clear that this came about only because Gordon Brown pushed the proposal and hastily announced an agreement.
- 38) Stop mixing all vaccines together in policy debate, and abusing the support for instruments to help solve the problems for one vaccine by suggesting that the same instruments work equally well for totally different vaccine problems. HPV is a very different challenge to HIV. Pneumococcal presents very different problems from malaria.
  - 39) Do not push narrow and ill-worded legislative Bills. Do not force politicians into positions that will only eventually make them look bad. Stop parachuting ideas into the legislative process and then doing nothing to make sure that they do not simply get badly enacted and even become a danger to others.
  - 40) Be much more ruthlessly critical with ideas and proposals. They must work, and in this case over huge horizons. Something that looks nice on a piece of paper, especially if built on a hugely simplified understanding of the scientific problem, is not a good guide to how things will work in practical reality. In particular, stop using obfuscatious language, such as that an APC for malaria is “potentially a powerful” scheme. Perhaps those who push simple ‘paper’ models, should be forced to practically implement what they propose?
  - 41) Spell things out better. At the moment there is no clear notion amongst many participants of what an APC actually is. The terminology has become hugely broad in its use. In December 2005, a range of PPPs signed up to something the details of which they mostly never understood. Perhaps we need some language to distinguish types of APCs, and far more understanding of when instruments are being used for R&D purposes for a non-existent vaccine, and when they are being used purely for procurement purposes for an already existing vaccine?
  - 42) Stop pitching at deficit countries just because a G7/G8 approach demands this, when instead it is possible to exploit surplus countries that will also be big beneficiaries. This has led to an obsession with certain funding instruments over others and ignores the benefits of getting, e.g. China, Russia, India, and Latin American countries (who would all be non-eligible countries under current APC proposals) more involved. Ask these countries what initiatives they are prepared to be part of and what they are prepared to fund. There are ways to exploit the fact that some major potential benefactors of HIV, TB, and malaria vaccines (China and Russia in particular) run heavy balance of payments surpluses, compared with most G8 nations which are heavily in deficit.
  - 43) It is claimed that “donors have nothing to lose; if no vaccine is developed, the commitments are not disbursed.”<sup>1052</sup> Stop encouraging such dangerous thinking. Failure is not an option. There is no free lunch. All members of society pay for

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<sup>1052</sup> Tremonti, G, Background Papers, 2005, p1.

- R&D via their investments in pharmaceutical companies. If APCs fail to get a result, all members of society bear the cost of this failure. Those who do not get vaccines bear an even greater cost. If failure is the result of those who set up APCs, the cost is either via the sponsors getting sued, or via the extra deaths on account of the failure. The costs of the latter would far outweigh the ‘benefits’ of not having to disburse funds.
- 44) Perhaps the APC idea is seen by some as a process to be ridden to lock in funding for something else, such as a late-stage vaccine procurement fund, even if an APC will never be used. However, at some point either the APC idea will have to be abandoned in favour of something better for malaria, or it will have to bite and be operationalized in spite of its faults. Do not get backed so much into a corner that the latter outcome happens even if really it was the former outcome that was being desired.
- 45) Stop taking huge gambles on policy instruments. We should stress-test policy instruments for each vaccine case. Having an APC in place for, say, HIV that is not working is not a trivial problem. Since an APC is a commitment device, it is really difficult to write terms in to them that allows them to be wound up early, or such that their terms to be heavily revised later (such as offering much higher payments later), since this creates disincentives to invest early.
- 46) There are a huge range of underused products, including many underused vaccines. Funding priority should be put on to achieving the wide use of these, in addition to including malaria drugs and control. This will show that there is more of a market. Indeed this has increasingly been going on, and has proved the point. This involves fully funding the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies. The emphasis in the case of many recently-developed products (including HPV, rotavirus, pneumococcal, but also hepatitis B vaccine, haemophilus influenzae vaccine, a cholera vaccine emergency supply, and the conjugated typhoid vaccine emerging from research at NIH, IVI, Vietnam, and elsewhere, the meningitis C vaccine being developed by a consortium under WHO and PATH, etc.) is about getting product price down, which requires much more use of creative IP and know-how, and the opening up of the market to competition at late stages of development and procurement. In particular, not that long ago there was wide agreement on setting up rolling purchase funds for neglected products without product exclusivity. This consensus has, in the language of one correspondent, gradually been “hi-jacked” (and the purchase fund idea abandoned) in order to put the emphasis on to APCs with all their exclusivities, even if they do not work or turn out to be extremely expensive compare to alternatives.
- 47) Emphasize well-implemented accelerated disease-control and prevention strategies, development of public-health infrastructure, health systems capacity,

- and distribution issues (including their interaction with R&D issues). In fact make such issues key to success, rather than just peripheral.
- 48) Commit to remove the barriers to the provision of healthcare in developing economies themselves, especially the tax and regulatory barriers that often prevent the poor from obtaining essential medicines, and make a commitment to tackle institutional failures, governance problems, and corruption that hold back provision of healthcare and access to medicines. Certainly do not add to the corruption by using schemes such as APCs that positively encourage corruption.
- 49) There are a huge range of current distortions that destroy the value of new products and R&D towards new products. At the moment, all political capital has been sunk into blue-sky R&D solutions, rather than the seemingly more mundane practical questions. The development of malaria, HIV, TB and other vaccines is all about the many bits done well, and not the big blue-sky fix via a big lump of funding. Emphasize the boring, not the panacea.
- 50) There needs to be some fundamental rethink of funding flows into lobbying efforts. Ideas make it up the political agenda the more money that gets thrown at them, and not, it seems, necessarily because of the quality of the underlying idea. Where do the analysts who churn out biased ‘cost-effectiveness’ evidence, and increasingly dubious reports about seemingly magical new solutions, get the funds from to do it? Why are there never any checks and balances? Why is there no quality control of what is being produced and of how it is being used? Quite how did the flow of funds into ideas and the policy process come to emphasize some things while downplaying or even ignoring many others?

### ***12.3. Time to ditch hollow big-gesture politics?***

Probably, we naturally have to go through cycles of novel, if largely unworkable, ideas. Perhaps, we simply have to go through an ‘APC phase’, dump it later (with litigation if a few firms responded) and move on to the next thing? Perhaps we need a rolling set of ‘policy initiatives’ to look as if we are ‘doing something’ even if we are failing to do anything?

Perhaps, instead of working on fiddly and boring adaptations and improvements, and getting into the mess of the details (boring things like ‘risk’, and ‘collaboration’ and the complex science), it really is better to always be looking as if we are doing something ‘new’ and blue-sky and ‘big’? Lots of small things done very well have little appeal to lobbyists and image-hungry politicians. And policy lobbyists know that they can more easily fly better a big-gesture proposal instead of mundane, difficult, practical, hands-on, in-it-for-the-long-haul, low profile approaches (even more so if big-gesture means the details can also be more easily hidden). The reader might usefully read papers like Kaper

et al.<sup>1053</sup> to review the multitude of measures that need tackling – all essential, but often dull and unappealing.

Instead, the APC is an idea with all the advantages of something that can be made excruciatingly simple at a base and visceral level, and yet has never been tried before, and will not be shown to be unworkable till much, much later – way after most of the politicians and lobbyist who instigated it, and squeezed what they wanted out of it, will have long since moved on.<sup>1054</sup> Best still, since it ‘costs nothing’ as advocates repeatedly assert (we actually found it to be very wasteful), it is the perfect big-gesture hollow political promise of funding.

### **A policy rollercoaster**

Maybe we should just ride the policy rollercoaster, the thing that will get policy-makers ‘off the hook’, the thing that fits the tightening budgetary pressures of the moment, the ‘apparently’ astonishingly easy fix to a difficult scientific problem, the thing that only a tiny handful of voices have shaped under the lazy eye of a political rubber stamping process?

Maybe if we had discovered the power of such subsidy scheme ideas in the early 1950s we would not have had to hang around till the end of the 1960s to land on the moon? Just set the moon-shot APC a bit bigger? Maybe Kennedy in his speech to Congress on 25 May 1961 should have added a line:

“...I believe that this nation should commit itself to achieving the goal, before this decade is out, of landing a man on the Moon and returning him safely to the Earth. No single space project in this period will be more impressive to mankind, or more important in the long-range exploration of space; and none will be so difficult or expensive to accomplish... but, worry not, we have worked out what it is going to cost [or rather we worked out what it would be worth to us and ignored costs] and we have set up a simple and yet powerful new instrument called an APC to achieve it, and it has the added benefit that it will cost tax payers nothing until after we have landed on the moon...”<sup>1055</sup>

### **Why no desire to stress-test ‘big and novel’ proposals**

Of course, it ought to be possible to thoroughly stress-test the logic of major 20-30 year policy initiatives before trying them out, but since we are repeatedly told that there is no cost if the whole thing fails, maybe we should just not bother wasting our time stress-testing *anything*? The author cannot think of a single 20-30 year project of comparable complexity getting some of the experimental incentive devices now being proposed for malaria, HIV, or TB vaccines, without any thought even to *mentally* testing them out

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<sup>1053</sup> Kaper et al. 2005, *ibid*.

<sup>1054</sup> Sometimes I think they should be made to run it. It might clear out some of the principle-agent problems that lead to advocates spinning ideas that will make *someone else* look bad when they have to set up and run it.

<sup>1055</sup> Excerpt from “Special Message to the Congress on Urgent National Needs” [www.jfklibrary.org/j052561.htm](http://www.jfklibrary.org/j052561.htm) (including sound file).

first. If this was a policy proposal for the rich, it would get a great deal more scrutiny than this.

#### **Absorbing key systems capacity and detracting from alternative initiatives**

These APC subsidy schemes are *not* a risk-free costless option. Even if such devices do nothing useful for malaria in the short-term, they absorb much key systems capacity and detract from initiatives and funding proposals that could have had more of an impact. The biggest danger for malaria is that since such subsidy devices could do little useful for malaria in the long term, we could end up having to target a poorer-quality result to satisfy the APC, and to justify the huge amounts of time, effort, and resources that the sponsors put in to analyze the whole thing in the first place, and the huge costs of setting up and running such instruments for years without any apparent impact, even if it means devoting large resources to the lower efficacy goal, and harm to the other parts of the larger package and the greater goal. It becomes a parody of the very worst faults of publicly-funded projects that sponsors haven't the will to kill.

Since most of the “Big questions”<sup>1056</sup> identified in the Roadmap are “scientific in nature” and – work or not work – APC subsidy-based schemes will not do anything for 10 or 15 years, what is the big rush?<sup>1057</sup> The vast majority of private firms will not respond; yet terms would have to be fixed ‘for ever’ (given the discount rates, 20-30 years is effectively ‘for ever’). Terms would be set badly with unnecessary amounts of discretion (hence risk) left in the contracts, with ‘sunset clauses’ a risk to investors, and the ultimate credibility of the approach damaged. It will invite collapse. Even from a purely selfish perspective, do politicians want to rush in without checking that they are not selling a policy that will simply come back to harm their reputations later?

After years and years of relative inactivity, largely on account of political short-termism, and of relying on philanthropic funding and a handful of generous individuals to tackle neglected diseases, when an attempt is made to pass the baton and politicians are challenged to do something at last, why come up with APCs that do nothing more than feed to this same political short-termism and lack of vision?

#### **12.4. Closing thoughts**

Guerin et al. comment: “[Malaria] vaccine research over the past three decades has been characterised by lack of funding, a serious underestimation of the complexity of the parasite, faith in technology above scientific understanding, lack of appropriate models, and above all a lack of adequate knowledge about the immune mechanisms underlying protection.”<sup>1058</sup> At last we are getting some progress on the first of these. Unfortunately, recent policy making has been plagued by the continued presence of all of the others,

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<sup>1056</sup> MVTR p7.

<sup>1057</sup> No doubt some of the economic points may seem boring to non-economists. But, to labor a point (for the sake of the economists) there surely is a huge option cost to locking in terms early, and a huge option component in required rate of return to firms?

<sup>1058</sup> Guerin et al. *ibid.* 2002.

with the repeated assertion that the solution is “simple and practical”,<sup>1059</sup> and that “this can be done simply and cheaply.”<sup>1060</sup> Even as this report is being released, we are yet again being subjected to the myth that an APC is “a way to cheaply change”<sup>1061</sup> the lack of malaria, HIV, and TB vaccines causing millions of deaths. Hopefully, this report will have helped to balance the debate, and to demonstrate that these claims are simply not true. The science should drive the economic and financial instruments needed, and the political process should face the practical implications of this.

At the core of the critique is that APCs would struggle to incentivize a challenging high quality low cost outcome, by distorting away from parallel research leads, undermining collaboration, and ignoring a range of production cost issues. APC advocates for malaria vaccines have argued against this critique largely by suggesting their own straw man argument that “the criticisms are of a proposal that nobody is making... a straw man.” But they have never produced a defense based on logically taking the critique apart, even as they have ironically done more than anyone else, in response to recent scientific announcements, to go out of their way to encourage just such a poor-quality outcome.

There are dangers in treating the ‘first apparent success’ as overly salient. In a tough and highly uncertain scientific challenge, there are always dangers of forcing out an inferior result but nevertheless something that can be declared as ‘a result’, while the difficult-to-see better result, which would have been but now does not happen, going unnoticed and unmissed. Once politics intervenes this is aggravated. The better vaccine that does not happen on account of political failure and interference will fall outside of the timeframe of the current politicians driving policy. Policy advocates have ruthlessly played to this political weakness.

The paper concludes that it might be better to set a different operational target based on metrics other than fixed end-product characteristics. Exactly-fixed terms go against the uncertainty of the vaccine science and the uncertainty of the other components of the overall malaria package, but they are needed to serve the APC given *its* need for certainty.

The paper also urges attention to action that could make a *real* difference and be a real success, in place of the pseudo-success promoted by APC advocates, that does no more than crowd out attention to these more real potential successes. As Kenneth Arrow argues in the case of malaria:

*“The main condition underlying access to subsidised ACTs would be that they flow freely through public and private channels—just as chloroquine does now... Above all, in the case of anti-malarial drugs, centralised purchasing would provide the impetus for a swift change in the way the world treats malaria. Without a co-ordinated programme, the change is far more likely to be gradual and incomplete, the scenario most likely to jeopardise the effectiveness of artemisinins over the next few years... There can be no*

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<sup>1059</sup> [www.cgdev.org/section/initiatives/active/vaccinedevelopment/overview](http://www.cgdev.org/section/initiatives/active/vaccinedevelopment/overview).

<sup>1060</sup> [www.cgdev.org/doc/books/vaccine/MakingMarkets-summary.pdf](http://www.cgdev.org/doc/books/vaccine/MakingMarkets-summary.pdf) p2.

<sup>1061</sup> This really was the blurb sent in email accompanying release of Barder, et al. 2006.

*excuse for delay... All that remains is for the international donor and finance communities to embrace the logic, allocate funds and take action once and for all against malaria... What makes this situation more distressing is the existence of an effective alternative... With a modest global investment, these drugs could be mobilised today.*<sup>1062</sup>

This is the current priority. And making it priority will help set better priorities in malaria vaccine R&D.

**Wide discontents: Time to move on**

This report would not have been written had there not been such a widespread feeling across so many malaria experts, vaccine experts, health systems experts, pharmaceutical company executives, and policy experts (even including some of those promoting the malaria APC itself), that the APC scheme for malaria that we see emerging is a deeply flawed idea, and that the process that brought it forth has been deeply flawed. This report has used the Malaria Vaccine Technology Roadmap and the current push for an APC as recurring themes taken direct from the current malaria vaccine policy environment. Increasingly, the report has ended up being a defense of the former informal and open process and those involved in it against the closed deals, politicization, and personal agendas of the latter and those promoting it.

One correspondent, heavily involved in the World Bank process in late 2005 and early 2006, explained: “The promoters of the AMC idea seem to have succeeded in avoiding a careful analysis of whether it would actually have much impact on commercial decisions, which is to me the principal factor in deciding whether it is worth doing compared to all the other options/needs. It is a case study in how NOT to set policy for stimulating vaccine innovation for developing country needs (‘Advocacy’ trumps Analysis).” This seems a pretty good summary of the state we are in. The hope is that, as another correspondent put it to the author, “sound policy debate could drive malaria research” once again.

Like a spam email advertising some undervalued stock not to be missed, or a door-to-door salesman offering special money-making opportunities based on a financial loophole, if one is told to invest heavily in an idea because “Every so often, an idea comes along that makes you ask: *now why didn't I think of that?* This is such an idea,”<sup>1063</sup> maybe one should instead wonder, if it was such a wonderful idea, why did nobody think of it – and use it – before? If it seems too good to be true, it is probably because it is.

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<sup>1062</sup> See Arrow. K., 2005, *ibid.*

<sup>1063</sup> Nancy Birdsall, Preface to CGD, April 2005, *ibid.* pviii.

## **A One-Page Glossary of Useful Economic and Financial Terminology**

Economic and finance terms are explained as they appear in the text. However, a few terms appear frequently, and some readers have suggested that a short glossary might help.

**Capital costs/Cost of capital:** The financial costs to firms of investing financial resources in their activities. However, since many readers will not be financial economists, sometimes the terms ‘cost of finance’ or ‘financial capital’ is used to simplify. For an investment to be worthwhile, the return on capital must be greater than the cost of capital. This is distinct from ‘capital’ in the sense of fixed assets such as plants and machines.

**Crowding out:** To the extent that a subsidy, a tax break, or any other financial incentive fails to hit those it is intended for, there is a ‘crowding out’ of the power of the subsidy, tax break, or financial instrument to motivate the act intended. This increases the cost of using such instruments, but also decreases the output or quality of outcome for any given expenditure on such instruments.

**Discount rate:** The interest rate at which future streams of revenues and costs are discounted to derive their ‘current’ value, i.e. their ‘present discounted value’, that is their value in today’s prices once all financing costs and inflation are accounted for. This also incorporates returns to risk-taking.

**Hedge:** In finance, a hedge is an investment that is taken out specifically to reduce or cancel out the risk in another investment. If no market exists for creating and trading such hedging instruments, the risk cannot be cancelled out.

**Net Present Value (NPV):** The value in today’s prices and suitably discounted, of a stream of future revenue/costs/profits, etc.

**Opportunity cost:** The cost of something in terms the most valuable forgone alternative.

**Option:** “When a firm makes an irreversible investment expenditure, it exercises, or ‘kills’, its option to invest. It gives up the possibility of waiting for new information to arrive that might affect the desirability or timing of the expenditure... This lost option value is an opportunity cost that must be included as part of the cost of the investment.”<sup>1064</sup>

**Rent-seeking:** ‘Rent-seeking’ refers to what happens if a large amount of economic ‘rent’ is created that firms then have an incentive to spend resources trying to capture. A simple example of economic rent: Imagine what would happen if a radio broadcast announced that a pot containing a million pounds is hidden somewhere in a large central London park. The efficient result, using up the least collective resources, may be for one person to be selected by lottery to go and find it (spending a day looking around). The radio broadcast ensures that most of the value of the pot of money is wasted on transportation fares and the time of all those responding by rushing in to central London to search for it. ‘Rent-seeking’ may show up in various forms of corruption and mechanism capture, and those setting up systems may have to use resources fighting rent-seeking. To avoid the costs of rent-seeking, firms may prefer to avoid systems that deliberately encourage them to rent seek.

**Sunk cost:** ‘Sunk’ refers to something irretrievable. A sunk investment (as apposed to a fixed investment) is one that has no resale value in any alternative market; bygones are bygones. Fixed investments may be partly or all sunk.

**Time inconsistency:** In the context of vaccine R&D, ‘time-inconsistency’ refers to what happens when firms have sunk heavy R&D costs, and buyers subsequently have the power to bid prices down to levels that do not cover – through the product prices of the winning firms – the *collective R&D* costs of all firms. Knowing this *ex ante*, no firm invests.

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<sup>1064</sup> Dixit, A.K., and Pindyck, R.S., *Investment under Uncertainty*, Princeton University Press, 1994, p6.