The Global HIV Vaccine Enterprise, Malaria Vaccines, and Purchase Commitments: What is the Fit?

Andrew Farlow
University of Oxford
Department of Economics
and Oriel College[1]

Updated
12 June 2005

The most up-to-date version of this paper is available at
Innovation Strategy Today
www.biodevelopments.org/innovation
July 2005

This paper has the advantage of a table of contents

[1] Based on "The Global HIV Vaccine Enterprise, Malaria Vaccines, and Purchase Commitments: What is the Fit?" submission to the 'Commission on Intellectual Property Rights, Innovation and Public Health', WHO, March 2005, www.who.int/intellectualproperty. For more comprehensive explanations of some of the points in this paper, see the pharmaceutical, neglected diseases, and vaccine finance papers at www.economics.ox.ac.uk/members/andrew.farlow, especially "An Analysis of the Problems of R&D Finance for Vaccines: And an Appraisal of Advance Purchase Commitments" April 2004, www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf, and the PowerPoint Presentation "Purchase Commitments for Vaccines: Their Uses and Their Limitations." Since this is part of an ongoing debate, these papers and presentations are more of an exploratory exercise than a statement of a definitive, fixed, set of conclusions. The author very much welcomes feedback: andrew.farlow@economics.ox.ac.uk.

EXECUTIVE SUMMARY

This paper is an effort to put balance into the current debate about 'advance purchase commitments', APCs, for vaccines, while also analyzing a wide range of issues that impinge on vaccines in general. Particular attention is paid to HIV and malaria only because these have been especially heavily promoted as candidates for APCs.

The paper explores the highly heterogeneous nature of the underlying vaccine problem, ranging from the creation of complex and difficult 'early-stage' vaccines – such as those for HIV, malaria, and tuberculosis for which many scientific difficulties still remain – through to the insufficient or non-use of already existing, sometimes very cheap, vaccines – such as those for yellow fever, hepatitis B, and haemophilus influenzae. The term 'APC' has come to cover all of these things and has thereby become somewhat vague. However, the instruments needed for each – including the nature of purchase commitments – differ greatly.

Since the problems of using APCs for late-stage vaccines are a subset of the problems for early-stage vaccines, the paper starts with the more difficult case first. A benchmark model of an APC for early-stage vaccines is set down, and analyzed in detail. This takes up half the paper. In the case of HIV, malaria, and tuberculosis, an APC refers to a pre-set pool of subsidy to be distributed, after vaccine development, in a potentially complicated pattern across vaccine developers and 'eligible' countries over time, according to a system of pre-set contracts – yet with important elements of discretion – and the institutions and monitoring mechanisms required for doing this.

Early-stage APCs are found to face many challenges including the following:

● It is extremely difficult to set the 'size' of an APC so as to maximize the speed and efficiency of vaccine development. Setting 'size' too large or too small is wasteful for different reasons, yet there are limits to the ability to reset the 'size' later without negatively impacting incentives.

● It is extremely difficult to contrive product terms and payment rules to reward follow-on innovation and thus to encourage investment into a variety of vaccine approaches in the first place. In this sense, such programs struggle to replicate standard market features. This is especially problematic for vaccines that are composite or potentially 'only' therapeutic, or for which the first products are very unlikely to be the best.

Given the lack of any other way to drive 'quality' and follow-on innovation, currently-proposed APCs require a great deal of market risk be put back on to innovators – the very opposite of the reasoning behind purchase commitments for existing and late-stage vaccines. Given the dysfunctional nature of many eligible country health markets and the importance of scale in driving production costs lower, this undermines incentives to do R&D in the first place. It also ensures that

problems with production price, and delays in access, become part of the mechanism to incentivize the original R&D. This suggests that even under early-stage APCs the 'quality' of products, and risks to developers, should be dealt with more en route than totally via a crude mechanism to disperse a pre-fixed pool of subsidy at the end.

● Unlike late-stage or currently existing vaccines, it proves very difficult to set minimum product specifications far in advance so as to avoid later discretion, with consequent risk to developers. Setting the 'size', minimum product specifications, and the rules for follow-on products, all require knowledge of expected technology and R&D costs, the potential costs of manufacture and distribution, the future epidemiology, and even the future economic status of countries that may or may not be eligible for the program. The current proposal is that vaccine specifications can only ever be lowered. This is not found to be particularly efficient (or ethical). Such programs risk actively discouraging the development of highly effective and safe vaccines.

● Early-stage APCs vary in their ability to create genuine *additions* to current markets and to current push incentives. They therefore have varying ability to incentivize genuinely 'additional' private investment. This is especially problematic for HIV for which there is a highly variable current market, that has somehow to be factored out, and a complicated interplay of other research and funding mechanisms. All of the cost effectiveness evidence used to support APCs for HIV, malaria, and tuberculosis assumes that all of the value created by a vaccine can be ascribed to the APC alone.

● Non-eligible countries are found to be especially difficult to handle. It is not clear that these countries could be prevented from acting in ways to undermine an APC for eligible countries. Neither is it clear that non-eligible countries (perhaps including Russia, China, and India) would contribute to expensive efforts, such as the 'Global HIV Vaccine Enterprise', if they suspect that they will then become non-eligible countries at the APC stage and face higher non-eligible prices for much longer. Before they agree to take part in the 'Global HIV Vaccine Enterprise', their exact status vis a vis an HIV APC will need to be resolved.

● Any product that will take a very long time to develop and such that the epidemiology and distribution over poor and more lucrative markets is likely to change greatly over time, is also likely to face increasing complication and dispute. A medical condition that is exclusively attached to the poor is much easier to fit within such programs. This suggests that HIV is a less appropriate application for an APC than malaria, though the increasing evidence of more widespread malaria – it is projected that by 2010 half the world's population, or 3.5 billion people, will be living in areas in which malaria is transmitted – casts doubt even on this.

● If manufacturing capacity is limited – a highly likely scenario in the early days of a new vaccine – there are also dangers that incentives are created for companies to supply more lucrative markets first (including using research results for one HIV clade for another more lucrative clade first) and only after a delay the

eligible markets. This is part of a more general risk, given that the APC is an investment 'option' to developers.

● Meanwhile, countries eligible under the APC are also found to behave in ways that potentially destroy the dynamic incentives of the program. They have a veto over success, and developers also have a strong incentive to waste resources on 'rent seeking' behavior to secure the very high subsides attached to early sales. This leads to problems of long-term multi-institution and multi-country monitoring and policing so as not to harm follow-on innovators. Again, we are led to the conclusion that it remains problematic to have the subsidy for R&D paid via a large proportion of the high price of the first relatively small tranche of subsidy-favored vaccines.

● Those early-stage developers relying on APCs face a range of *new* risks, especially those of the mechanism itself. Expected difficulties of operating the mechanism efficiently and the risks of potential discretion and of collapse of the mechanism are all hugely damaging to the value of an APC to private investors. A comparison of APCs with government-backed bonds proves instructive. Unlike bonds it is hard to see who, or how, failure of an APC could be bailed out such as not to harm vaccine developers and the speed of discovery of vaccines. It would not be surprising to find that that at a 15-25 year horizon, 80% or more of the current impact of an APC for HIV would be absorbed in the costs of risk, making an APC a very weak way to drive current R&D for an HIV vaccine.

● Given these newly-created risks, and the extremely complex process and expensive cost to develop vaccines for HIV, it is likely, in practice, that any practically useful APC for HIV would lock in at a very late date in vaccine development and would not do very much to repay the total R&D costs of developing the HIV vaccine(s). Due to the large costs of HIV vaccine development falling outside of the APC, it would also require a different set of IP arrangements to those currently being suggested. HIV APCs would end up being all about scale and low production costs, the encouragement of multiple manufacturers, access to IP and know-how, and access to the vaccines. This is quite unlike the early-stage APCs currently being proposed.

● Vaccine development involves large sunk investments and, because of the inability to know many of the factors relevant to fixing the terms of APC contracts far in advance, developers working under an APC will continue to expect the risk of dynamic inconsistency – the situation that arises when investment is irretrievably sunk and more favourable terms can be extracted from developers ex post, with the expectation of this feeding back to numb the incentive to do the investment in the first place. Firms will find that they compete twice – at the R&D stage, and at the APC stage through rent-seeking behavior. Even small risks of this arising will generate large needed extra risk premia. The paper enumerates simple cases. Getting rid of this risk requires credible contracts, yet achieving this credibility in any meaningful sense for early-stage vaccines is far more difficult than is currently intimated. Dynamic inconsistency does not go away under an APC; it simply metamorphosizes from a problem in the marketplace and with patents, into a problem with sponsors, their delegated APC institutions, and firms. The large (expected) gains to be made from rent-seeking

the committee's decision also undermines the competitiveness of the program, especially deterring smaller, less powerful, players.

This yet again suggests that paying a large amount of the R&D costs through large subsidies to the first 'few' vaccines of early 'winners' is still going to create a range of problems. Into the bargain, dominant and rent-seeking players face a great deal of 'reputation risk' that they might rather have avoided.

● A large chunk of the value of early-stage APCs rests on their supposed ability to create long-term supply and cheap products – say at $1 per course of treatment. The current proposed contracts call for determining, at the time of signing contracts at the very start of the process, the 'guaranteed' long-term price or an ex ante methodology for determining it, and for the obligation of a company to supply *at that price* in the long-term – with penalties for not doing so – in return for having had the short-term advantage of initial sales at high, heavily subsidized, guaranteed prices. None of these parts of the mechanism are found to be viable. Indeed, failure on these points ultimately undermines R&D incentives. Current analysis is based on the unrealistic assumption that production costs will be as low as a dollar or so for both the first 200 million doses as well as for the long-term supply. A great deal more attention needs to be paid to the state of competition and the number of suppliers after the first 200 million-or-so treatments are gone, as well as to the production cost of the first 200 million treatments.

● The paper discusses a range of current problems in the process of R&D for complicated early-stage vaccines, including: an overly-narrow research focus; cost of capital difficulties when the same few large firms research both the vaccines and drugs for the same conditions; and the problem of insufficient (and shrinking) global vaccine production capacity. The paper finds that APCs, as currently proposed, tend to reinforce many of these problems. It is also not clear that the underlying financial basis to the model – an emphasis on free cash flow with reward all at the end of the program – and the repeated practical biases towards large pharmaceutical players, does not instead aggravate these problems.

It might be possible that some of these problems could be corrected through push parts of the overall mechanism – especially problems relating to the breadth of vaccine leads investigated – but this needs to be more fully explored. Similarly, alternative forms of finance to expand the number of vaccine producers needs to be explored, but it is unclear how an APC would adjust for this.

With the ever-increasing competition for the skills-base and resources caused by the expansion in research for bioterrorism, it may be more productive to target a wider range of ways to increase capacity, to provide wider forms of funding to a wider range of players, and to encourage technology transfer and similar measures – rather than emphasizing the response of the shrinking pool of current large pharmaceutical firms.

● APCs for early-stage vaccines place a disproportionate amount of their risk on to biotechs. 'Mechanism risk' and the risks of 'dynamic inconsistency' are especially high for such investors. And if the program collapses – indeed, biotech

investor reactions to just such a possibility may make this self-fulfilling – it is biotechs and their investors, and not large pharmaceutical firms, who will pay the heaviest price. Ordinarily, large pharmaceutical firms would set milestone payments into contracts, *given* the expected market. However, because of the many risks of substitute-market mechanisms such as APCs, biotechs may wish (and, indeed, they have requested) to be protected from these risks by interim payments contained *within the program* itself. This imposes large informational and monitoring demands on those organizing the program. It is hard to imagine that they could structure such interim payments to be remotely efficient, given the extraordinarily complex distribution pattern of subsidy payment that it would entail overall.

● There are also a large range of institutional, legal, and IPR issues that are still to be resolved. Given the presence of many other funding mechanisms and research interests (including PPPs), and the mix of eligible and non-eligible countries, APCs would generate a potentially highly complicated IP, institutional, and legal tangle with potentially very unclear jurisdiction. Some of these issues could be resolved in interesting ways – for example via technology/know-how transfer as part of an APC, or IP ownership in the hands of more than just the 'winner' after a certain point in time. However, resolving this in a piecemeal way simply makes APCs more opaque, harder to operationally evaluate, and even less clear as an incentive signal to private finance.

● Liability issues impact at many levels, from those setting the APC terms right up to firms and regulatory institutions seeking to satisfy the terms. The current proposal is that the sponsor(s) fully indemnify the committee running the program – even as control over their funding is lost to a committee with discretion – with the eventual designated supplier to defend and indemnify the sponsor and members of the committee. As currently proposed, this therefore narrows down the potential participants to only the world's largest companies. There is also heavy reliance on third parties, such as the WHO, but they are nevertheless expected to relinquish all decision-making powers to the controlling committee. It is not at all clear that this could work. What firm wants the PR disaster of suing the World Bank, the Gates Foundation, a PPP, or the WHO? To help achieve 'credibility' it would be desirable for APCs to be operationally independent of sponsoring institutions, but it is not clear that this could be so.

This attitude seems to have been modified somewhat recently, and issues of liability risk have been separated out, in discussion at least, from the actual program itself. It will be interesting to see how this develops.

Having reviewed a range of early-stage APC problems, the paper turns attention to late-stage and already existing vaccines. For this latter group of vaccines, purchase commitments are all about removing risk, creating stability of demand, incentives to invest in production capacity, the tailoring of an already existing product to new users, the creation of low product prices, and access. The paper emphasizes these positive merits and strongly encourages these sorts of commitments. To try to elucidate what purchase commitments can and cannot achieve, the paper reviews a range of past and future vaccines, including hepatitis

B, haemophilus influenzae type B (Hib), smallpox, African trivalent meningitis vaccine, and meningitis conjugate C, pneumococcus, and rotavirus.

None of these case-studies remotely matches any APC being proposed for HIV, malaria, or tuberculosis. Many of the problems discussed above fall away the more late-stage a vaccine is. Commitments become increasingly more efficient, and easier to set since good information to guide the setting of terms is increasingly available, including through standard competitive tenders and through access to scientific information. Commitments become much more easy to make 'additional', via procurement and other devices. There are 'relatively' low levels of capital costs (compared to, e.g. the case of HIV vaccines), and there are much lower risks to biotechs. Many of these reasons are 'fungible' – they apply whatever the source of funding and whoever carries out the research.

The case-studies illustrate a range of current faults in need of rectification. These include an over-reliance on short-run contracts, a range of current market-based risks such as poor demand forecasting, and the need for 'distribution commitments', 'vaccine/health infrastructure commitments', and commitments to tackle market risk at many levels.

In many practical case-studies the breakthrough was through lower production costs. The volume of current purchases is a key variable in this, as are technology issues. What are the incentives and sources of competition for this? Since achieving multiple producers will depend on access to technology, IP, and know-how, especially at the manufacture and distribution stages, how is this achieved sufficiently early (bearing in mind the high fixed cost and long lags in creating new vaccine capacity) and to ensure long-term supply at low price?

In the cases of vaccines for the poor, there has been an increasingly important role for developing/emerging country developers and manufacturers. For these countries, improvements in their own regulatory infrastructures were important in lowering costs, as were wider sources of finance – and not just the 'deep pockets' finance of big pharmaceutical companies – for a wider set of players. Many of these features are mutually reinforcing, with purchase commitments also having features of coordination devices for other parts of the overall solution. Yet, many of these purchase commitments are *not* 'committee-driven' over long horizons. Indeed, the precommitted early-stage APCs in the literature would have conflicted with many of these purchase initiatives.

The paper reviews the many scientific difficulties of developing HIV vaccines. The reality is not found to match particularly well that being presumed in the economic models underlying APCs for HIV vaccine(s). Instead of a simple, linear, unidirectional structure of discovery, the structure is found to be much more cumulative and reflexive, with knowledge links back and forth. Much HIV information discovery has large public-good features rather than the pure private-good nature presumed in the simple underlying models.

The complications and challenges posed by combination and therapeutic HIV vaccines are also explored. How the structure of an APC of the sort being proposed could reward such vaccine developments is not at all obvious. Indeed,

APCs as currently proposed for HIV would tend to aggravate this. The case of HIV especially illustrates the need for a broader research front, and, again, on its own, an APC would not obviously encourage this.

Some first thoughts on the nature of a 'Global HIV Vaccine Enterprise' are introduced. Several features are drawn out including the importance of continuous, ongoing competition, rather than competition through a committee at one point based on out-of date 'rules'. It is not obvious that the best approach would be to 'save up' the reward till the end, rather than distribute it over time.

The paper (extremely) tentatively suggests what the structure of such a 'Global HIV Vaccine Enterprise' might look like. It suggests a combination of at least four *interlocking* components. It argues that each is necessary; to have one without the others is, in most cases, worse than not having it at all. These components include: a range of IP changes and more use of certain kinds of 'novel' IP instruments; financial instruments that are connected to IP; an open collaborative information processing mechanism – including expanded highly transparent clinical and preclinical trials and harmonized regulation – that is linked to IP and to the financial mechanism; and (for lack of a better phrase) 'contingent purchase commitment' contracts, with much more emphasis on production and distribution, the terms of which could not be set in advance. Indeed if there had been less obsession with creating an instrument of value for one or two large pharmaceutical players, the currently proposed instruments would, it is argued here, likely have looked much more like these contingent contracts rather than the benchmark contracts described above.

The paper looks at the case of malaria vaccines, in light of the recent interest in a potential vaccine being developed by GSK Biologicals, and seeks to articulate the much greater complexity and challenge of the scientific problem than is often communicated in the media and, indeed, in the discussion about APCs for 'a' malaria vaccine. In particular, it argues that different vaccines will be needed, and that if an APC of the sort described in the literature is used and if incentives are not to be distorted, this will require the extremely complicated disbursement of APC funds across vaccines over time, even as the rules governing this disbursement must be credibly fixed in advance based on knowledge of the future science and vaccine needs. It is hard to visualize that this could ever be done in practice, or, more importantly, that investors would ever believe that it could be done. Current (UK) policy pronouncements seem to be interpreting the notion of an APC as a first-come first-served 'prize', rather than this more complicated interpretation.

Indeed, GSK is currently negotiating a further major injection of funding from the Gates Foundation, suggesting that GSK are themselves less convinced of the power and usefulness of the benchmark APC route than politicians. The conclusion is that the terms of the current malaria deal, and the mechanism in which *it* is embedded, have to be set out (and, for the sake of efficiency, be completely transparent) along with a commitment, backed up by resources, to find the much 'better' vaccine, with this intent spelled out to GSK and others from the start. Indeed this larger effort should be initiated *now*, so as *not* to make it less likely to happen, and should be part of the thinking about *this* case. The political

danger is that the early, partially efficacious, vaccine is much more salient and politically valuable than the lost, much more efficacious, vaccine that is never seen or felt. Given the huge range of extremely positive activity going on – with up to fifteen PPP-backed vaccines entering clinical trials in the next few years – it is not at all clear that the APC mechanism would be the best route to fund all this activity.

We discuss a range of APC issues that the malaria vaccine case illustrates well, including: the problems of interacting a benchmark APC with a complex PPP setting; the problems of generating ultimately 'better' vaccines, especially when there are at least three general approaches to malaria vaccine development with one currently much more explored than the others, and the risk that this poses to those working on current approaches; and the impact of the malaria genome – especially in creating risks for investors into current vaccine projects. It also discusses the importance and priority of a range of treatment and prevention initiatives, all of which are greatly underfunded.

The paper discusses the politics of APCs. It warns against a PR-based approach taking over from an approach based on rigorous and critical economic and financial analysis of early-stage APCs, and against the use of evidence that has been heavily selected, and even selectively created, to bolster a case for APCs for HIV, malaria, and tuberculosis. It is also argued that promoters of the APC route early-stage vaccines are often too off-hand in their treatment of failure of the approach. There *are* costs to failure: the real resource costs have to be borne by pharmaceutical firms and their shareholders; it is not clear that the program organizers would not *themselves* face costs and litigation if part of the fault lies with them; and the real losers are those who do not get vaccines if the approach fails or if alternative approaches that might have succeeded have lost out to this approach.

The paper argues that APC advocates, inadvertently perhaps, also run the risk of providing intellectual succor and reassurance to those thinking of cutting back vaccine research, especially for HIV, in the face of tightening budgetary pressures, and that, indeed, this risks deterring private investors – whose projects feed off this research. The sensible approach in the light of the inherently experimental, speculative, nature of such instruments, the dangers of further delay, the dangers of losing IP rights, and given that we have never *tried* such instruments on *anything*, is to cross-examine – 'stress test' – every aspect of the proposal, and to appeal to independent empirical evidence. It is argued that enacting APCs for HIV, malaria or tuberculosis without learning a great deal first through practical application to other cases runs a series of large risks.

In light of an impending G8 Summit with health issues as a high priority, the paper finishes by suggesting an order of G8 priorities:

First, fully funding the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies, as a way to boost vaccine developers *now*;

Second, securing a seriously large injection of funding into existing global/regional consortia/PPP's and emerging vaccine enterprises, and increasing the accountability and quality of evaluation of these mechanisms, rather than issuing huge way-off financial promises and setting up yet more complex institutional mechanisms that will simply act as a drain on current 'systems capacity';

Third, purchase commitments for all of the late-stage products in which they are likely to have at least some strength, with the emphasis on getting product price down, the creative use of IP and know-how, and the opening up of the market to more competition at late stages of development and procurement;

Fourth, putting in place an 'Advanced Distribution Commitment' commiting to fully funding the delivery mechanisms for HIV, malaria, and TB vaccines once developed, including a commitment to remove the barriers to the provision of healthcare in developing economies themselves;

Fifth, downplaying early-stage APCs and – instead of falsely raising policy-makers hopes – concentrate on convincing policy-makers that they need to bite the bullet about paying for up-front HIV vaccine work through a much more collaborative system than we now have, and by fully backing the 'Global HIV Vaccine Enterprise' and other vaccine enterprises. It is argues that such vaccine enterprises should have complete control over whether or not they choose to set up purchase commitments and should not have a large separate APC mechanism imposed from outside, given that this (especially the IP implications) risks aggravating the problems of such enterprises. Such APCs would have little impact for many years yet be an irrevocable, but badly fixed, experiment that would aggravate more collaborative approaches.

The paper finishes by analyzing the likely outcomes of the 2004-6 G8 Summits. It concludes that the 'Global HIV Vaccine Enterprise' could have been much more strategically promoted – as one of the few things that might have achieved G8 agreement and success. The Enterprise approach has the great benefit, compared to many other items on the agenda, of already having the commitment of the US. Furthermore, the next G8 holder, Russia, has *more than any other country to gain from a 'Global HIV Vaccine Enterprise'* and could be a great deal more willing to take the baton than currently seems the case. From Russia's perspective, an HIV APC is the least desirable outcome, since by being a likely non-eligible country it would face much higher prices than for vaccines generated under a 'Global HIV Vaccine Enterprise'. Passing an emerging 'Global HIV Vaccine Enterprise' from the USA 2004 G8 agenda onto the Russia 2006 G8 agenda would have the double impact of helping Russia and others to face up to their impending crises. Given the increasing budgetary pressures both in the US, the UK, and elsewhere, now is a better time than later to be doing something to push the initiative forward and to lock in funding. This would be no mean achievement, whatever else comes out of this year's G8 summit.

PART 1. INTRODUCTION AND A BENCHMARK MODEL

1.1. The General Policy Environment

Several thousand people in developing countries will die of infectious or parasitic diseases by the time you have finished reading this paper[2]. Many could have been saved by access to already developed vaccines and drugs, and much unnecessary pain and suffering avoided. In addition, barely more than one percent of total global spending on pharmaceuticals goes into the research and development of *new* products for diseases affecting 90% of the world's population[3]. It is a sign of hope, of frustration, of the craving for the human dignity and worth of others, that a variety of groups are currently engaged in a wide-ranging – and sometimes uncomfortable – debate about how to redress this imbalance.

Important strides have been made recently with the announcement of large fresh funds to purchase vaccines and to roll out immunization programs. The UK has promised $1.8bn (£960m) over 15 years, the Bill and Melinda Gates foundation a fresh $750m, and Norway $290m. One of the highlights of the UK's presidency of the G8 and the European Union this year could be significant progress on the vaccine front.

A highly heterogeneous problem

The vaccine problem is highly heterogeneous. It ranges from the low or non-use of many already existing, already cheap or even practically costless, vaccines[4], to the tantalizingly slow development of 'late-stage' vaccines – where most of the science is already known and a viable product is close to development –, to the dim and distant prospects of the development of 'early-stage' highly complex vaccines, such as those for HIV, malaria, and tuberculosis – where there are either no viable vaccines on the horizon or the current candidates fall well short of 100% effectiveness, and many of the scientific difficulties have yet to be resolved. In the media, this range of problems has tended to be lumped together, and the term 'advance purchase commitment'[5], APC, has also come to conflate them somewhat.

---

[2] 40,000+ per day divided by the time taken to read this paper.

[3] 10%-15% of global pharmaceutical spending goes into R&D, and barely 10% of this goes into 90% of the global disease burden.

[4] In the marginal cost sense. Once one gets above a certain production scale, most of the cost of an additional vaccine in the case of many already existing vaccines is the device for administering the vaccine and its wrapping. The actual vaccine itself may cost as little as a few cents; most of the value is in the 'information', contained within the vaccine, that is the result of the R&D process that led to the discovery of that information. The combined diphtheria, tetanus and pertussis (DTP) vaccine costs about $0.09 a dose, and the measles vaccine costs about $0.14 a dose. Nevertheless, some more recent vaccines and future vaccines, such as those for HIV, may not be as cheap to manufacture, at least in the first instance.

[5] 'Advance Purchase Precommitment', APP, would be a more precise descriptor because in some cases policy-makers really would be asked to commit themselves before they knew very much about what they were committing themselves to. The term Advance Purchase Precommitment was used a great deal in the early days of development of the advance purchase idea. However, due to its more common parlance, 'advance purchase commitment' or APC for short, is used here. This paper also uses the phrase 'advance purchase commitment' instead of 'AdvanceMarket

Recent confusions

This confusion has been reflected in recent policy pronouncements. In discussing the proposed new International Financing Facility, IFF, the highly effective and hugely laudable use of funds to make current purchases of already existing, cheap, vaccines (for diseases such as measles, pertussis, tetanus, and for Hib-related diseases), to roll out major treatment programs, and to save millions of lives, has often been treated in the same breath as 'paying' for a long and expensive R&D process – through APCs – for currently non-existent and way-off HIV and malaria vaccines. Much of the recent body of work generated on 'pull' mechanisms has not helped either by constantly using late-stage language to discuss early-stage vaccines, suggesting that there are few, if any, distinctions, and ignoring many problems special to early-stage vaccines. Indeed, the core model used to describe HIV APCs[6] makes no concession at all to it *not* being a late-stage vaccine.

The pull strength of APCs varies greatly, and it has not helped to constantly conflate potentially useful and comparatively straightforward uses with much weaker and much more problematic cases. Worse, it has lulled policy-makers into a false sense of security. In many ways this paper is a call for balance in this debate, for better use of terminology, and for better assessment of the relative use of the various R&D instruments.

Redressing the balance

This paper may come across as lop-sided in its pursuit of the problematic in early-stage APCs, and some may also ague that too little attention has been paid to problems with *alternative* incentive mechanisms. However, given the relentlessly positive presentation of APCs for early-stage vaccines – from the heavily-biased cost effectiveness estimates presented in the original No. 10 Policy Unit material, through a series of CGD reports that repeatedly leave out problematic details, to current APC cost-effectiveness papers[7] that ignore all costs of developing a vaccine *other than* the APC itself and are thus able to claim: "Three Billion Dollars Per Disease…At this price, the advance market commitment would be a

---

commitment' for several reasons. First, it captures the notion that it *is* a commitment to purchase. Second, because in a previous paper (Farlow, 2004, ibid.) 'advance purchase commitments' were described in ways that are essentially the notion captured in 'AdvanceMarket commitments' when they are properly articulated; once one recognizes that advance purchase commitments are complicated devices supposedly attempting to create *additional* market – through a precise set of rules but also with layers of institutions and discretion – then there is no difficulty in using the terms interchangeably. Third, the sort of contracts negotiated will likely not be based on 'AdvanceMarket' logic anyway, but will be based on much narrower remits, such as just being an implicit subsidy to a domestic firm. Fourth, the language of 'AdvanceMarket' would tend to suggest a fact rather than a hypothesis in need of evidence. It is not immediately apparent that much of an additional 'advance market' for an HIV vaccine would actually be created by an 'AdvanceMarket' instrument. That this can be achieved needs to be proven, not prejudged in our use of language.

[6] Kremer, M. Appendix 3 http://www.pm.gov.uk/files/pdf/Appendix%203.pdf.

[7] NBER Working Paper Series "Advanced Purchase Commitments for a Malaria Vaccine: Estimating Costs and Effectiveness" Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., Williams, H. Working Paper 11288 www.nber.org/papers/w11288, April 2005.

bargain compared with many other development expenditures"[8] – this is to be expected in any effort to redress the balance.

Besides, there is a vigorous debate about the alternative incentive instruments, and one can hardly be criticized when one is trying to fill out a niche in the debate that one is not adding to the already voluminous material on other incentive mechanisms[9]. Besides, each mechanism must survive or fall based on its ability to survive critical evaluation. This paper seeks to contribute some of that evaluation. Others have to decide the outcome on the basis of this and that much greater body of other material.

Recent pull analysis

Recent influential work on 'pull' mechanisms has been produced by the Center for Global Development in Washington, D.C. with financial help from the Bill and Melinda Gates Foundation. This current paper analyses that work, especially 'Making Markets for Vaccines: A Practical Plan'[10] and the book 'Strong Medicine'[11], and will make frequent references to these publications. Much of that work takes as given the large body of earlier work deposited at the UK's No. 10 Policy Unit website[12] – with its heavy bias towards early-stage vaccines – created almost entirely by one or two individuals who also wrote much of the later publications too. For all the names attached to these files, surprisingly few are involved in any great capacity.

This earlier work raises many fundamental issues that require full and transparent discussion before large permanently-set early-stage APCs could ever be enacted for complicated vaccines such as HIV, malaria, and TB. Yet neither the No. 10 Policy Unit nor the UK Treasury independently analyzed what they were given. An extensive previous paper[13] took a closer look at the No. 10 Policy Unit material, and argued that the proposal raised many questions that still had not been answered. That paper was handed over and briefly discussed with a few key individuals at the Center for Global Development. However, and in spite of

[8] CGD press release, 6 April 2005, page 1. This is an extraordinary way to judge APCs. If developing an HIV vaccine were to take $1.2billion per year for at least 15 years (as currently suggested by IAVI) and an APC locked in to pay for very late activity and to allocate the IP rights, this would be like a plumber turning up to fix the plumbing on a $1million house and then claiming that they had added $900,000 of the house's value by making it liveable and that their work should be valued accordingly.

[9] It might also be added that there is only one of me, whereas many of those making these points are part of huge teams working specifically on these issues (the Berndt et. al. paper alone has seven co-authors), and have much higher levels of resources and much more time to do these things than just one author, who also happens to be working on many other areas of economics besides this. That I don't do a voluminous literature review on the problems of other approaches is, to the say the least, a little unfair. Perhaps those making this criticism should stick to trying to make a better case for advance purchase precommitments for HIV, malaria, and tuberculosis and see if they can't beat the case being made here?

[10] Center for Global Development, 'Making Markets for Vaccines: a practical plan' 2005, www.cgdev.org/publications/vaccine. This is referred to as 'Making Markets' from now on. Also go to http://www.cgdev.org to see the great variety of other, often very excellent, development-related work carried out at the Center for Global Development.

[11] 'Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases', Kremer, M, and Glennerster, R, Princeton University Press, November, 2004.

[12] http://www.number-10.gov.uk/su/health/default.htm.

[13] Farlow, 2004, ibid.

agreeing at the time with many of the unresolved issues, many of the issues remained unresolved more than a year later.

Some of those issues form part of the basis of what follows. One would expect for something that has to be *permanently and irretrievably fixed* to have any effectiveness[14], that teams of financial and industrial economists, and many more experts on the practical aspects of developing, distributing, and using vaccines, would have been set the task of 'stress testing' the framework against all eventualities. But this has not been the attitude. And one must wonder why not.

Indeed, many of these issues have been a source of concern for many years[15]. That they still persist more than eight years after the idea first surfaced (though only very recently taking on the guise of an "Advance Market Commitment") and after a great deal of effort by a great number of individuals – not to mention of a great deal of funding – says something about the underlying problems of relying on such programs to drive R&D for these vaccines.

A wide variety of individuals involved in pull analysis

Those involved in advising on 'pull' and other proposals are themselves a pretty heterogeneous group, with some indeed promoting the approach as a panacea for all vaccine R&D ills and hardly ever referring to anything else, and others having a much less exaggerated perspective, trying to see how the proposals might fit into a larger picture running from currently existing vaccines right through to early-stage vaccines[16]. There is a danger of reducing this wide and complex set of viewpoints to a caricature of the most blinkered, and this must be avoided. It would be wrong to suggest that some do not have their doubts about the greater journey ahead. And, in spite of sometimes strong differences of opinion, we should also not lose sight of the fact that *all* of those involved (including those that this author strongly disagrees with) are motivated at a very deep level by the need to tackle the suffering they see.

1.2. The Structure of This Paper

The first half of this paper reviews early-stage (Section 2) and late-stage (Section 3) APCs for vaccines, and attempts to delineate situations when they are likely to be strong. The concern here is with whether or not such instruments can be made practicable. It argues that there are cases when this may be so – already-existing products and some current late-stage vaccines when the contract is designed properly. However, the efficiency of APCs for complicated early-stage vaccines like HIV is not just unproven but likely to be very low, even as the presence of such instruments creates unwanted complications and side-effects later and faces any large pharmaceutical firm that might show any interest in pursuing them with

[14] Given the discount factors involved, 15-30 years is effectively 'for ever'. The dangers of signalling to investors that the program might be allowed to collapse, and hence sending capital costs dramatically rising thus bringing about collapse, also militates against opt-out and sunset clauses and against making the program reversible.

[15] The Sabin Vaccine Institute colloquium held at Cold Spring Harbor, New York, 5 – 7 December 1997 identified many of the issues and reservations still unresolved in the CGD's 2005 report (see Muraskin, W. "Vaccines for Developing Economies: Who will Pay?" Albert B. Sabin Vaccine Institute, New Canaan, CT, USA., 2001).

[16] This means that many of the critics, including this one, fit into the group of pull advocates!

an unenviable set of reputation damage-limitation exercises. Such firms, and thus any biotechs relying on them, might prefer alternatives that inflict less risk.

In the case of late-stage vaccines, there are relatively low levels of capital costs, low levels of crowding out (explained below), good information on how to efficiently set terms (especially if competitive tenders are possible), ability to use IP in ways to encourage competition and to keep the market open to many potential developers and producers, and incentives to create cheaper vaccines. Throughout this article, 'capital costs' refers exclusively to the costs of the finance used, and includes the required return to cover *all* risk being borne, including the potentially high risk created by the mechanism itself (i.e. 'capital cost' does not refer to physical real capital investment but to the costs of finance). With early-stage vaccines, most of the APC funds get eaten up paying for extremely high capital costs, there is high crowding out and poor additionality of the incentive, poor information on how to set terms correctly leading to serious under- or overshooting in the size of the incentive, problems in encouraging 'quality' vaccines, problems with very tight IP and secrecy leading to large players being heavily advantaged over small players, insufficient competition and poor incentives to create cheaper and follow-on vaccines, and far too much risk placed on developers by the 'tendering' mechanism which is nothing like a standard tender and certainly not likely to be especially competitive.

In addition, since the 'framework agreement', policed by a committee, *is* the tender, a great deal of risk is fed onto developers if the framework agreement fails to work (or even is just *expected* to have problems in working) or if the committee malfunctions (or is expected to 'malfunction', including via 'capture') or if there is not enough competition (the most likely outcome in the early-stage vaccine cases discussed below). This is *very* different from a standard competitive tender. Designing and implementing such instruments to incentivize high-quality early-stage products, and follow-on products, is a great deal more complicated than ever made out in this literature. And, it is argued here, largely unworkable in practice.

Since most of the problems fall away the later in the process purchase commitments are placed, it is extremely important to get a handle on the problems in order to work out exactly where in the R&D chain to place such commitments. Indeed, when we look at the sources of success in concrete examples in Section 3, in many cases one of the reasons that late-stage vaccine purchase commitments might prove so effective is precisely because early-stage purchase commitments are not in place to get in the way.

In the second half of the paper, the possible workings of the Global HIV Vaccine Enterprise are considered (Sections 4 and 5)[17]. Interestingly, research into both this and purchase commitment approaches have been financially supported by the Bill and Melinda Gates Foundation. Just as in vaccine and drug development, when it is unclear *a priori* which of various approaches might work, it is eminently sensible to spread resources widely and to explore multiple potential

[17] For similarities with a previous global effort, see Waterston RH, Lander ES, Sulston JE, 2002, "On the sequencing of the human genome". Proc Natl Acad Sci USA 99: 3712–3716.

leads. Unfortunately (and ironically) this is interpreted by some of those who get funding as somehow *endorsing* their approach over that of others[18].

Within such a vaccine enterprise, purchase commitments have a place, but they are much more like standard competitive procurement contracts than the contracts described in 'Strong Medicine', do not involve a pre-set size of additional blockbuster market, have terms that would not be fixed many years in advance of much of the science being known, involve much more risk sharing – largely in exchange for collaborative behavior and more sharing of IP –, and involve financial instruments that include stock market finance but are less dependent on it as a proportion of overall finance.

Section 6 takes a look at the unfolding case of a malaria APC to illustrate a range of issues in need of a great deal more care and attention.

Section 7 focuses on the growing movement to cut global HIV vaccine research, and the role of APCs in encouraging and justifying this movement. It finishes by discussing the dangers that APCs for HIV are diverting attention away from more bold opportunities, and it suggests an alternative set of priorities for the 2005 G8 Summit.

Probably the main policy conclusion of this paper is that the ground should be cleared for the Global HIV Vaccine Enterprise and similar-styled enterprises for malaria and tuberculosis and other vaccines. If there are ever any 'advance purchase' commitments put in place, it should be at the behest of such enterprises as and when they feel that they would be useful, and that such commitments should not be set up independently, since that would complicate the situation facing the enterprises and be potentially damaging to what they are trying to achieve. Meanwhile – and especially given the strong current pressures to cut global funding for HIV vaccine research – the British government's strategy for the G8 must be to ensure that these enterprises are fully-funded, and that the next holder of the G8, Russia, is in a position to take the initiative forward.

1.3. An 'Early-Stage' Vaccine Commitment is an Experiment

Until very recently it seemed that an approach to early-stage vaccine APCs was evolving, with awareness of the many potential difficulties and plenty of room for movement in thinking. However, with policy-makers suddenly very interested in enacting *something* – maybe even *anything* – initial reservations have been cast aside, and the aim has shifted to getting policy-makers to agree to large HIV and malaria APCs and to worry about the details later. Instead of critical and balanced analysis, there has been ever increasing positive and simplistic spin and the brushing aside of key 'problems'.

[18] At least this is being consistent with the underlying logic in the advance purchase literature for HIV vaccines of knowing all of the information about the vaccine or vaccines being sought before setting out to write the terms that will help one find them – of knowing where to find success before one goes looking for it.

This is quite the wrong way to enact good economic policy, and even more so for an economic instrument that *has to be irreversibly fixed*[19] to even stand a chance of working, and that is also, by definition, an *experiment*. Since we cannot conduct experiments in real-life problems such as this, the only logical route open to us is to: i) stress-test in every which way possible the concept of APCs, especially the financial and industrial sides to the modeling underlying them; ii) look at past examples and see what experience can be drawn from them; iii) experiment and build up from simpler to more difficult applications, and not jump to the more difficult applications first. The attitude has been to have none of this. Instead, we are supposed to just try the instrument and see what happens:

> "*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.*" [20]

So, it is fixed 'for ever', and yet it is an experiment? If the reader has not started to worry by now, this alone should start the process. The current rush to fix large, irrevocable APCs for HIV and malaria, regardless of evidence of cost effectiveness, or knowledge that they will work (and, indeed, that they will not simply 'get in the way'), is likely to be not just expensive but counterproductive, slowing down the speed of vaccine development and the quality of vaccines, for a given budget, compared to alternative approaches.

This paper argues the need for a more rational, open, and above all critical, discussion of this material, not just to work out where problems lie, but for the more positive purpose of working out exactly when such instruments are likely to be powerful, how they might be modified to actually work, and how they should be set vis a vis other instruments. In many ways this paper only goes over some of the ground the Center for Global Development Pull Working Group should have gone over in its deliberations, and lays down some of the awkward issues that those chairing that group should have laid before it for discussion[21].

1.4. The Idealised Benchmark 'Advance Purchase Commitment'

The phrase 'APCs' has come to have varying degrees of strictness in both interpretation and application. At one extreme it has been interpreted as just a generalized notion of 'willingness to pay' for vaccines. However, at the other extreme, there is a benchmark for when such devices are used to stimulate privately financed R&D, and it is worth setting that out exactly, so that we can compare and contrast *that* with real-world enactments. No incentive instrument ever achieves an idealized enactment. The interest is in how far short applications fall, and how easy it is to achieve an idealized application. One of the presuppositions of much of the 'empirical' APC literature is that an idealized

[19] Given standard rates of time discounting, 30 years is effectively 'for ever'.

[20] 'Strong Medicine' p84 and 'Making Markets' March 2005 p46. This statement *really is* in both of these publications. The skeptic can go and read if for themselves. Incidentally, we really would have to wait thirty years to abandon the approach if it was not working, as will be explained below.

[21] It's job, after all, was to evaluate the feasibility of the proposal and *not* to advocate, or to rubber-stamp, policy made elsewhere.

enactment is achieved each time. However, it is sobering to think that we have never had an APC meeting conditions even remotely approaching the benchmark criteria for even the most simple of drug or vaccine cases, nor, indeed, for any other product. And recent policy pronouncements for early-stage vaccines (malaria and HIV in particular) do not begin to approach the benchmark either. How far they fall short, and the implications of this for vaccine development, is an interesting policy issue in its own right[22]. Quite why policymakers would even consider starting with what must be some of the most complicated possible applications ever is quite beyond this author.

The idealized benchmark

APCs for vaccines are *legally binding* contracts (on only the funders in the case of early-stage vaccines[23]) that, to all intents and purposes from an economic perspective, *commit* '*for ever*' a sum of money for the purchase of a vaccine or vaccines for a particular disease. According to the literature, this would be anything in the region of, say, $3bn-$10bn per major early-stage vaccine though the eventual sum is not clear and could – and would – be a great deal higher. The suggested appropriate figure has kept falling and is now $3bn[24] though that is now described as only 'illustrative'[25] and has gone back up to $4bn in recent policy pronouncements[26]. One would think that if there was anything scientific at all about the approach, a billion dollars here and there might matter. Again we get evidence that the figure is based, as a vaccine expert put it to the author, on no more than 'kitchen table' calculations. Pitching to the lower end of the range (indeed pushing the lower range ever lower) has become popular just recently, but we will later see that this is very damaging behavior if the true requirement is much higher.

This is not the whole cost of developing a vaccine. The overall cost includes all public funding needed outside of the mechanism in order to make it work, as well as subsidies, tax-breaks, and other benefits private firms are granted for their research[27] (to the extent that a large *multiple* of these is not removed later from payments, as will be explained below).

---

[22] The worst case is when they promise the level of payments supposedly based on an application of the benchmark idealised model (i.e. a large 'pot') but then don't actually enact any of the rest of the framework (though this paper argues that they could not, in all likelihood, enact much of the theoretical framework even if they wanted to).

[23] Though, funders may also have an opt-out if the contracts fail to stimulate '*enough*' research.

[24] See "Making Markets for Vaccines," Chapter 5, "$3bn per disease," and CGD press release: "Three Billion Dollars Per Disease…a market of about $3 billion is needed," and The Commission for Africa, February 2005: "For Malaria, the market size needed to deliver the malaria vaccine is $3 billion (CGD, 2004)." (http://commissionforafrica.org/english/report/thereport/cfafullreport_copy.pdf page 409, Chapter 6 Footnote 92).

[25] "Answering Concerns about Making Markets for Vaccines," Barder, O., Kremer, M., and Levine, R, 9 May 2005. Page 8 refers to the "the illustrative figure of $3 billion…intended to illustrate the concept, not fix a precise amount." www.cgdev.org/Publications/vaccine/_files/Response to Concerns.pdf.

[26] Gordon Brown (The Observer Newspaper, June 5, 2005, page 30) quotes $4bn for malaria.

[27] Indeed the Gordon Brown op-ed mentioned a new tax credit to stimulate UK research into diseases prevalent in the developing world, but does not clarify whether that would come off any APC payment or would be an additional publicly funded cost to the APC.

The size of the fund (and its distribution over developers) must be set *precisely* high enough to re-create the *precise* size of *additional* market needed to encourage the entry of the *precise* amount of venture capital and stock market finance needed for the *remaining* research and development needed to produce a 'high quality' vaccine or series of vaccines (that will be needed over time, especially in the case of malaria and HIV). R&D costs would then be fully repaid through the purchase of a *successful* vaccine or several vaccines in a particular period in time (if there are several meeting eligibility conditions in any one period of time), or series of vaccines over time, and *only* the successful vaccine(s) or series of vaccines. In this sense, the 'benchmark' idealized APC is a complex subsidy program over multiple vaccine developers, with the allocation of a fixed overall amount of subsidy determined, in the absence of standard price signals, by a mixture of pre-set rules based on whatever information can be garnered at the start, and ex post discretion.

Payment would come from the taxpayers of richer countries, by foundations such as the Bill and Melinda Gates Foundation, and through co-payments made by developing countries tied, in advance, to the mechanism. The program is thus entirely foundation- and publicly-funded when it succeeds, and entirely financed by pharmaceutical firms if it fails.

Observe the multiple directions for decisions about eligible vaccines – across vaccines at a given point in time and across vaccines over time – with all expected decision rules set in the terms of the 'contract' at the start. In order to overcome any risks (as perceived by developers) that buyers will bid terms down after development, the funds are legally committed *in advance* to pay for those (and *only* those) vaccines generated in response to the mechanism on the basis of the pre-agreed rules. This is important, since one of the key justifications for the mechanism is to solve the 'time inconsistency' problem – that describes what happens when firms have sunk their R&D costs and then buyers have the power to bid prices down to levels that do not fully cover those collective R&D costs, and, knowing this in advance, no individual firm will therefore perform R&D in the first place. We will see that 'time inconsistency' continues to be an extremely difficult issue to get around under an APC. Indeed, it turns out to be intractable whatever the mechanism used to stimulate early-stage vaccine R&D, but especially so for those mechanisms concentrating payment in the end period. In addition, the more complex the science, the greater the ex post discretion, and the greater the time inconsistency. Time inconsistency can be reduced by stripping out all hints of scientific complexity (as is done in Kremer Appendix 3), but this is hardly appropriate for these early-stage vaccines.

What the winner(s) get

The 'winning' vaccine developer or developers would be paid the value of *all* the privately-funded (and *only* the privately-funded) R&D costs (including *all* capital costs) of *all* firms (both the successful and the unsuccessful, not just of itself) and *only* the private firms, who used such private funding on R&D towards the vaccine since the time the purchase commitment had been announced (and *only* since the announcement) and *only* for 'eligible' countries covered by the mechanism. The winner gets all the vaccine IP for both 'eligible' and 'non-

eligible' markets – although this is very unclear if there are PPP aspects to the creation of vaccines.

A 'blockbuster'-style model[28]

For the time being we take at face value the presumption that there will be competition between developers – though we will find that it is increasingly less obvious that this will be the case. As with the 'blockbuster' drug-development model, an individual firm will therefore treat its vaccine R&D as a lottery with a very large 'prize' that just makes it a fair risk-adjusted gamble. Individual firms calculate the expected value to it of the 'prize' on the basis of the *privately-funded* R&D activity of all other private firms. If others, not firm *i*, do more R&D, then this will reduce the chance that firm *i* will win the contract and hence the expected value to firm *i* of its investment. 'Others' *should* refer only to other firms working under this funding mechanism, and not to any other researchers working under any other funding mechanism. We will see that achieving this proves fiendishly difficult in areas of complex science involving the interplay of many different funding mechanisms and a complex mix of public and private researchers[29]. Worryingly for firm *i*, 'others' could refer to those being paid for under other funding mechanisms if these other mechanisms are not factored out of payments[30].

A first look at some *very* vague 'size' figures

To frame the thinking, it might help to have a quick overview of possible scenarios, though we also recognize that insufficient evidence has so far been presented to properly analyze early-stage vaccines, so that the figures are, of necessity, extremely rough and only 'illustrative'.

When it 'wins' the contract to supply the vaccines, it turns out that a firm's out-of-pocket costs are a tiny fraction of the contract size. For example, if 10 firms[31] put in equal effort on an early-stage HIV vaccine (again, maintaining the presumption of competition for now), and we presume that this is the optimal number of firms (we can't), and that (because of all the risks and because of the high cost form of finance being used[32]) they face an expected 70% of capital costs[33] by the time a product is developed (and we ignore all crowding out for

[28] For some reason this description has been criticised (see Barder, O., Kremer, M., and Levine, R. ibid, 9 May 2005, p8). But if the APC model were chosen as the route to develop an HIV vaccine, we really would be scuppered if the model did *not* work in a 'blockbuster' fashion with multiple competing developers and few 'winners', with winners therefore expecting 'blockbuster'-size payments. The 'blockbuster' nature of the model is a fact, and not a criticism. This fact does, however, lead to a number of consequences. In particular it is not clear how easily such frameworks work in an area of science that involves a great deal of need for coordination and 'sharing', such that investors may worry about sufficient return on their own investment. Neither is it clear that this feature does not create a range of dynamic consistency, credibility, and reputational risk issues for firms.

[29] Kremer Appendix 3 removes all of this by presuming only one mechanism and only one 'type' of researcher is actually present.

[30] Since Kremer Appendix 3 factors other mechanisms out, by default this issue never arises.

[31] This is highly simplified. There are chains of firms – biotechs and large pharmaceuticals – pursuing different product leads, with each 'chain' visualised here as a 'firm'.

[32] For some inexplicable reason this has been described as some sort of 'criticism', when in point of fact it is a straightforward, and well understood, fact.

[33] We can only guess at these figures since none have been calculated. See the discussion below.

now), and we presume for the moment that only one firm wins (though, in most cases there would, supposedly, be a complicated split over time and across firms), then a $6.25bn 'purchase commitment' will go to a firm having spent, in present discounted (2005) terms, less than $200m, on private out-of-pocket research costs. This is the efficient and 'fair' outcome and is not being critiqued here. It is in the nature of 'blockbuster' mechanisms that this is the outcome, though it does create problems for firms and for the committee running the program, as we will see below.

Incidentally, the response of one pharmaceutical executive when this was spelled out precisely was that winning such a contract for HIV would be just as much a "PR disaster" as developing an HIV vaccine under the current set-up. Throw in some of the discretionary elements (discussed below) that the firm would have to very publicly fight over in order to get a fair return in *the ex ante sense*, and it would be a "complete PR disaster", and much worse for such firms than some alternative approaches to funding.

In this case, if there were no 'crowding out' (explained in more detail below), the $6.25bn fund would 'pay for' $1.875bn of out-of-pocket R&D costs across all firms and $4.375bn of capital costs. If there is crowding out and other inefficiencies, the ratio of 'payout' to the out-of-pocket private costs could be even more extreme. In this simple case, if there were 50% crowding out, the $6.25bn fund would pay for about $900m of new out-of-pocket research costs, or about 9 months' worth of what those working on the Global HIV Vaccine Enterprise argue is actually needed. The most likely short-run response of firms to such an incentive would be to not respond at all.

But for HIV it would need a mega-blockbuster commitment

Indeed, if it really is the case that HIV vaccines might take 15 years to develop and need $1.2bn per year of out-of-pocket research and trial costs, as those working on the Global HIV Vaccine Enterprise argue, then replacing this $1.2bn per-year flow for 15 years with venture-capital funded biotechnology firms and equity-financed large pharmaceutical firms and an APC at the end of the whole process, would, on not outrageous assumptions of required rates of return given all the risks discussed below – nominal required rates of return of 15% to 25% per year (real rates of 12% to 22%) – require an APC of about $65bn to $165bn[34].

Maybe this is why private firms spend so very little on HIV vaccine research? It is hard to believe that rich markets would not pay $25 or more per course of vaccine treatment, generating a multi-billion dollar market in such countries for an HIV vaccine. Maybe that is simply not large enough to cover all the risks faced by developers and the mega-blockbuster price tag they would need to justify the risks

[34] These are extremely rough figures to illustrate a point. The required rate of return, as well as capturing the required market rate of return, is also assumed to capture uncertainty about internalising the value of research, of ever getting a vaccine, of the dangers of the misuse of discretion and of time-inconsistency in the mechanism, the risk of collapse of the mechanism, the reputation risk for the last big player in the chain, and the high required rates of early venture capital funding. Some have argued that these rates are even too low. We also presume no 'crowding out' at all and that the winner(s) get immediately paid everything at the end. These are low required rates by venture capital standards (normally 30%-40%), but they may be too high for other sorts of investors.

via the APC route? Maybe it also has something to do with the target being more than just creating a single vaccine? Maybe if those advocating for an HIV APC were to work out the potential size of *any* high-value market for HIV vaccines, and take one look at the pitifully low levels of private vaccine R&D funding for *that* market, they might come to a quite different conclusion to the simple 'lack of a market' argument?

Even simple math casts doubt on the notion that an APC "may provide the incentive that has been so desperately lacking"[35] and that if only we had one in place, all would be well. An HIV vaccine APC – if that is the route chosen – would, given all the risks, have to be a mega-blockbuster, and a great deal higher than anything currently being proposed. The best a $3bn APC would do in such a situation would be to allow one big, influential firm, at the end of the whole, expensive, largely publicly- and foundation-funded process to maneuver to claim all the IP. Even big firms might prefer some other approach to avoid being put in a position so potentially damaging to their reputation. This potential damage ways heavily against the expected value of the APC compared to other approaches less risky to reputation.

For vaccine purchases of currently existing vaccines, these proportions would, naturally enough, be completely the converse, with low capital costs because of lower risk, no crowding-out because of the ability to use competitive tenders, and much more easily set terms.

Specifying vaccine characteristics

Each purchase commitment would try to specify in advance – on the basis of expected science and the difficulty of development, costs of production and distribution, epidemiology, expected size of future eligible and non-eligible markets, etc. – the characteristics of a vaccine that would be acceptable for those eligible countries covered by the program[36]. In truth, this could not be remotely set in advance for conditions such as HIV, malaria, and tuberculosis. Observe how it is not just the characteristics of the medical condition alone that enter the decision process. There would therefore have to be a great deal of discretion left in the terms set. A contract might, for example, specify 250 million treatments for a malaria vaccine at $25 per course of treatment (making $6.25bn overall[37]), with distribution thereafter to those covered by the mechanism at cost-plus pricing.

There would be one, or supposedly several, big winners of the supply contract with decisions about winners and losers and allocations made by a committee, based on a mix of rules and discretion. In the literature, this has come to be called an 'Independent Adjudication Committee', or 'IAC'. We use the same nomenclature here, but make no *a priori* presumption about its independence since this is highly unlikely to be the case, or, more importantly, highly unlikely to be *expected* by investors to be the case *at the horizons of interest*.

---

[35] http://www.cid.harvard.edu/books/kremer04_strongmedicine.html.

[36] It would also need to be acceptable to 'non-eligible' countries, as will become clearer below.

[37] 'Making Markets' p 61 ($20-$25x250 million treatments). Recently this has been trimmed to $15 a treatment and 200 million treatments (i.e. less than half the $6.25bn). Given the time it has taken to prepare this paper, it has become a sobering experience to have to keep going through it trimming the figures down every time a new policy pronouncement is made.

In the above 'best-case' scenario (of no crowding out, though high capital costs), a vaccine costing $25 for the first 200 to 250 million treatments might compose $1-$2 for production and distribution, $6-$7 for out-of-pocket R&D costs of all firms (not just the winning firm), and $16-$18 for the cost of the finance (again of all firms). With 50% crowding out, only about $3 of the $25 would go towards fresh out-of-pocket R&D costs. Incidentally, it is not at all clear that the first few tens of millions of an HIV vaccine could be manufactured *that* cheaply (especially if there is no competition between manufacturers to drive production prices *that* low). We will discuss this in more detail later (in Section 2.14) when worries about this being the case would undermine incentives to do R&D in the first place.

Competition, supposedly

Freedom of entry and exit in the R&D process and competition to try to win the $6.25bn (now $3bn) contract will, we are told, lead to the 'optimal' number of firms working on vaccine trials and hence the optimal speed of development. However, 'competition' is essentially driven by the expected behavior of the committee, as well as expectations (and worries) about the behavior of other firms with respect to the committee. The number of firms in equilibrium is dictated by the initial size of the 'pot' of funds, so that having an optimal number of firms requires that the size of the 'pot' be chosen optimally at the start, which requires knowledge of both the science, likely costs of developing and producing a vaccine, epidemiology, etc. If the 'pot' is too small there will be too few firms and progress will be too slow and chances of discovery low. If the 'pot' is set 'too large' there will be 'too many' (showing up in overlap, waste, lack of cooperation, rent seeking behavior, efforts to capture the mechanisms, etc. with some of this showing up in harm to other parts of an overall mechanism for discovering vaccines).

The underlying economic notion is that if, for any given 'pot' size, there are *too many* firms 'competing', then the chances of any individual firm winning the pot, or a part of the pot, are too low, the risk-adjusted rewards are too low, and firms will leave (or they will simply not enter in the first place). However, if there are *too few* firms, then the chances of being a winning firm are higher[38] and more firms will enter. In *both* cases, the laws of motion supposedly push in the direction of the optimal number of firms working on research leads in equilibrium[39]. That these laws of motion work, requires huge amounts of assumed competition. If terms could be permanently set in advance, firms would supposedly form their optimal strategies on the basis of their expectations of the strategies of other firms, and never on the behavior of the distributor of the 'pot'. When terms cannot be known in advance, ex ante competition between vaccine developers is policed via the expected ex post behavior of the committee (very unlike a standard competitive tendering).

[38] The individual chance may be low, but given how few other firms there are, if one firm wins, the greater the chance it will be oneself.

[39] In practice, leading advocates have not hidden the fact that a few big companies are seen as driving everything, so most of this argument would not apply.

Prices of vaccines to those not covered by the mechanism

Populations *not* covered by the mechanism (say Russians purchasing HIV vaccines for their 'non-eligible' program, and plenty of other countries such as, perhaps, China, India, Brazil, etc.) would *somehow* (since it is difficult to see how it could be done) continue to pay 'non-eligible' monopoly prices, since their markets would be treated as separate from the program. This is an important feature in the case of an HIV vaccine, but, given the recent evidence of the more widespread nature of malaria, it may also be an increasingly important feature in the case of malaria vaccines too. However, given the presence of the advance contracts in poorer markets, this could mean that the prices faced by those not covered by the mechanism in 'richer' markets would be higher than they would have been without the contracts in place[40]. This may constrain the interest of non-eligible countries in supporting any HIV vaccine research, including the Global HIV Vaccine Enterprise, if it employs an APC at the end of the process, as well as making such non-eligible countries a big threat to the workings of the program.

From now on, this is the benchmark R&D model against which all remarks in this paper will be directed. It will be argued below that advance contracting and commitments of various sorts are useful devices, and that late-stage vaccine work can be helped by contracts that commit funders to pay for 'performance'. But these have to be very clearly separated in the reader's mind from the notion being suggested (though none of the actual mechanism is laid down) in 'Making Markets' and 'Strong Medicine' for early-stage vaccines which is based on the notion of recreating, from the very start of the process, a precisely sized *additional* blockbuster market, and a precise set of rules (though, still, large elements of discretion), based on the notion that this will drive a large amount of the development of vaccines. Clearly, purchasing commitments for currently available and cheap vaccines are a degenerate case of the above mechanism, since most of the features described above have collapsed to zero. Such contracts are not capable of telling us a great deal about the above mechanism.

[40] See Farlow 2004 Section 7.16. The notion is that control over IP generated by the mechanism, and the market segmentation, strengthens ability to price higher in the non-eligible 'richer' market.

PART 2. THE DIFFICULTIES OF EARLY-STAGE ADVANCE PURCHASE COMMITMENTS FOR VACCINES

2.1. Drastic Simplifications

'Making Markets' is interested in both early-stage and late-stage vaccines, and recognizes that for the former vaccines "significant scientific barriers impede the development of vaccines for these diseases."[41] 'Strong Medicine', on the other hand, expends most of its firepower on early-stage vaccines for HIV, malaria, and tuberculosis[42] on the basis that this approach is the way to incentivize the discovery, development and production of these particular vaccines.

For ease of exposition we look at the more complicated case of early-stage vaccines first. Far more issues are raised for these vaccines than for late-stage vaccines, and it proves easier to explain things by working outwards from the more difficult cases towards much simpler late-stage vaccines.

A number of observations about Part 2 are in order:

1) Part 2 is full of critical and 'problematic' observations. But this is largely because the supportive APC material for early-stage vaccines contains very little of this. If it had, there would be no need for this paper. Achieving balance may create the impression of imbalance. The reader is strongly urged to read the "Making Markets" report alongside this paper and to make up his or her own mind[43]. The second half of this paper tries to make up for this by being more constructive;
2) All tools for incentivizing R&D for vaccines are imperfect. One of the jobs of policymakers is to assess the *relative* imperfection and usefulness of each tool. This suggests that negative commentary about one tool – in this case APCs for early-stage vaccines – should be placed within a broader context including negative and positive commentary about other tools. This obviously cannot be achieved if the discussion of each tool only includes that tool's positive merits;
3) The efficiency of each tool varies greatly depending on the underlying problem at hand. The case for APCs for early-stage vaccines was not helped by the early decision to trivialize the science of HIV and malaria vaccine development to one that is 'linear', fixed, simple, and static, when for early-stage vaccines it is instead highly complex, and dependent on feedback loops, collaboration, and comparison of results and sharing of information, and with a mix of private and public-good features to the problem;

[41] 'Making Markets' March 2005 p6.
[42] Other diseases affecting the developing world for which no vaccine is available include shigella, schistosomiasis, leishmaniasis, chagas disease, and dengue. There is a vaccine for tuberculosis, BCG (Bacilleus of Calmette-Guérin), but it provides only short-term imperfect protection against infection.
[43] www.cgdev.org/publications/vaccine.

4) Some of the criticisms below are fundamental to the nature of APCs. Others pertain much more to particular designs of APCs, especially the ones currently being proposed for early-stage vaccines. Separating out the two is not always obvious and will be part of the exploration and the creation of a range of instruments, including suitably-modified APCs.

1) The science is fixed, simple, and static

To strengthen the case for complicated early-stage vaccines, the underlying modeling in all of this advance purchase literature drastically simplifies the state of difficult, unpredictable, and dynamic science to one that it is *fixed* and known at both basic and applied levels, even for viruses as technologically challenging as HIV. Indeed early-stage vaccines are modeled *as if* they are late-stage vaccines. It is even pointed out in the literature describing the model which ultimately drives the case for early-stage APCs that "this model is *best suited* for comparing different policies under *consistent assumptions about the state of technology*,"[44] (italics added). Linguistically, the phrase "consistent assumptions about the state of technology" means that the state of technology may be very inconsistent, but that the assumptions about it are consistent. Similarly the model is described as driven by "a consistent set of assumptions about the scientific difficulty"[45], which again means that the scientific difficulty can be very inconsistent, but that the assumptions about it are consistent.

But these phrases are misleading. For some reason, Kremer *never* uses the phrases "assumptions about the consistent state of technology" nor "a set of assumptions about the consistent scientific difficulty," even though that is *exactly* how the model is mathematically set up. This is at the heart of the misapplication of the approach to early-stage vaccines, and the exaggerated claims for the models 'strength'. It has been claimed that "[It] is wrong to say that the proposal depends on a particular model of scientific progress."[46] However, there is, in principle, a potentially infinite set of 'states of scientific difficulty', and the modeling device used selects only one 'state' from this set. When dealing with such difficult and complicated issues as HIV, malaria, and tuberculosis vaccine research, it is not particular useful to have a model that is 'best suited' to a world that we do not have, and then get around this by *assuming* a world that 'suits' the model.

In addition to the presumed given state of science, the other chief simplifications are:

2) No patents on anything other than the end products themselves. Some will find this contentious. Others will find it simply 'odd', given the observation in 'Making Markets' that uncertainties around IP protection (p17, p19) are part of the problem.

---

[44] Kremer, M., Appendix 3. at the No 10 Policy Unit, http://www.strategy.gov.uk/files/pdf/Appendix%203.pdf p 25.

[45] The No. 10 Policy Unit Executive Summary, Kremer, M., page 1.

[46] Berndt, E.R., WHO Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, http://www.who.int/intellectualproperty/forum/en/Discussion2_text.pdf, 17 December 2004. All Forum comments listed below are to be found on this one website.

Although strong patents and strict secrecy requirements can diminish scientific discovery as well as enhance it[47] (and raise the costs of vaccine developers as well as lower them), patents are modeled as functioning perfectly, or some curious sort of 'open source' arrangement is being presumed. There are no financial constraints, investment hold-ups, strategic behaviors, constraints on flows of information, or concentrations of market power based on patent ownership. In fact, patents function so perfectly that they are simply *removed* on all but the end products. In real-world settings, however, intellectual property issues are shot through the entire R&D system. When the Malaria Venture Initiative (MVI) 'mapped' the patent status of the MSP-1 antigen, it found 39 different families of patents with monopoly scope impinging on it[48].

Because of the build-up of large private capital costs of those who invest in the hope of winning an APC, a core component holding a real-world, as opposed to an idealized, early-stage APC together would be a chain of IP rights and/or secrecy. This would be very much so for very early researchers who would otherwise worry that they would not be able to internalize the value of their private R&D efforts, but equally or more so for those near to the end of the R&D process who find themselves with up to $6.25bn resting on their hold of IP. In the underlying model there is essentially no distinction between those doing early and those doing late stages of vaccine research since there is no sense of a 'process' over 'time'[49]. Research projects are also modeled as entirely independent of each other so the notion that the results of one project can be 'taken' by another project is stripped out of the reasoning. Unfortunately, none of this describes HIV (or malaria) vaccine research particularly well.

At the very least, the empirical basis for excluding patents on all intermediate products or processes in the modeling process should be presented. If part of the current problem with complicated vaccines like HIV is lack of information 'sharing', it is not obvious that imposing even less sharing and even more secrecy is the optimal way to proceed. If more collaboration and information sharing is to be encouraged under a global HIV vaccine enterprise, it is not clear how repayment can be structured so as to fully internalize the benefit of a firm's own activities if repayment depends on a system based on secrecy and low information sharing. The results of the WHO Commission on Intellectual Property Rights, Innovation and Public Health[50], due at the end of 2006 (though much material is

[47] See "Biotechnological Inventions", Chapter 13 in "Patents for Chemicals, Pharmaceuticals and Biotechnology", Grubb, Oxford University Press, 1999. For examples of overly-broad patents on gene sequences with consequences for research into global health problems, see also "Patents in Genomics and Basic Research: Issues for Global Health", J. Barton, 2001, CMH Working Paper No. WG2:13. For a 'classic paper' on the situations where overly-tight IP can harm research incentives, see "Can Patents Deter Innovation? The Anticommons in Biomedical Research", Heller and Eisenberg, Science, Vol. 280, 1 May 1998. The notion of the anticommons – the under-use of scarce resources – is the opposite of the 'tragedy of the commons', the over-use of scare resources. Anticommons behavior happens when there are so many owners of IP relevant to a particular innovation that the power of some to block the others (even just the expectations of this) deters innovative activity and leads to fewer useful products for improving human health. This is said to bite especially in very technical fields such as biotechnology.

[48] www.malariavaccine.org.

[49] Indeed, there is no notion of time.

[50] www.who.int/intellectualproperty.

already becoming available), should give us some further pointers on this[51]. The Kremer modeling device short-circuits that debate, placing itself firmly at one end of the spectrum of views on the issue, pre-judging there to be no IP problems of any sort from the start.

3) No benefits in sharing information across vaccine developers and no 'know-how' monopoly. 'Know-how' is especially important for vaccines – far more so than for drugs – and particularly so when some developers or potential developers are already at a technical or financial disadvantage. One obvious danger is that existing developed economy patent holders, facing a potentially emerging-economy competitor, will be able to exploit 'secret' know-how (as well as more general technical know-how, and undisclosed test or other data)[52], including refusing to contract to transfer necessary know-how, thus creating a barrier to entry of the competitor. In such cases, compulsory licenses are much less useful than in the case of drugs; it is of little consequence to have such a threat if lack of know-how makes it non-credible. It is not clear how any current 'know-how' gap might be exaggerated by a mechanism that emphasizes those with 'deep pockets' and free cash flows and (if not correctly screened out in payments) those with access to various other forms of subsidies.

4) No variation in the probabilities of discovery over the vaccine development process, so that there is no problem in keeping cumulative R&D projects together, no risks to those making investments early in the development process, or in ensuring optimal intensity of R&D at *all* points in time[53].

Part of this varying probability is also a function of variation in the underlying push research and variation in the regulatory environment, such that fixing probabilities of discovery is tantamount to fixing push research and the regulatory environment.

5) No ways for technology to improve or deteriorate over time. There are no technology 'revolutions', such as the 1980s advances in molecular biology, nor technology 'shocks'. Neither do we have to worry about incentives to *improve* technology[54]. If such revolutions and shocks are possible, it then becomes a tradeoff between – on the one hand – 'insuring' firms via a fixed payoff structure (with the contract sponsors facing the technological risk) which helps to keep firms' risks down and hence lowers the capital cost component of a purchase commitment, but gives them no incentives to improve technology, or – on the other hand – giving firms the incentive to improve technology through a variable contract (and observe how the committee running the program needs to know the potential 'technology' in order to set the variable terms). But the latter contract faces firms with risk that also has to show up in a higher required purchase commitment.

Technology *does* change over time:

[51] Farlow, 2004, ibid. Section 10.2 explores some of the issues.
[52] Observe how the desire to keep things like this secret will conflict with the requirement later that firms reveal all to the IAC for it to set the terms of the mechanism correctly.
[53] Farlow, 2204, ibid, Chapter 5.
[54] Farlow, 2004. ibid, Section 6.3.4.

> "*The scientific basis for the development of new vaccines has accelerated greatly over the last 20 years. Major advances in the understanding of the pathophysiology of infectious diseases and a wealth of revolutionary technologies are expected to greatly enhance the feasibility of immunization against diseases for which vaccines do not currently exist.*"[55]

APCs either have to be set in expectation of this change and try to predict it, or they fall behind and need modifying[56]. Currently, the advance purchase literature says that any improvement in technology that is *not* caused by the firm's efforts, will not be offset by tougher terms. Imagine, for example, how terms of an early-stage APC would have been set *before* the success of the human genome project or the impact of the cracking of the malaria genome, and how an APC would have struggled to deal with this without wrecking its credibility. In both of these cases the bias is in the direction of this being a more costly – and never a cheaper – approach.

It might be very useful for those promoting the commitment mechanism to ignore this issue, and to fix the underlying state of technology as for ever the same. Appendix 3 of the Number 10 Policy Unit submission does just this. But it removes a major driving force for improved vaccines and lower vaccine costs, and sweeps aside difficult problems when setting the terms of such commitments.

The removal of all variation in probability over time, all shocks, technological revolutions, and ability to improve technology, is needed in order to remove all IP issues from discussion. It also greatly simplifies the decisions made in other parts of the research process not covered by APCs.

6) No build up of sunk costs. This might surprise those who work in the pharmaceutical industry, but it helps to remove many potential distortions in the model[57]. Shortly, we will see that it is the source of many of the practical problems in using APCs.

7) Good understanding of the state of current and future science (the science is, after all, fixed in the models) so that a reward system to incentivize vaccine 'quality' can be created. 'Making Markets' recognizes that price would have to vary to "take into account the *likely complexity* of identifying and producing a vaccine"[58] (italics added), but there is no convincing evidence that this could ever be done remotely correctly, especially for a complicated early-stage vaccine. The danger (we see it already in the way policy in this field is already being enacted) is that this subtlety is lost in practical applications, especially if policy-makers have been persuaded that achieving success on early-stage vaccines requires

[55] W. Ripley Ballo, The Vaccine Book, p85. Eds. Bloom, B, and Lambert, P-H, 2003, Academic Press.
[56] See Farlow 2004 Chapter 6 for the problems that this can cause.
[57] In Kremer, Appendix 3, ibid, there is the same per-period 'continuation' game – a device that removes any connection across periods via, for example, sunk R&D costs.
[58] 'Making Markets' March 2005, p52.

essentially the same as achieving success on late-stage vaccines (i.e. a 'pot' of money, and little else).

8) No large incumbent firms but, instead, perfect competition everywhere and always. This is needed to keep risk down, especially that of small firms, developing countries, and not-for-profit researchers[59]. This somewhat contradicts the stated intention of targeting large pharmaceutical firms: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more."[60] In reality, entry and exit of the required number of firms cannot be presumed, given that there are only a few large firms being targeted by the mechanism, and the value to each of these firms of multiple vaccine leads is greatly reduced compared to more competitive scenarios. This is explained in more detail in Farlow 2004 Chap 10.

Lack of competition also creates problems targeting in the 'quality space' since there may be too few firms to generate quality-driving incentives[61].

9) No strategic behavior of any sort, and of any firm, based on sunk costs, patent ownership, finance, or any other real-world factor[62] There has been such a growth in the number of patented inventions in biotechnology that issues about the strategic use of patents should not be overlooked (especially when considering the relative bargaining strength of large pharmaceutical firms versus biotechs, developed versus developing country firms, profit versus non-profit firms, etc). Again, *expectations* about such behavior matters as much as the actual behavior itself.

Relevant examples to consider might include: products such as micro-organisms in a living but attenuated state, (recombinant) antigens and antibodies, an adjuvant or a vaccine delivery device; and processes, in particular relating to a method or steps in a method for producing a vaccine. Who has the balance of power in patent infringements in such cases for example? What if the IAC is biased, or just appears biased, in favour of large pharmaceutical firms in developed countries? The fact that next to no vaccine players from developing or emerging countries have been involved in the current discussion process for setting up APCs suggests that this is not a trivial worry. Kremer Appendix 3 essentially contains no interesting industrial structure, other than perfect competition everywhere and a level 'playing field', with no centers of regulatory 'power' even in what is such a heavily-regulated system.

---

[59] Strategic issues are considered at much greater length in Farlow 2004, ibid, especially Chapters 10, 11, and 12. The general argument is that there are all kinds of ways that the advance purchase mechanism can be undermined by lack of competition, and by strategic behaviour (and worries about such behaviour) that lead to lower levels of competition.

[60] Kremer, M., No 10 Policy Unit, Appendix 1 p9.

[61] Farlow, 2004. Section 7.18 on the argument about 'quality space', and Chapter 7 on general problems with the quality issue. It turns out that there are lots of paradoxes in the quality of vaccines if 'quality' is driven through a committee at the end. See below and, for example, Farlow, 2004, Section 7.11.2 which discusses the paradox of needing poor quality vaccines to discipline behaviour of firms.

[62] Farlow, ibid, Chapters 10 and 11.

10) No coordination problems across public and private sectors in their research decisions at a single point in time and over time. This may involve coordination of several layers of decision-makers. In reality there would be high and uncertain variability in the interaction between those parts of early-stage R&D on vaccines covered by an APC and those parts covered by mechanisms other than the commitment[63]. This would increase risk and hence capital costs for developers. Incidentally, most of this risk already exists and is part of the reason that private firms have low incentive to do R&D for 'neglected' vaccines.

As a concrete example, we will see later that the research leads for HIV vaccine trials that are currently being created are only in one area of potential research leads, and that there are several areas of 'neglected' leads. Were it to be set *now*, the size of the APC for an HIV vaccine would have be set *either* on the basis of the current limited set of research leads *or* on the basis of expected future research leads and future expected trial expenditures by IAVI and others. In the first case, if IAVI 'unexpectedly' expands its own trials it would have to compensate firms working under the APC. The 'surprise' expansion of trials would reduce the chance of those working on the 'old' set of leads 'winning' a purchase commitment, and destroy the value of *their* already sunk investments. Advance knowledge of *this* 'danger' would deter investment under the APC. In the second case, the contract is inefficient in the short-run and this distorts both short- and long-run outcomes. This problem never arises in a complete private sector system such as that described the 'Appendix 3' model.

Clearly, setting terms a long time in advance of clarification of these other factors will feed higher capital costs to private firms via the extra risks they face[64].

11) No coordination problems across public and private sectors and all countries in their vaccine purchase decisions and in their provision of vaccination delivery systems (whether these sectors and countries are covered by the mechanism or not) at a single point in time and over time. This is another result of trying to adjust quality ex post. Without this coordination, self-reinforcing choice of poor quality vaccines would be difficult to avoid[65]. It is impossible to coordinate these decisions in a way that is not risky for those operating under APCs.

This coordination is presumed efficiently achieved at all times in the modeling underlying 'Making Markets' and 'Strong Medicine', by a simple scientific presumption: There is no other sector other than the APC-motivated sector, so there never is any interaction between the sectors to worry about. In the Appendix 3 model, all other sectors, including the public sector, have been 'partial-ed' away, so that, in effect, everything is *conditioned* on coordination somehow having already been achieved for all points in time for all processes. Neither is there worry at any point in time about breakdown of coordination at any other

[63] This naturally goes through if the APC part of R&D is fixed in spite of required flexibility. However, it also bites even if the APC is allowed to be variable but where the variability does not match that strictly needed for optimality (for example, if the science varied). This is discussed in Farlow, ibid, especially sections 8.3 to 8.7.
[64] In fact there is an extra option-price component to be priced in to very early research.
[65] Farlow, ibid, Chapter 7.

point in time. This is not just unrealistic, but very unfortunate given that this is one of the big problems that APCs are supposed to tackle. It hardly makes sense to presume it away. It might be an acceptable assumption in the case of bidding to manufacture already existing vaccines (using standard competitive tenders), but absolutely not so for early-stage vaccines like HIV. Perhaps there are some – so far unmodeled – global treaties on R&D, global adjustments, and purchases of vaccines, that somehow efficiently insure against these coordination problems for those working under the influence of expected purchase commitments[66]?

There are large risks faced by private financiers if there is breakdown of this pre-agreed coordination, or, simply, difficulty in achieving precise coordination between the APCs and other layers of the research, development, and delivery process. Indeed, this is a fundamental problem that has always plagued those private investors into HIV, malaria, tuberculosis, and other vaccines – in the shape of insufficient levels of non-private research funding by governments and insufficient funds for vaccine distribution. As far as developers are concerned, perhaps 'advance push commitments' and 'advance distribution commitments' are missing as much as 'advanced pull commitments'? *All* of *these* missing commitments *have* to show up in extra costs for developers. Putting too much emphasis on the pull commitment and not enough on the push commitments and distribution commitments, is bad for the pull commitment. This problem is simply presumed away in much of the analysis (it is nowhere to be seen in Kremer Appendix 3). It is not clear, for example, that making eventual payments depend on the 'willingness' of developing countries to distribute the outcomes will ensure incentives towards 'highest' quality in such circumstances[67].

12) An idealized, non-cyclical, set of financial markets. In reality, moral hazard and adverse selection are not just faced by public funding bodies but also by private-sector managers and financial markets. By modeling on the basis of very simple underlying science, managers and financial markets never really have to struggle with many of these informational issues, are not harmed by secrecy, and end up performing a pretty trivial function[68]. Since a major driving force for the claimed effectiveness of APCs in achieving quality vaccines is through the power of stock-market based finance to perform much of the choice over research leads and 'quality', it does not help greatly to strip out most of the awkward features that make this choice challenging[69].

---

[66] That these coordination issues and treaties do not seem to be part of the current thinking is confirmed by Berndt, E.R. ibid. who argues that it is 'wrong to say that it would require centralized control of global public research – the proposal requires relatively little prescription on the part of governments.' This is an argument relevant to late-stage and, indeed, most of all to currently existing vaccines, but is entirely inappropriate to early-stage vaccines such as HIV.

[67] See Chapter 7 of Farlow 2004 ibid.

[68] See Farlow, 2004, ibid. Chapter 12 for more on the general problems faced by mangers and financers of vaccine and drug research.

[69] See Farlow, 2004, ibid Chapter 12. If nothing else, that chapter demonstrates that capital market difficulties are fairly common to many of the suggested approaches to dealing with the vaccine R&D problem and need to be tackled too. These problems also bite more strongly, the more complicated and difficult the technology. The answer is not, automatically, to be found in an ever-larger purchase precommitment, or, indeed 'prize' in prize-based models. By drastic simplification some important financial market problems are left un-tackled in 'Strong Medicine', and, indeed, in the 'prize' literature generally. Policy makers need to face up to these problems and find new

13) No pipelines of products, no problems with resistance, and no therapeutic vaccines. In truth, drugs and vaccines usually necessitate a continued pipeline of new products. This is both to improve quality (especially of therapeutic vaccines in cases when preventative vaccines are not possible) and to keep on top of resistance. This bites particularly sharply for the big killers of malaria and HIV, but also for tuberculosis. Early-stage APCs struggle to achieve this[70]. This is similarly linked to the quality problem, since the optimal acceptable vaccine in an early period may have to be set higher than would be the case in a pure one-off vaccine creation. We will repeatedly see that tackling a whole range of 'quality' issues proves extremely difficult for APCs to achieve without a great deal of external control over quality and/or extremely heroic assumptions ex ante. Naturally, this defeats the notion that somehow early-stage APCs are non-interventionist, low on discretion, and avoid dynamic inconsistency problems.

This overly-simplifies the problem

Removing all of the complexity of points 1-12 greatly overly-simplifies the modeling of early-stage APCs. In particular, it drastically reduces the number of values such commitments might take and the number (and size) of degrees of discretion of the IAC and others, and it increases the ability of policymakers to set the size and distributions of allocations across vaccine players correctly and make APCs 'credible'. Credibility (and the complete legal bind of contracts from the start) is indispensable to the efficiency of such contracts and the reduction of capital costs. The best form of credibility is being able to fix an irrevocable payment. Having assumptions in place that practically guarantee this in an idealized model is extremely useful for this purpose – but it is not a good description of 'reality'.

Every time one of these simplifications is breached, the extra cost imposed would have to be factored into the APC otherwise the power of the contract to stimulate R&D is reduced. Each simplification touches on an important area in need of further analysis. Sweeping these problems under the carpet by simplifying them away is not bound to lead to good practical policy-making.

2.2. Difficulty in Efficiently Setting the Size

While it is "difficult to know how much a vaccine commitment would speed vaccine development"[71] and "there is no way of knowing in advance how big a return needs to be in order to induce an increased level of research and development"[72] nevertheless policymakers must *somehow* be able to work out how large to set an APC. That policymakers can set the size perfectly (or, at least, well enough) is, after all, central to its supposed superior performance compared to alternatives. Indeed, the original cost-effectiveness figures deposited at the No.

---

financial instruments to overcome these risks. More on this below in the section on the Global HIV Vaccine Enterprise.

[70] Farlow, 2004, ibid. Sections 7.3, 7.6, and 7.7.

[71] 'Strong Medicine' p95.

[72] 'Making Markets' March 2005 p55.

10 Policy Unit presumed a perfectly-set size every time, without even spelling out the problems of achieving this.

Wasteful if set too high

If the overall size[73] is set too high, there is waste (especially duplication, overlap, strategic rent-seeking, etc.) and reduced resources made available for other vaccines and health treatments, sanitation, nutrition, etc. Since the resources have to come from tax-payers or philanthropic foundations or facilities such as the International Financing Facility, IFF, there are all the extra deadweight losses of taxation and the opportunity cost of the other projects that foundations, governments, and the IFF are prevented from doing. If the IFF itself bares many risks, then overly-large APCs add to that risk.

Wasteful if set too low

If the overall size is set too low (maybe because not all capital costs were correctly factored in or because it seemed politically expedient to set a low target), there will be too few active players, sub-optimal research and development, and discovery is wastefully slow. But it is worse. Once set too low it is hard to rectify. The act of continuously revising upwards the size of the commitment acts like an extra discount factor raising the expected costs of those investing early; the *expected value* of a unit of investment is lower than for those who simply delay and get, in probabilistic sense, a higher price. This creates the perverse incentive to delay investment and discovery of the vaccine or vaccines[74], and the vaccines likely to be generated and paid for under the mechanism are lower quality on average.

Wasteful if R&D costs are highly uncertain

Maurer[75] points out the consequence when development costs are highly uncertain. Since CGD "after a long deliberation process did not narrow down beyond the range of $15-$25 per treatment," – the upper bound being 167% of the lower bound – Maurer suggest it might be useful to explore what might happen if the wrong part of the range was chosen. If the size of the APC 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 takes 8 years till the APC has any effect (or it collapses first). If real R&D costs also grow at 5% per year, it takes 15 years to have any effect. This leads to delay, but also strong pressures towards 'poorer quality' (broadly defined) at any given APC size since policy makers may feel pressure 'to get a result' whatever the 'quality' cost. Similarly, if sponsors chose the higher bound when the lower bound was a better reflection of R&D costs, they would expect to overpay by an average of thirty-four percent. Either way, the expected price-quality tradeoff is much poorer than it at first appears. As Maurer points out, significantly "proponents do not promise to deliver more refined estimates in the future. They only argue that sponsors should choose a price based, *inter alia*, on "the willingness of sponsors and recipient governments to

[73] With 'size' here presupposing some appropriate split of funds across developers and over time too.

[74] This is all explained in Farlow 2004 ibid chapter 11 on auction mechanisms for setting the APC terms, but also recognised in the early, Kremer, literature. It is not discussed in 'Making Markets'.

[75] 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 p 75.

pay."'[76] Observe how these observations are based only on the R&D costs dimension of setting the APC size. We know that there are several other dimensions to the setting of optimal APC size and these can clearly only make this problem even worse.

Not a good idea to set on the basis of 'typical market size' for drugs

The current approach of the Center for Global Development is to base the size of the purchase commitment on some measure of the typical market size deemed necessary to stimulate the discovery of a developed-economy drug. *Implicitly* this means that the size of the APC is based on the typical costs of developing such drugs, since, in equilibrium, investment in drug development should be driven to the point where this is so[77].

The paradox is that – to the extent it is believed that privately-paid[78] R&D via an expensive APC is the route to developing complicated HIV, malaria, and TB vaccines – if it turns out that HIV, malaria, and tuberculosis are a great deal more difficult to develop than typical vaccines and drugs, then the size of the purchase commitment will turn out to be too low via this method, with very damaging consequences (including giving all the vaccine IP to a firm that has 'done very little' to justify it). This is not inconsistent with the notion that the instrument may grossly overestimate the (per unit) innovation costs likely incurred by developing and emerging country developers and suppliers, even while it may underestimate the costs of development of complicated early-stage vaccines by developed country developers. Yet, even in this case, for the sake of credibility and to prevent the dynamic breakdown of R&D incentives and loss of credibility, policy makers could *not* come along later and abolish the commitment or dramatically reset it.

It certainly seems very strange that while the Global HIV Vaccine Enterprise, in the face of strong budgetary pressures to cut HIV vaccine research funding, is arguing for global HIV vaccine research budgets to double to $1.2bn per year – by far and away the greatest research budget devoted to any vaccine in history – and leading vaccine experts are suggesting that this may have to be the level for the next fifteen years at least[79], nevertheless those advocating HIV APCS are basing all their calculations on recent market sizes of much simpler drugs and still nevertheless arguing that a HIV APC is the solution "that has been so desperately lacking"[80]. We toyed above with possible – and no doubt very wrong – figures for the needed APC to replace this stream of up-front payments for HIV and came up with $65bn to $165bn; nowhere near the amounts being suggested[81]. Either HIV

[76] Referring to "Making Markets" March 2005 p 52.

[77] It is elementary economics. If the average cost of developing drugs is lower, and if investment in drug development is driven to the point where the marginal 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. Large needed market sizes are driven by large underlying costs of development.

[78] At least at first. It is all paid publicly later.

[79] Apparently Bill Gates, on the day he received his honorary knighthood, said that he would eat his hat if a HIV vaccine were discovered in the next fifteen years.

[80] http://www.cid.harvard.edu/books/kremer04_strongmedicine.html.

[81] Incidentally, instead of criticising the no doubt very 'wrong' figures discussed here, perhaps CGD and others could come up with some calculation of the replacement figure for this stream of

is a fiendishly more difficult virus to create a vaccine for and will cost a great deal more to develop than probably any other vaccine in history, and the Kremer-inspired figures are simply and plainly wrong, or the figures are right and APCs operate at such a fantastically higher level of competence compared to all the alternatives that the Global HIV Vaccine Enterprise and other such approaches might as well be abandoned at birth. Going for lower-sounding figures might make an idea fly better with politicians, but it is extremely foolish – especially if one of the potential consequences is a collapse in HIV vaccine research.

The economic logic should be that each APC needs to be set at a level commensurate with the difficulty of the underlying science and the cost of R&D of developing the product at hand. The only reason it seems that one would use 'typical market size' for drugs at all in calculations for conditions as scientifically difficult as HIV is to window-dress the idea for public consumption and avoid having to discuss the costs of vaccine development or any of the underlying science. Why else would one use an approach that is bound to generate a completely wrong figure every time[82]?

Auction theory is no help for early-stage vaccines, so lots of monitoring

No evidence is provided that the size could *ever* be set remotely correctly for an early-stage HIV, TB, or malaria vaccine. An auction is mentioned[83] as a way to set size, but like the original cost-effectiveness figures before it, this is another part of the argument that was once heavily promoted but has now been largely abandoned. In particular, since raising the size of an APC in an 'auction' acts like an extra discount factor – making early investment even more expensive and incentivizing firms to delay investment – size can therefore only be raised at the rate of interest rate, but *no faster*. But the rules about how to do this are difficult to set. How is the start 'size' chosen? How is the speed of rise set? Are politicians willing to sign on to such open-ended programs? Will developers believe that an ever-exploding APC size is credible? How is judgment made that not enough investment has taken place, necessitating further rise, if monitoring is weak and given that the 'result' on which to base this judgment is only ever provided at the end of the process by the generation of the vaccine? The Current CGD thinking is that this is too difficult (or politically unacceptable), and is not being planned (or CGD are not yet saying how this later re-adjustment will happen).

HIV vaccine R&D were it to be replaced with an APC – especially given all the current budgetary pressures to cut HIV vaccine R&D funding that the CGD is, perhaps unwittingly, helping to encourage?

[82] Think of the underlying economic logic for a moment. Things that are trivial to discover get $3bn, just the same as those things that are extremely difficult to discover. The former are massively over-incentivized which is wasteful, the latter are massively under-incentivized which is also wasteful. Total waste in the system is maximized. The $3bn is given for something trivial, while the extremely difficult is now assured to be totally impossible.

[83] Kremer, M., Appendix 7, No 10 Policy Unit; Kremer, M., "New Vaccine Market II: Design Issues" in "Innovation Policy and the Economy", NBER Volume 1, pp73-118, and many other places.

Optimal R&D *intensity*, and therefore the size of a vaccine APC, could *not* be based on the information only provided by the actual development of the vaccine itself[84]. The chicken cannot come before the egg.

The solution, 'Strong Medicine' *now* suggests, is to pay great attention to the egg. This comes in the shape of further institutional layers and a "system of monitoring how much research was being undertaken on a vaccine"[85] at *all* stages of development inside *every* company that remotely hoped to eventually apply for a purchase commitment (or even might apply but just doesn't know it yet), with purchase prices and quantities updated in light of this information. This means, usually, a rise, since there is a bias in the mechanism towards raising but never lowering the size of the commitment. If some of the figures above are even remotely correct (with only a fraction of the 'pot' capable of actually going on early-stage out-of-pocket research) there would be large risks of seriously large future rises in the size of the HIV pot (if not abandonment before). It is hardly likely that this open-ended contract would be set up. And it would be wasteful anyway.

Would firms be so free and easy with their information?

All firms, it is claimed, would be able to trust that their highly sensitive information would be kept 'confidential' even if the committee handling it to set size and terms included others from the industry. To enforce truthfulness, failure to hand over all information would, it is claimed, lead to firms losing eligibility and having to write off all research costs so far incurred (though it is very unclear how firms could be barred from using any of their results in later activity, either inside or outside of the mechanism; for example, on a competing non-mechanism HIV vaccine and in non-eligible countries). This monitoring contradicts the claim made in 'Strong Medicine' and elsewhere[86] that policy-makers do not need to know much about what firms are doing under the mechanism, nor have to police them. It also contradicts the claim that the reliance of other R&D approaches on the truthfulness of firms is fatefully flawed[87]. It also contradicts the line taken in 'Making Markets' that "requirements on the developers would be minimal, consisting of only light reporting obligations"[88].

The previous concern to run an auction was justified

One would think that the strong emphasis on an auction in previous versions of the APC proposal might suggest a very real worry that terms could not be set efficiently. The fact the auction proposal has now been abandoned does rather suggest that all the recent spin about the terms of HIV and malaria APCs being set 'correctly' should be replaced by more sober reflection. Even more so when one realizes that the replacement mechanism for the auction ends up relying on an incredible degree of monitoring and intervention, something that was flatly

[84] Farlow 2004, ibid, Chapter 11 shows how difficult it is to get an auction to work to reveal information about the correct size of an HIV vaccine advance purchase precommitment.
[85] 'Strong Medicine' p106.
[86] Berndt, E.R. ibid.
[87] Incidentally, it also sets up a conflict with the incentive to hide information (discussed in a moment) in order to try to avoid repaying large parts of purchase precommitments based on the proportion of research and development not funded by stock market finance.
[88] 'Making Markets' March 2005 p44 (see also March 2005 p38).

castigated as something to be avoided by those now relying upon it. We observe how under the auction mechanisms, price should *not* be a great deal higher than that originally fixed, since the act of continuously revising upwards the size of the fund creates the perverse incentive to delay discovery of the vaccine and raises the expected cost and makes it ever harder to monitor the level of activity going on and the level of required activity[89].

How likely is it that firms will reveal this information? Or that some (large pharmaceutical firms) will find it easier to hide such information than others (biotechs)? As Graham Dukes points out:

> *"Any government considering entering into such an arrangement will demand an extremely thorough and audited breakdown of the costs of research, development and production of the product in question, in order to ensure that the price being asked is fair. It is here that any specific agreement might run aground, since firms have as a rule been extremely reluctant to provide detailed and audited data to justify their prices."*[90]

According to 'Strong Medicine' all this information would have been handed willingly to the authorities on a plate.

Clearly the best-case scenario has it that the size of the fund is set correctly at the start, with monitoring totally dispensed with, and the many and various necessary ex-post adjustments guided essentially information-free. This is the way things are done in the key Appendix 3 model.

Recently, any notion to set the size correctly at the start has been abandoned anyway. All this talk of auctions and monitoring and firms giving information to help set the terms efficiently and so forth is obsolete. The current $3bn APC for HIV, malaria, and tuberculosis is set with no reference to HIV, malaria or tuberculosis at all, but relative to the "typical market size deemed necessary to stimulate the discovery of a developed-economy drug", which, from the perspective of the underlying science and cost of developing an HIV vaccine, effectively means that the APC for HIV is completely random. Since the winning firm gets all the HIV vaccine IP – after a long and expensive public- and foundation-funded process – this is a spectacularly inefficient way to do things.

2.3. Difficulty in Efficiently Distributing the Subsidy to Incentivize 'Quality' and Follow-on Innovation

It is not just overall size that matters. This mechanism has a variable subsidy at its heart. There is a multidimensional 'quality' problem to contend with – a quality 'surface' across products, and across time, all hugely aggravated by the fact that the 'quality', science, and costs are all highly uncertain. This problem has

[89] Economically, there is not a smooth relationship between the ever-rising price and the R&D activity that is taking place. As the level rises, or is expected to rise heavily, the level of early R&D activity falls. This is why it is always bad to set precommitments too low at the start. The act of revising up (at a rate greater than the interest rate) causes investment to fall.
[90] Dukes, G., CIPIH Forum, 25 November 2004.

probably never been anywhere near as acute with previous vaccines as it is with HIV, malaria and TB, for which there is no such thing as '*the* vaccine' but instead a set of 'multiple and diverse vaccines' to be discovered over time. Farlow 2004 section 7.8 reviews the many facets to this 'quality' issue, and the rest of chapter 7 of that paper gives more details on some of the problems. Many of the problems highlighted in that chapter and this section are going to be present under all kinds of incentive mechanisms. The critique in this section is not to be read as indicating that the problem goes away under other approaches.

The CGD model calls for the setting of minimum requirements for a vaccine at the start, and a small committee with the power to lower those standards yet further when determining how to distribute the funds – but never, under any circumstances, to raise standards. However, predicting an efficient technical specification resembling the ultimately useful vaccine – or, indeed, the series of ever-improving vaccines to reward a series of developers – would be impossible to set years in advance for HIV, malaria, and tuberculosis. The Working Group was advised of this difficulty. If one knew everything of interest for all time, and there were no sunk costs[91], one might just be able to set one target for all time and dispense with rules and discretion (the approach taken in Kremer Appendix 3). Otherwise, it is not particularly helpful to ignore these problems. Similarly:

> *"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."*[92]

When the author discussed these issues in April 2004 at the Centre for Global Development it was clear that most of this problem had not been tackled. The idea of "Making a Market", rather than what was essentially at the time a prize, is a much later innovation in thinking, and is reflected in allusions to quality and redistributions of the fund, etc. The whole point of the observation, however, was that the needed hotpotch of rules and discretion would be impossible to set up in advance in order that innovation over time would not be stifled. One can write warm-sounding allusions to such rules but that is very different from actually *creating* and *using* such rules. HIV, malaria and TB probably challenge us more on these issues than just about any other diseases. It really is quite surprising to see the problem being treated quite so lightly.

Some thoughts on the 'quality space'

[91] Even if everything were known for certain, sunk costs, the time-cost of delay, and the limited size of the 'pot' of funds work together to create an incentive to accept outcomes lower than the target, disadvantaging those heading higher than the target (see Farlow 2004, ibid. Chapter 10 and also section 7.11.4).

[92] International Policy Network "Incentivising research and development for the diseases of poverty," 2005 p15.

Crucially, it is *expectations* of how this problem will be dealt with that feed investors' behavior, with the risk that if the issue is handled badly it makes less-than-optimal vaccines self-fulfilling[93]. As Kremer puts it: "mis-specifying eligibility and pricing rules could misdirect research incentives away from appropriate vaccines."[94] We also know that it is not just the attributes of the medical condition that matter: "The type of technology in question will influence the formation of eligibility and pricing rules."[95] This is a tall order.

To try to encourage work on 'higher-quality' vaccines, rather than 'lower-quality' vaccines, and in an attempt to reduce the risks of those who finance this activity, there would need to be a set of potentially *very* complicated rules about qualities of acceptable vaccines, and variation in allocations and prices of vaccine purchases across multiple developers and purchasers, and over time and division of the fixed pot of subsidy. We say 'try to encourage', because it turns out to be hugely difficult – and probably even impossible – to use contracts to create the credible set of beliefs that enable the control of 'quality' through ex post adjustments after sunk costs have already been sunk.

Intuitively, 'quality' varies over the 'technology space' (interpreted as distributions over research leads). The job of the commitment setter is to set the rules so that 'effort' towards the more difficult and expensive parts of the space – where the 'quality' lies – is relatively more rewarded. If the IAC knew the technology space *exactly* (which includes knowing firms' costs and the scientific difficulties) they could set a precise rule with larger rewards the more difficult it was to get to a particular part of the space[96]. If they do not know the space exactly, they can only create a highly imperfect rule, taking great care over where in the technology space rewards are placed in case they cause distortion. Policy makers are reduced to more average rewards everywhere, and, indeed will *never* achieve the highest quality results. Hence, on average, achieving 'quality' is more expensive. In addition, because of all the uncertainty to players, the APC cannot simply pick out the highest quality area (even if the setter knew where it was) with a huge payment compared to the rest of the space (which might seem the most logical thing to do), since this would face players with huge risks should they fall onto other parts of the space where the payments are tiny. This is central to the argument that APCs should not be set up to just reward 'one firm'. So the rule over 'how much the quality rule varies', itself requires knowledge about the characteristics of firms, such as their access to finance, degree of risk aversion, etc.

Removing the quantity guarantee

By removing the 'quantity guarantee'[97] the intent is to remove the risk that the sponsor will end up funding a non-used product and harming those working on more useable products, and the foreknowledge of this, *so long as it is credibly*

[93] See Farlow 2004 ibid. Section 7.18 for 'quality space' proposals.
[94] http://www.pm.gov.uk/files/pdf/Appendix%207.pdf p10.
[95] No 10 Policy Unit, Kremer Appendix 2 p2.
[96] Imagine also the dimensions and complications of this technology 'space' if research projects were also not independent, the case with HIV, malaria, and tuberculosis.
[97] 'Making Markets' April 2005 p45.

believed, will incentivize firms to work on products that are suitable for developing country settings.

This is also supposed to incentivize follow-on vaccines, something especially important in the cases of HIV, malaria, and TB where the first vaccines are not necessarily going to be the best (more so if they are only therapeutic rather than preventative vaccines) and where a complicated 'arms war' may take place in the interplay between virus, drug treatments, and vaccines. Supposedly, by optimally 'holding back' on the distribution of the (fixed) 'pot' of funds, resources are left over for follow-on, improved, vaccines (including therapeutic vaccines), and incentives are created for *their* R&D[98]. But, how much to 'optimally hold back'? Notice the way that the special needs for monitoring in the case of therapeutic vaccines and the need to create incentives to replace *such vaccines*, should form a big part of thinking about the overall 'holding back' strategy. This is not easy to set up ex ante before much of the science is known.

2.3.1. 'Me toos', 'me similars', and vaccine replacement

It is argued that: "Subsequent vaccine suppliers [will] be allowed to *share the market* as designated suppliers, provided their products are deemed (by the Independent Adjudication Committee) to be *material improvements* on the first designated supplier" (italics added)[99]. Similarly: "If a firm developed a subsequent, *superior* vaccine (as agreed by the IAC), that product would *also* be eligible for the price guarantee (the price guarantee would apply to the first 200 million treatments, *shared* among the eligible products *according to demand*)"(italics added)[100]. This was clarified recently as follows:

> "*The sponsors guarantee to pay the developer a pre-determined price for the vaccines they buy, but they do not guarantee how many they will buy. The sponsors commit to topping up token co-payments by developing countries. So while Vaccine 1 is the only vaccine available, it will sell well, and Company 1 can expect good revenues. But when Vaccine 2 is approved, and* ***if it is a substantive improvement*** *over Vaccine 1, then it too is eligible for the guaranteed price…a firm can expect to sell their product at a reasonable price, but there is no guarantee that a better product won't come along and* ***cut into the market share***" (emphasis added)[101].

None of this makes any economic, never mind eithical, sense. The 60% or 70% efficacious HIV vaccine should *immediately* replace the 50% efficacious HIV vaccine and take all of its sales. How would, and why should, any developing country be forced to continue taking the 50% efficacious vaccine? Especially given: i) There is only a token level of copayments (that the country may not itself be paying anyway); ii) The huge costs of treatment (and economic losses) and

[98] Notice the way the trade-off between waiting or paying is tipped towards paying and not waiting because of the way capital costs are wracking up in the meantime.
[99] 'Making Markets' March 2005 p52.
[100] 'Making Markets' March 2005 p87.
[101] Barder, O., posting on behalf of the Center for Global Development, to Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 29 November 2004.

suffering for those who go on to get the disease on account of taking the 'weaker' vaccine; iii) The large costs of roling out a vaccine program that are in addition to the costs of the vaccines themselves; iv) The dangers of build-up of resistance, leading to an even more expensive vaccine and drug treatment program later; v) The political cost to leaders; vi) The general suspicion there may be concerning the motives of pharmaceutical companies and the use of inferior products on the poor.

International trials need developing country trust

Any international trials program will be utterly dependent on the trust of developing countries, something that should not be risked by keeping poor quality vaccines on the market (and trying to conceal this fact). Given the ongoing controversies over clinical studies for nevirapine[102], it is inconcievable that developing countries could have the less efficatious vaccines forced on them. Indeed, pharmaceutical firms themselves would not want to risk the reputational and financial hit across their portoflio of products by keeping such vaccines on the market. And why would any developed country ever devote its development budget (and political capital) to vaccines known to be of lower quality? In addition, if there was an intent to set up further APCs for other products, why would policymakers not be mindful of reputational hazards onto those later commitments?

Sharing a market makes sense if the second product is in some sense a useful 'me-too', or perhaps more precisely 'me-similar', vaccine. This is not to be ruled out here, especially when many factors impact on the effectiveness of vaccines, and there may be a lack of clarity about long-term effectiveness anyway, and hence room for 'similar' vaccines[103]. Similarly, if a vaccine is so closely similar to the other product, then the capacity that has been put in place to produce it might as well be used, especially if manufacturing capacity and supply is heavily constrained (which is a very real possibility in vaccine production given the long lead-times needed for investments in capacity)[104].

Generally though, if the later vaccine is better, the firm should not have to compete with, but, instead, simply replace an 'incumbent' producer's product.

The problems of allowing total replacement

Indeed, it should *always* be a fully credible possibility for a vaccine to be totally replaced by the 'superior' vaccine of a competitor. This would be potentially expensive for the first firm, unless somehow they had been sufficiently insured by up-front payment. But then, paradoxically, it would be especially difficult to achieve replacement if most of the fund had already gone on the first vaccine.

[102] See, for example, "Under suspicion: the HIV drug that held out hope for millions: Fresh cause for concern over the side-effects of nevirapine" Neville Hodgkinson, The Business, 30/31 January 2005.

[103] For example, if the true long-term effectiveness of a vaccine is only revealed over time, it is not clear that an apparently short-term, less effective, vaccine should be discouraged, in favour of one that is seemingly 'more effective' in the short run.

[104] Though this obviously creates problems for the first firm and may make it difficult to police firms not to strategically exploit this.

Clearly, the two requirements conflict. The issue then is to what degree and how this is be factored into total payment schemes given this fundamental conflict.

Observe that when replacement comes about, the firm being replaced may, in the eyes of the public, have already received more than adequate returns for its investment (the public only see things in the ex post sense, and not in the ex ante sense required for the investment). What rules and institutional set-up could possibly credibly commit to replacement based only on ex ante criteria?

Observe also that since replacement is only a statistical possibility, the APC will have to be set high enough to allow for this outcome even if, on average, some of the advance purchase fund is 'left over' unused. The only alternative to this is for firms to understand that: i) Either governments and taxpayers will step in ex post to ensure full replacement (but then we are back to the problem we have today, though after having already spent a great deal of money), or, ii) incentives will have to be created that make replacement less likely in the first place. This is where a truly independent IAC comes in, since it has to be prepared to enforce something extremely expensive and (to the firms) possibly controversial. For example, it has to be prepared to totally 'replace' the vaccine product of a developed economy firm with that of a developing-economy firm.

It may well be that, whatever way is used to motivate research, being totally replaced is a large, but necessary, risk for developers of vaccines for complicated and evolving viruses such as HIV and malaria, where resistance, therapeutic, and composite vaccine issues bite much more than for just about any other vaccines. And this risk also has to be priced into private capital costs. It could even be that this risk is much higher in the case of such vaccines than in the case of drugs. In particular, complex biological products such as vaccines are sentitive to the production process generating them, and are much less likely than drugs (though, maybe, not the newer 'biotech' drugs) to be able to rely on bio-equivalence comparisons, so that each vaccine is much more likely to have to undergo clinical trials and seek licensure on the basis of its own unique data. This generates a great deal of sunk capacity that has no use if the vaccine is replaced. This raises a further issue: If a product is clearly better and should replace all previous supplies, what incentives are there to expediently create the manufacturing capacity to do so?[105] Again, this suggests that directing quality of complicated vaccines like HIV through sales of vaccines may be more difficult than is sometimes made out.

The dangers that poor vaccines drive out better vaccines

There is of course a simple way to avoid ever having to face this conflict: Set one payment, put little else of the framework in place to adjust for quality or to encourage replacement, and ensure that the 'better' products never arise in the first place to challenge the products that would otherwise likely be replaced. The

[105] The Bolar exception allows activity relating to registration of generic products in the run-up to products going off-patent. This helps to speed up generic competition when a drug finally goes off-patent. But given that these are biological products and therefore needing their own individual set of test data, and given that know-how is so important, it follows that it is not clear how well this would work in practice either for vaccines going off-patent or for vaccines going 'off advance purchase commitment'. Certainly it would work a lot less strongly than for drugs.

dynamics of the mechanism, in practice, also help to insure that the replacement situation would not arise in the first place, since – for all its talk of competition – the capture of the mechanism would (by the late stage of the process) ensure that the number of large pharmaceutical firms active on a vaccine would be very limited anyway and the number of potential vaccines would therefore be insufficient to pose a threat to those already holding contracts[106]. The exact workings of such commitments need to be set very carefully to avoid poorer quality vaccines 'driving out' potentially better quality vaccines, and large 'deep pocket' firms driving out smaller, financially constrained, firms.

2.3.2. Composite vaccines

As a very practical example of all this, suppose various companies are working together to try to develop a composite HIV vaccine. The last thing they would want to face is a reward system that only pays for their 'additional' therapeutic value on top of some other less composite (or even non-composite) vaccine that might arrive more quickly[107]. Indeed, it would be a disaster to arrive on the market *after* the first 200 million vaccines had been produced, the quantity cap breached, and most of the fund already gone (no doubt also gone to the 'easier' portions of the market). The expectation that *all* of the value of the composite vaccine[108] will not be extracted, will disincentivize it from the start. Yet, this problem is only captured in a footnote: "The Working Group intends that terms should distinguish between those developers who are second because they are simply copying the first developer's vaccine and those who are second simply because their independent research program happened to take longer."[109] But this is a wish only; no details are provided as to how it would, or could, in practice be achieved. Clearly one would *not* want to incentivize away from more complicated composite vaccines in rules set up many years in advance.

2.3.3. Market risk and risk to developers

What does "*according to demand"* mean anyway? Such phrases only make sense if developing countries have the resources and know-how not only to work out the nature of vaccines currently available (a therapeutic vaccine for HIV for example), but – given the need to create dynamic incentives for vaccine R&D – the nature of *potential* future vaccines too. The danger is that the 'market test' puts a huge amount of risk onto the shoulders of companies. After all: These are resource-poor markets; most buyers are relatively uninformed; there is no marketing as such, though there are plenty of ways to encourage decision-makers to take one firm's product over another firm's product (more so if the 'other firm's' product does not even exist yet[110]); vaccine usage needs a good distribution system, with such systems generally *not* under the control of vaccine companies; there are heavy knock-on costs to purchase decisions; there are multiple organizational problems; there is a severe lack of qualified personnel on the ground; there are multiple political interests; there are cultural barriers; and there are strong 'self-fulfilling' pressures driving towards lower-quality outcomes in the co-payment mechanism used by 'eligible' countries to pay for vaccines

[106] For more on this also see Farlow, 2004, ibid. Chapter 10.
[107] Again, the logic in all of this analysis is based on 'expectations'.
[108] To include a penalty for delay.
[109] 'Making Markets' March 2005 footnote 85 p115.
[110] Yet again, we are talking in the expectational sense, with an eye to dynamic incentives.

under the program. Given the historic record of good-quality and cheap vaccines being underused, it is not immediately obvious that the expectation of investors would be that 'good'-quality products automatically would get used while 'bad'-quality products would not. This, ex ante, feeds investor expectations and R&D incentives towards the 'lower-quality' outcomes.

The irony of facing firms with demand risk

It seems very odd to face firms with the very thing – demand risk – that is at fault in the current system. And ironic that late-stage vaccine APCs work largely by removing demand risk, only then to see early-stage vaccine APCs relying on demand risk. The only reason we are forced to do this is because quality is not being controlled *en route*, so the APC approach has to feed demand risk on to developers at the end. It is not clear that firms themselves would not just rather there be some guarantee of revenue even if the quantity take-up is low because of faults in the distribution system, with policy makers and other institutions responsible for ensuring that the distribution system works. Otherwise, this adds another decision-maker and further increases uncertainty about whether a product will get used, generating yet higher capital costs, which only feeds into yet higher vaccine prices anyway. More on this later.

A basic economic principle is that to incentivize firms, they should only face risks generated by factors over which they have control and which matter for the objective of interest. They should not be forced to face risk, including demand risk, that has nothing to do with their own acts. Exactly how much firms should be insured and how much risk they should face, is still a mute point in this literature.

2.3.4. Pricing rules to generate a split

In recognition of this problem it is suggested that the "pricing structure *can be designed* to provide substantial insurance against demand risk for prospective vaccine developers so as to yield a net present value of revenue *comparable to commercial products even under pessimistic uptake scenarios*," (italics added)[111]. But this simply indicates the complicated tradeoff that needs to take place, not that it *would* take place or ever *could* take place.

It suggests that there must be sufficiently up-front payment to insure against the 'market risk' (including the risk that generics, 'me-toos', and others take market share, but also the risk of vaccine health infrastructure failure, and a range of other risks), but that there has to be a sufficiently low level of payment up-front that it gives firms the incentive (because they are not insured) to develop a distributable product, whilst also leaving 'enough' resources over (in just the 'right amounts' too) for later developers. However, there is no way of knowing *in advance* how the degree of 'up-front-ness' should be set if the split of funds is to be fixed and not to rely on discretion, unless we know from the start the exact nature of the expected underlying technology and, indeed, the expected 'uptake scenario', 'market risk' and a host of other risks that are outside of the vaccine firm's control (including the risk that earlier vaccine developers who have already sold their 'allowance' will still try to take the market of later vaccine developers –

[111] 'Making Markets' April 2005, p105.

a logical act if capacity is already in place). Observe that, again, this comes about because quality is not being guided *en route* to development but by firms' expectations of the IAC's behavior after development.

An alternative approach might be to allow the IAC to be much more involved in clarifying quality issues at much earlier stages of development than the commitment literature currently suggests. But, if so, this intervention runs the danger of all the faults that the mechanism was supposed to be removing from policymakers' hands. In addition, if members of the IAC are drawn from a subsection of the industry, it risks deterring some vaccine developers if they perceive that their power to influence decisions will be much weaker than that of other much larger players (at 10-20 year investment horizons this is a big risk). Again, we find that the approach is becoming just as interventionary and full of monitoring as the push approaches it was supposed to be replacing, with the added complication that all the intervention takes place after heavy sunk and privately paid for investments are in place.

The sums do not add up anyway

The sums do not add up either. If even after "pessimistic uptake scenarios", revenue streams "*comparable to commercial products"* have nevertheless been handed over, the cost of actually getting a viable vaccine will have risen even higher. Yet again we have to remind ourselves that the 'commercial return' refers to the *ex ante* $6.25bn and not the much smaller, but still seemingly profitable, *ex post* return. If a 'commercial' return is deemed to be $6.25bn, and the scenario dictates that this has to be given, then once this has gone, resources have to be *expected* by other developers to be provided from *somewhere else* to pay for their products. Once the $6.25bn has gone, it has gone! And worries about this fact will destroy incentives to explore better vaccines unless somehow payments can be made much more open-ended. But the latter open-endedness destroys the point of the mechanism.

Knowing when to stop 'holding back'

The 'holding back' of payments described above is only optimal to the extent that improved vaccines are to be expected and to the *degree* they are to be expected. As an extreme example, if there really is only ever one vaccine possible for a particular virus, then terms should be set such that *it* gets all of the potential funds so as to maximize the chances of discovering *it* and the speed of getting *it*. To offer less than the whole fund is suboptimal. If less than the whole fund is nevertheless offered and subsequent follow-on vaccines prove impossible, then the rules should specify how the 'left-over fund' is to be spent on the first-only-ever-discoverable vaccine at a later date (though also somehow designing *this* further mechanism so as to avoid paying for the non-best vaccine by mistake), even though this will also involve a yet higher dose of capital costs[112].

[112] Where do fresh funds come from to compensate the firm for the loss of capital costs in the meantime? Strictly speaking this should be additional to the advance purchase precommitment funds.

2.3.5. Is this just the beginning of the needed funding?

Or is it that the first APC is only the start? Given the problems of incentivizing follow-on products, maybe the implicit assumption is that there will be follow-on financial instruments?

> *"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 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."* [113]

The problem is that if investor incentives are not to be harmed, this 'additional money' for follow-on products should be credibly promised in advance if it is not part of the original APC – but that makes this 'additional money', by default, part of the original APC-type arrangement! The danger is that the fund becomes unbounded at top, yet the eventual size is highly uncertain – killing dynamic incentives in a very wasteful fashion. The original (Appendix 3) model, by being entirely static and presuming one vaccine target, was able to ignore these issues.

This is not like other markets

This is all very different from standard developed economy drugs markets, where firms can 'take' market share from existing firms without the need to appeal to a committee to do so, and they have access to marketing budgets. Policy makers do not need to work out 'rules' – many years before the science or quality of products or epidemiology is known – that will generate optimal ways to split a fixed pot of subsidy over products, and firms do not have to rely on the discretion and extreme competence of a committee and of the poor countries themselves, that are somehow free from even the possibility of ever being captured.

This also sets up a range of institutional issues. Usually 'quality' follow-on is performed through the patent system, with patent offices and/or courts deciding if a patent is valid or infringes. Marketing does the rest. The APC seems to be suggesting the creation of a supra-body to determine these issues. If so what is the jurisdiction and how does this interact with those parts of the overall R&D system (PPPs, IAVI, etc.) working within the current patent and court system?

2.3.6. The dangers of promoting the lowest common denominator

One of the dangers is that the requirements would be set at the very lowest level that would be of any epidemiological value. In successive drafts of the CGD

[113] 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.

report, the requirements for a malaria vaccine gravitated ever-lower, standing in the final report's contract term sheets at a suggested 50% efficacy for 24 months from up to four doses, with room to lower the requirements even further. There was no clear rationale to support this. It may have been a response to a malaria candidate vaccine making the headlines in late 2004. Unfortunately, though promising, this candidate is based on a single component of one stage of the life-cycle of the parasite causing malaria, and may never have enough efficacy to be worth using widely. Even if it is successful in upcoming trials – by no means a foregone conclusion – there will be need to encourage the design of subsequent generations of better vaccines with much broader activity and higher efficacy. Blindly pitching minimum requirements ever lower simply works against this long-term goal.

The consequence of pitching lower is that there is no incentive for competing teams to develop vaccines that exceed the minimum requirements, because the first company to satisfy the requirements would have a huge incentive to try to harvest the full $3bn from the small portion of all potential sales that get the high subsidized price, even if its vaccine is later abandoned and follow-on vaccines are also stymied. No follow-on privately-financed innovator would invest the additional time and resources into a superior vaccine if the development of that vaccine would take several years longer than the minimum requirement vaccine and risk 'missing the subsidy'. Because the discretion to lower standards is especially risky to smaller and less powerful developers, and because the risk of political capture is high, most of the world's research teams and venture capitalists would be put off from investing private funds in the first place.

To make matters worse, the greatly reduced reward obtained from exploiting improvements in technology to generate higher quality products, destroys incentives to make such breakthroughs in the first place; there is no relevant price signal.

Therefore, from many different angles, such approaches run the risk of actively discouraging the development of highly effective and safe vaccines.

2.3.7. The conflict with low prices and rapid access

Would we want to guide 'quality' this way anyway? Shortly we will see the key role of manufacturing scale in previous vaccine case-studies – for getting vaccine prices low – and capacity for rapid access. What we have just described conflicts with both of these objectives. If scale and capacity are key variables, it does not make much sense to be using the holding back of quantity of production and of sales in order to discipline 'quality', nor to be inflicting uncertainty on those investors seeking to boost manufacturing capacity. The only reason we find ourselves considering doing this is because, by basing *everything* on the splitting of a fixed pot of funds at the end of the whole process, the only route we have left open to us for disciplining 'quality' are restrictions on the dispersal of that pot, especially the early dispersal.

If we knew for certain that we already had the best vaccine possible, then we could dispense with all these restrictions, scale up and go for mass access from the start. It might be argued that the mechanism with the 'pot' of funds at the end

could be adapted so that those running the program could guide firms en route, so as to weaken or dispense with these restrictions at the end. However, this contradicts the APC advocates' claim that those running the program are hopeless at such monitoring (given all the sunk investments, they would certainly face an even more difficult job than push funders in getting firms to be truthful) and, anyway, it takes us back to a model much like the alternatives that we were supposedly trying to avoid with information held in the hands of those running the program, but with the added problem of a large prefixed pot at the end.

If the mechanism is made ever closer to the alternatives anyway in order to get around this problem, how does it not lose the supposed virtue that 'firms choose' their research strategies and not the sponsors? And are we prepared to pay the heavy capital costs to get back to a system much like the one we were trying to get rid of anyway?

The paradox is that the mechanism that disciplines 'quality' en route is better able to achieve large capacity and low prices, than is the mechanism that disciplines 'quality' via holding back in the end market. Indeed it is hard to see that, with the base level of treatments set at 200 million or so, any 'quality' control over the whole development process could be done in the end-game without conflicting with the need to get the manufacturing costs low. This aggravates the problem, discussed shortly (see section 2.14), that firms will not believe that manufacturing costs will be pushed low enough ex post to make the whole investment exercise worthwhile ex ante.

Yet again we find that it is better to control 'quality' en route, and we are led away from commitment-based approaches for controlling 'quality'. And yet again we find that the pull working group should have called in one or two specialists, in this case industrial economists, to analyze some crucial underlying assumptions.

2.3.8. Countries not covered and those who use 'other approaches'

This 'quality' problem has many subtle implications for countries *not* covered by the mechanism – mostly because of the need to protect the 'initial market' for the products of the program. If Russia, India and China were, for example, not covered by an APC for an HIV vaccine, their markets must still be stopped from using any vaccine motivated by the mechanism (including those failing it though motivated by it) unless purchased from the 'winning' developer[114]. Vaccine developers would have to understand that if they did not make the standard required of the APC, they would be denied access to these *other* markets, otherwise their sales to these *other* markets would crowd out portions of the 'initial market' on which the vaccine that is being paid for under the purchase commitment is supposed to depend. An APC is a market 'enhancement' instrument after all, and the market being 'enhanced' needs to be protected. Just

[114] See Section 7 of Farlow, 2004, ibid for more on this point.

the knowledge that this protection will might fail will make 'higher-quality' vaccine development more risky and hence more expensive[115].

No 'me-toos'

In addition, once a vaccine is developed under the mechanism, these non-mechanism countries would have to be barred from using 'me-too' vaccines based on it (even if the vaccines are not of the same clade but are somehow build off the first vaccine). Instead they would be have to be charged monopoly or tiered prices by those firms receiving payments under the APC with vaccines manufactured under the terms of the mechanism by such manufacturers with 'me-toos' prevented. Given the segmentation of the market, this might even be at higher prices to them than would have been the case without the APC in place. Indeed, they would be tied by a much different and much longer mechanism, based on TRIPS-style IP or TRIPS-plus IP, than those eligible to vaccines under the APC. Clearly, this would get extremely complicated if the APC was itself allowing degrees of 'me-too' vaccines to eligible countries.

None of this is discussed in the 'Making Markets' or 'Strong Medicine' literature, but is central to an HIV vaccine developed under the mechanism having 'additionality' of market. Incidentally, such problems (in particular *expectations* about such problems, given that it is investors who must worry about these things) are much less important for those vaccines[116] that already have much more exclusively 'poor' markets, and the more late-stage and scientifically understood the vaccine is.

Russia, China, India won't go along with this surely?

It is not clear that Russia, China and India would, or even could, bind themselves such that 'high-quality' vaccines do not suffer market erosion of 'initial' market. This is not referring so much to parallel trade in vaccines; being biological products and heat sensitive, vaccine procurement and distribution is strictly controlled, and essential vaccines are often distributed free or close to free. These factors greatly reduce the likelihood (compared to drugs) of vaccines entering into parallel trade or any forms of resale or piracy. Instead, the issue here is stopping others from using the *technology or science* of such vaccines in research or manufacturing processes. Incidentally, this creates a conflict with any 'vaccine enterprise' present if part of a collaborative mechanism is to encourage technology and information sharing[117].

At a very practical level, it is not clear that denying sales in non-eligible countries of non-APC vaccines or of 'failed' APC vaccines could be achieved, even more so if the competing vaccine achieved a similar or different result through the use of a different technique (plasma derived versus recombinant vaccines for

[115] Remember that supposedly there is no control over 'quality' by policymakers. The *whole point* of the exercise was that policymakers 'don't know' such things, and that it is therefore better to have a mechanism paying 'by results' than having interventionist policymakers handling 'quality' en route to those 'results'.

[116] And any other product, the R&D for which is being stimulated by an advance purchase precommitment.

[117] In non-collaborative settings, also observe the offsetting impact created by the lack of 'know-how'.

example), or even if it was based on similar technologies but was hard to 'police' out, or if capacity for both eligible and non-eligible markets were severely constrained. Additionally, the conditions in the TRIPS agreement that enable competition during the lifetime of a patent may also have some impact on the ability to protect the 'initial market'[118].

The effect on the dynamics of vaccine sales to non-eligible countries and R&D incentives is still largely unexplored, especially by those working on HIV vaccine APCs.

Similarly, if some sponsor countries or foundations had chosen not to join the APC and instead had chosen to adopt an alternative approach, then vaccine developers using those alternative approaches must somehow be denied access to payments under the APC to stop their use of the APC from damaging the investments of those relying on the APC exclusively. However, it is not clear that such developers could be denied access to the APC payments (especially, but not only, if they have a better vaccine) or barred from selling to countries supposedly covered by the mechanism (never mind those not covered).

2.3.9. Ex ante versus ex post information problems: Unhelpful caricature

'Push' approaches try to target 'quality' ex ante *during* the development process and naturally face a series of informational asymmetry problems between funders and researchers. APCs, on the other hand, (supposedly[119]) tend to let firms and those financing firms choose research leads, but with committees disciplining 'quality' ex post through sets of rules about distributions of APC funds across products, over time, over purchasers, over technology, etc.

So, while it is correct that pull mechanisms "require less knowledge on the part of policy-makers about the likelihood of success *of particular approaches*" (italics added)[120] and that sponsors do not "need to identify promising avenues of scientific research,"[121] nevertheless sponsors do need a huge amount of qualitative and quantitative information – about the *overall set* of potential scientific, epidemiological, expected research and manufacturing costs, market possibilities, and chances of success – well in advance of product development in order to get the distribution rules right. It is claimed that those using APCs avoid the "need for them to take a position on the feasible approaches and the likelihood of success,"[122] but this is not true outside of individual approaches. Indeed, to be credible and to minimize the risks to firms, firms *themselves* need to trust that policy-makers have this ex ante information. If the exact science is not understood at the start, rules will have to be 'made up' at the start and discretion used later to 're-optimize' the rules, and hence the allocations.

---

[118] Though, control of 'know-how' limits the effectiveness of these provisions in the case of vaccines.
[119] Since we just described the way that 'pull' can end up doing as much control en route as the push mechanisms they were supposed to be replacing.
[120] 'Making Markets' March 2005, p27.
[121] 'Making Markets' March 2005, p38.
[122] 'Making Markets' April 2005, p26.

Firms know that it is easier to say that that there will be 'payment-by-results'[123] than it is to ensure that this actually will be the case, given that firms need to work out the value of their investments many years in advance of payments, based on the rules about distribution of payments and expectations about this discretion. Yet, we are told, the size and terms of such contacts could be set "even when there is less clarity about scientific prospects."[124]

If practical applications of the mechanism are going to have to make heroic assumptions at the start about how to set payments to encourage higher-quality, or will have to adapt rules over time to target quality and be much more interventionary 'en route', it is not immediately clear that this is less demanding or problematic than what other approaches are trying to do. The mechanism ends up relying on a great deal of ex post discretion – the very thing it was meant to avoid. Worse, most of this discretion takes place *after* a great deal of private costs have been sunk, and this raises a new set of 'dynamic inconsistency' problems – the very things the approach was supposed to avoid!

None of this is spelled out in 'Strong Medicine', or the No 10 Policy unit material, where the problems of multiple developers and quality issues are largely swept aside as of minor importance. The issues are discussed somewhat in Advanced Markets – where it is pointed out that it was "determined not to pursue a winner-take-all approach,"[125] and that "there is no winner-take-all"[126] – although the exact workings to get around the various problems are very confused and not practically resolved, never mind theoretically resolved.

Conclusion on 'quality' issues

Without very precise knowledge – at the time the APCs terms are initially set – of the underlying state of current and future technology and research and manufacturing costs, and without any external control over the quality of research, it is impossible to set terms in early-stage APCs that will allow *optimal* re-adjustment, after vaccine development, of quantities, prices, and, indeed, of eligible firms. These adjustments, but most importantly *expectations* of these adjustments, are essential if such commitments are being used to encourage investors into R&D on vaccines of the highest possible quality, and to prevent pressures towards lower-quality vaccines[127].

It is not clear that ex post indirect control of quality via rules that are not likely to be credible or – now we discover – even desired, is to be preferred to ex ante, more publicly open, guidance of such quality issues, for example, via the more collaborative mechanism described in sections 4 and 5 below. The ability to manipulate outcomes for early-stage vaccine R&D through the end product market is based far more on optimism than on any concrete evidence that it can be done. It is a false dichotomy to suggest that some approaches suffer major informational problems while others do not.

---

[123] 'Making Markets' March 2005 p38.
[124] 'Strong Medicine' p63.
[125] 'Making Markets' March 2005 p115, footnote 85.
[126] 'Making Markets' April 2005 p 29.
[127] See Farlow 2004 Section 7.9 and 7.10 for a range of other pressures pushing towards 'lower quality' outcomes, in that case driven by problems with developing country incentives.

Again, most of this discussion is largely now redundant. It is obvious that creating incentives for 'quality' is important, but it is increasingly evident that the current $3bn being proposed by the Center for Global Development for each of HIV and malaria are largely stand-alone pots of funds with none of these quality issues even thought about, never mind resolved. Again, the issue seems to be to more about getting a 'policy success' than to actually getting a good policy.

2.4. 'Crowding Out' and the Difficulty of Achieving 'Additionality'

The effectiveness of early-stage APCs as described in 'Strong Medicine' and 'Making Markets', *compared to other mechanisms*, and the incentive to develop higher-quality rather than lower-quality vaccines, depends on the creation of *additional* privately financed research and *additions* to currently existing vaccine markets. These are, after all, chiefly instruments of "market enhancement"[128]. It is claimed that APCs are especially cost-effective because "expenditures are highly targeted."[129] To the extent that this 'targeting' fails there is crowding out of a proportion of the commitments, and APCs are less cost-effective. In practical applications this targeting would fail in a very big way. To work out effectiveness, we would therefore like to know how much potential 'crowding out' will take place, and how it is suggested that it will be avoided. We would be interested in the following:

2.4.1. How are other forms of research support handled?

How are tax breaks, subsidies, and other push payments, and how are all other research activities covered by international initiatives such as IAVI, MVI, the European Community, WHO's Special Programme for Research and Training in Tropical Diseases (TDR), the U.S. Agency for International Development (USAID), the U.S. Department of Defense (malaria), other public-funding, and Foundations, all to be policed out of the payments received under APCs? After all "the proposal is that *private* investment would underpin R&D by *private* firms" (italics added)[130]. The mechanism should *only* reward the suppliers of this *new* private finance to avoid placing undue risk on private investors. If those using other forms of funding are not made *ineligible* for APC payments *in proportion* to their use of these other forms of funding, their activity will destroy the value of the APC for those who *are* relying on the APC to give a return to *their private* investments. Without a proper system in place to efficiently deal with this – especially in an area of complicated interplay between push and pull funded activity – those supplying this private finance will face large risks (in the expected value sense) and will refuse to invest in the first place without a large increase in APC to compensate (though this will also aggravate the problem further).

MVI case study

As a very simple practical case, what if, encouraged by the presence of an APC for malaria, MVI bets all its available funding on one or two candidate vaccines in

[128] 'Making Markets' March 2005 p94.
[129] Kremer, M., No 10. Policy Unit Executive Summary p1.
[130] Barder, O., CIPIH Forum, 19 November 2004.

the hope that others will place *private* bets on other candidate vaccines? What if it is not clarified from the start that the MVI vaccines will never be allowed any of the APC? Otherwise, its chances of taking the APC fund will feed a lower expected payoff to other privately-funded investors (run the benchmark model to see) and MVI's behavior will crowd out some of these other privately-funded investments (one-for one if it is equally efficient, more than one-for-one if it is more efficient). But what if the MVI vaccine is the first and best vaccine? Surely it should be allowed to crowd out the privately-generated vaccine[131]? Why should the APC then make an award to an inferior privately-generated vaccine that meets the requirements even though it is never used, just because it was incentivized under a 'separate system' to MVI? Observe that even a better MVI vaccine, developed under its own 'separate system', should not be allowed to replace the vaccine developed under the APC system, since breaking the 'separate system' rule will increase, ex ante, the risk to private vaccine developers and will deter them from the start. But this seems to suggest that only if the MVI vaccine is worse, does it not create a problem. But that is perverse.

What if MVI then wants to distribute its vaccine or vaccines at cost-price even in markets waiting for the APC-based vaccines? Should it be barred from this too? Since the commitment works on the basis of demand for the product, why should the MVI not be free to compete in those markets even if it means undermining demand for the APC-based vaccines? What if MVI allows its IP to be 'technologically transferred' to emerging developers for close to free, and, maybe even for free?

How *exactly*[132] is it proposed that PPP activities "complement" and not conflict with APC-based private activities? As always, this all shows up in investor 'expectations' and investment incentives. The most likely result is that private investors will simply avoid facing potential unresolved dangers.

At first ignored: Now, accepted, but no explanation of how it is done

At first, this issue was stripped out in the key Appendix 3 model and everything based on it since no other research support devices were modeled as being present. Only very recently has the issue been recognized, but still it is largely ignored in practical proposals. 'Strong Medicine'[133], for example, argues that "if push funding had been allocated before the announcement of the pull program, the winner might be required to use *some* of any pull revenue to repay *part or all* of the push funds it had received." (italics added). Regarding push funding received *after* the program was announced it is "up to the push funder to decide" on any repayment and on the IP arrangements put in place in order to enforce repayment. This is not just simplistic; the economic logic is wrong[134]:

---

[131] All of this is done on the basis of there being just one vaccine, when in fact there would be a complex set of vaccines over time.

[132] This is a polite way of expressing exasperation at the way the Centre for Global Development repeatedly asserts that something is so (in this case that purchase precommitments "complement" other activities) but *never* spells out how it is the case practically.

[133] 'Strong Medicine' p106.

[134] All of the following is presaged on the notion that there are *many* competing developers. Most of this makes little sense if the number of developers has collapsed down to just the one. Maybe this is why those currently lobbying heavily for APCs – with their emphasis on feeding a large contract to one big player – seem to see very little in this problem.

i) It is *not* up to the individual funders to decide. To keep their capital costs down and in order not be discouraged from their privately-funded research, those relying on purchase commitments need to be *completely assured* that a *coordinated* response is being taken to deal with all activity that was *not* incentivized by the APC. Either other funders *should* be required to ask for push funding back from any purchase awarded, *in proportion to that funder's contribution* to any successful project, and they should collectively coordinate *their* behavior to support the efficiency of the APC, or – more likely – the APC to each 'winner' should be reduced to cover only the part of private activity actually incentivized by it. There is no excuse for allowing funders to act in an uncoordinated way by allowing the individual "push funder to decide"[135];

ii) If coordination of 'repayment' is not achieved, there will be temptations for individual countries and foundations to 'cheat' and unfairly advantage their own firms and researchers by allowing them to take advance purchase payments that are out of proportion to the private costs they actually engaged in, thus disadvantaging, and disincentivizing, those being more honest. With the free-for-all emphasized in some of the commentary[136] it is clear that these countries would not deliberately weaken their own domestic producers by disciplining repayments of push funds (multiplied many fold) out of pull rewards. Who will police countries and foundations? Where will the information they use to police them come from? This would call for a global treaty and another committee/regulatory layer to police countries and firms.

In the best case, where there is wide participation of players and countries in response to the APCs (something very much doubted in this paper with respect to early-stage vaccines), this would not be an inconsiderable problem. In developing countries such as India, and China, and increasingly South Asia, Africa and Latin America, the governments have launched major programs of research and development for diseases of concern to their people, often in collaboration with the private sector both within their countries as well as with international companies outside of their borders. The paradox is that the more intense this activity is in response to those health conditions targeted by APCs, and the less coordinated is the removal of APCs payments not linked to fresh injections of private capital, then the more the value of an APC is crowded out as an 'additional' funding instrument. In such circumstances it would make more sense to use the funds that would otherwise have gone into the APCs by simply directing it at such emerging economy initiatives from the start, with more funder control over IP and with low prices in part-reward for financial assistance (i.e. through PPP support).

iii) That firms would have to use "some of any pull revenue to repay *part or all* of the push funds it had received" (italics added) is wrong. Pull payment to any firm would need to be reduced by *many times* the 'push' payments *it* had *ever* received. As a simple example, if ten firms are working with equal strength on

[135] This is also a route for countries to inefficiently favour their own developers, generating a negative-sum game overall.

[136] e.g. Berndt, E.R. ibid. "The proposal requires relatively little prescription on the part of governments."

malaria vaccines (again we are presuming competition when this is not obviously going to be the case), and 70% of costs are capital costs[137], and we presume for now that there is one outright winner (we here presume no splitting of the $6.25bn), but the 'winning' firm benefited from 50% of subsidies, grant support, and all manner of non-private funding, then this firm would have to be denied just over $3bn of the fund[138], with the rest of the fund – for the sake of efficiency over time – left 'in the pot' for follow-on malaria vaccines. However, having only spent an expected $187.5m on out-of-pocket research costs (and an expected $437.5m on capital costs), the expected loss to the firm is nearly *seventeen times* what they would have spent on real out-of-pocket research. The marginal incentive to avoid that loss is *extremely* high.

iv) It could be that if PPPs are active in a particular field, those funding PPPs could specify a multiple of the PPP funding as potential future payment. An organization could fund, say, ten PPPs, one per vaccine lead and stipulate the one winning lead to, on average, repay *all* the PPP funding. However, this would require: All PPPs to use the same rules and all PPPs to be behaving in the same way with none of them 'cheating'; a much more complex accounting and repayment system; dangers of tensions between the foundation/public part of the PPP and the private part; to the extent the PPP was 'old' PPP funding (i.e. funding that would have been used anyway) it would have to be understood that the APC payment would be returned to the APC funder, etc. And there would still be difficulties in correctly allocating payment.

v) Since repayments would need to take account of the *specific conditions of each firm*, it would require a great deal of monitoring of firms and high-quality historical evidence (adjustment would, for example, have to be made according to *when* the funding took place in order to appropriately account for capital costs[139]). None of the APC literature for early-stage vaccines deals with this. For a scientific area with a complicated interplay of push and pull funding and great opportunities for the pull-motivated to lose out to the push-motivated, this is simply not good enough;

vi) It is impossible to correctly 'price' these streams of 'other payments'. For example, what is the worth of the implicit subsidy on large pharmaceutical firms' capital costs of NIH research? And how is information on publicly-funded research and tax subsidies that is *only* connected to the research at hand to be correctly derived from aggregate firm-level data? Kremer himself argues that one of the big problems of tax subsidies targeted at certain strains of HIV is that large pharmaceutical firms can 'hide' the way they spend the subsidy on research for strains that already have rich-economy markets. We face the same problem here. It creates a headache to have to value all of these inputs, and is paradoxical given the argument that the approach is supposed to avoid all of this sort of monitoring

[137] We are yet to be provided with any figures.
[138] Presuming constant intensity of effort, and we presume that all firms started from scratch. Everything is in the expectational sense since we do not really know when success would occur. Another way to think about the logic is that it is a 'gamble' and half the fee to enter has been paid from public sources.
[139] Imagine the argument over the capital costs!

activity. And it generates yet more layers of committees, discretion, and treaties, and/or 'repayment' side-contracts that may not unfold for ten or twenty years.

vii) In the last simple example, for every $1m dollar of subsidy and grant support that the firm could hide, they would benefit to the tune of nearly $17m. And who does this advantage? Large pharmaceutical firms have a heavy advantage in hiding such information, since smaller firms, biotechs, not-for-profit firms, etc. would have many fewer ways to hide research supports – if they could get them in the first place. Most biotechs simply work on one area, and their funding flows are much less opaque. This simply reinforces the argument that APCs are primarily an instrument of support for large pharmaceutical firms;

viii) In order to work out an optimal strategy, every firm needs to know how much *privately*-funded activity is taking place overall in response to the APC, and how much is being covered by other research support devices. But the above logic suggests that there would be great incentives to distort activity and hide information to avoid 'repayment' of subsidies and tax breaks. If this hiding were widespread, it would make it extremely difficult for individual firms to work out how much to optimally spend on R&D since it would become extremely difficult to know exactly what genuinely new privately-funded research is actually going on in the aggregate, in an attempt to win the commitment. This is made even worse if the push part of the mechanism has expanded too.

ix) Incidentally, standard procurement tendering for late-stage vaccines *is* capable of generating purchases that *only* pay for the additional private funds required to finish a process off or to cover manufacturing costs. The competitive tender in effect separates out the push from the pull funding. The problem is that the 'Framework Agreement', policed by the IAC, *is the tender*, and an extra, highly complicated side device has to be slapped on to *it* to achieve a property otherwise inherent in more standard tenders. It is misleading to suggest that the properties of the two tenders are the same.

A simple example

As a simple example of the problems, if it is deemed that $10bn of incentives is needed to get a vaccine developed, and the current incentive is $5bn (push and market combined), if a $5bn APC is set up, this would seem to make up the $10bn required. If developed economy developers with access to tax breaks however do not have their tax breaks removed, they will spend up to $5bn, with a sizeable proportion in tax breaks (lets say 50%, or $2.5bn for now) and the whole exercise has generated only 2.5bn of genuinely new private funding. Those developers who did not have such push advantages are crowded out. It is much more complicated than this. See Farlow Sections 8.4-8.7 for more details of even greater complications.

'Others' should not be allowed to get payments

The above discussion too is a largely superfluous worry. The current Center for Global Development proposal, with its emphasis on getting a 'policy success' with politicians at any cost, has little interest in genuine *additionality*. Indeed this is the source of the myth (indeed encouraged by some of the supporters of early-

stage APCs) that an APC would be 'open to all'[140] and that public- and foundation-funded projects could equally apply for payments under the scheme. However, to the extent that they had *not* used private finance, they should *not* be allowed to draw on the APC. If investors are putting private resources into projects that are dependent on an APC award in order to be viable, the last thing they want is large numbers of publicly-funded and foundation-funded developers also able to take the award, thus greatly reducing the expected value of the award to those using private finance exclusively[141]. In the expected sense, they simply cannot generate enough return for private investors. Allowing publicly-funded developers equal privileges on the APC will crowd out privately-financed activity, severely weakening the power of the commitment, and sending the cost to the public sector of eventual vaccine development much higher than originally claimed.

2.4.2. How is the 'currently existing' market dealt with?

How is the currently existing market for products factored out so that the market created is genuinely 'additional'? This difficulty is also recognized in 'Strong Medicine'[142] but, it too, is skated over. 'Making Markets' simply states that "The commitment *would extend* the overall size of the market in which firms operate" [143] (italics added) on the basic presumption that *existing* markets can be somehow fully excluded. This is a statement of pure hope; there is no mechanism proposed for how this might be made so in the case of HIV vaccines, for which the 'initial' existing market might be large, and also highly epidemiologically non-stationary. This is further complicated by the way the HIV virus is increasingly affecting countries with widely varying levels of income, and by the difficulty of excluding wealthier users within countries covered by the mechanism from accessing vaccines produced under the mechanism, but without payment.

On the other hand, it is fair to say that the more exclusive to the poor a product is, the more likely it will be possible to achieve this condition. We find yet again that APCs are highly variable instruments that belie the simplistic notion that all vaccine problems are the same.

In the case of HIV, developing countries would have to sign up at the start, as would even countries *not* covered by the mechanism such as, maybe, Russia, China, India, and Brazil. These non-eligible markets must *still* be protected for private sales of any vaccines generated by the mechanism. There would have to be the *credible expectation* that vaccine developers that did not make the standard required of the APC – even if they were motivated in their research by it – would be barred from selling to Russia, India, China, and Brazil, etc., even if there was still no alternative vaccine for anyone including these countries. Otherwise sales to *these* countries would crowd out the *initial* market for vaccines being paid for under the APC (with this being especially bad news for those trying to develop 'higher quality' vaccines).

---

[140] Payment "rewards scientific advances *however they are achieved*," (italics added) Berndt, E.R. ibid.
[141] Indeed, given their higher capital costs they should expect to be disadvantaged unless somehow they can be protected from this.
[142] 'Strong Medicine' p98.
[143] 'Making Markets' April 2005, p37.

2.4.3. How are incentives to improve technology not harmed?

How is the incentive to improve technology (in particular production technology) not harmed when the fixed technology assumption is dropped[144]? This is a form of crowding out, but probably very hard to quantify.

2.4.4. How are priorities not distorted?

How would governments, firms, foundations and others be policed so as not to distort activity away from drugs and vaccines not covered by APCs towards those that *are?*[145] This crowding out shows up in research incentives of those *other* drugs, vaccines, and health products. For example, to the extent it has an impact, part of the rise in finance for HIV vaccines may be at the expense of finance flows into microbicides research[146]. The exact size of these effects we do not yet know. Indeed, one justification given for advance purchase commitment-type arrangements is to encourage the public and foundation sector to put more emphasis on research into neglected diseases. However, as a way of encouraging such involvement it is not the most efficient direct way of doing so. It sits uncomfortably with the notion that fresh private-sector finance into neglected diseases should be protected from public-sector and foundation encroachment on the APC. And, to the extent public activity does shift across, one of the added costs is the loss of activity in neglected diseases (and other areas) not covered by APCs.

2.4.5. How do the necessary tight patents not cause harm elsewhere?

Will the strong patents, secrecy, and increasing pressure to clamp down on compulsory licensing elsewhere in order to help an APC to function, help or harm research costs and access to drugs and vaccines *not* covered by such mechanisms?

2.4.6. How do Intellectual Property (IP) claims not eat up payment?

The development of vaccines involves a continual process of IP accumulation and assembly. Developers have to identify the need for patented purification techniques or for patented adjuvants or for patented antigen synthesis methods. Any developers that have signed an AMC contract would be forced to 'share' the expected value of the $3 billion payoff and thus would be constantly remortgaging a future income, thereby reducing the value of the payoff. There is no clear methodology in the CGD report for preventing this from reducing the 'additionality' of the AMC, diminishing its power.

---

[144] This links also to the problem of credibility. If, for example, technology is greatly improved via push parts of the process, the value of the pull part should be reduced, but if it is those who are working on pull-based approaches who improve technology, they should be rewarded and not be exploited in later parts of the price setting process. The Appendix 3 technology has ignored this, but it is a standard example of the trade-off between the need to insure and the need also to create incentives.

[145] If large pharmaceutical firms do this sort of research partly for PR and 'responsible investment' reasons or as part of PPPs, the fungibility of their investments across projects might generate a larger distortion than might at first be expected. And public funders too might be tempted away from activities with no 'payoff' towards those that do now have a 'payoff'. It would be hard to control for this behaviour.

[146] The problem is compounded by the fact that the products compete somewhat.

2.4.7. How is overlap and waste not encouraged?

How does the overlap of research and waste under this mechanism compare with that under other mechanisms? Below (in section 2.13. and section 4) we show that overlap and waste persists under early-stage APCs and investigate whether some of this could be avoided under more collaborative approaches.

More dangerous forms of crowding out exist, but are ignored. The exact details of these are in Farlow 2004 Chapter 7, but especially sections 7.11 and 7.16. The following two subsections provide a cryptic overview:

2.4.8. How is market segmentation, lower quality and more extraction of consumer surplus avoided?

Because: i) There is loss of control over the ultimate intellectual property rights; ii) countries and firms are segmented into those covered and those not covered by APCs; iii) and co-payments are committed, a new incentive is created to segment the market, raise prices and extract more, deter others from research, and reduce the quality of vaccines. Again, just this possibility will raise the risks and hence the capital costs of 'higher-quality' developers. It is not so much that firms choose to behave these ways; most developers may be dissuaded from investing to try to avoid opening themselves to being in such situations.

This is aggravated somewhat by capacity issues. Initially, supposedly, manufacturers will have to provide much higher volumes – to supply a large initial push of vaccinations – than the eventual annual production size. Given the 5-7 year lead times needed to put capacity in place, and the real possibility that only a low or medium level of capacity will be in place, who will get vaccines first? The poor or the rich? Those paying $15 a course via the program or those prepared to pay, say, $50 outside the program? There is likely no credible threat to make manufacturers serve the $15 segment first. The program organizers can build in a threat to override IP, but this is of little use if alternative idle capacity is not somehow available to make good on the threat, or if the vaccine just falls short of the initial terms.

A similar issue arises once the first 200 million or so high-value sales are gone, and the original IP owner chooses to devote their capacity to the higher value sections of the market. Why should they install more capacity to supply the low value sections? If they relinquish the IP rights for the poor section to the mechanism creator, what capacity does the mechanism creator have? What know-how?

2.4.9. How does it not become a financial option?

Early-stage APCs also create a financial 'option value' based on the fact that firms – since they own all the IP to the vaccine – can supply the end product if it is more profitable for them to do so, but that they are not *obliged* to do so. This option value may boost research even as it runs the risk that the results are not given to the 'eligible' countries covered by the program, or are given to them but with delay (maybe by allowing the manufacturing price to remain high for a while

to get around having to supply the 'eligible' countries[147]). This is an especially knotty problem for HIV vaccine research because HIV cuts across a range of countries with widely varying income levels, it has different clades, and the existing non-stationary market size is growing and hard to control for in the terms of the commitment.

The details of all this are contained in Farlow 2004 Section 7.14. Key advocates of APCs were once in complete agreement with this problem, but it has now been politely dropped form discussion.

2.4.10. A summary on 'crowding out'

All of these problems have been ruled out in the Kremer Appendix 3 model underlying all of the APC literature. Payments only ever go to those who were incentivized by them, mainly because there is no other mechanism present in any of the modeling anyway. Failure on any of these fronts will weaken, by 'crowding out', the power of an early-stage APC for, say, HIV, and raise its global costs as an instrument for stimulating vaccine research. At a minimum, various treaties would be needed to ensure that all countries (both eligible and non-eligible) only purchased vaccines that satisfy the conditions of the contracts and the decisions made by the IAC (even if they disagree with those decisions), adopt the same post-development rules on purchases, police each others' research behavior, and rule out parallel trade for all times both between countries and within countries (both the eligible and the non-eligible).

Before giving the go ahead for a multi-billion dollar APC, policymakers should be given some evaluation of the size of these potential crowding-out effects. We also have to remember that it is the *risk* of these outcomes that matters for private investors, not just whether these outcomes actually materialize, since this risk has to feed into capital costs. The effects will also vary depending on the vaccine being covered. There would be very much higher levels of crowding out for HIV than for, say, pneumococcus or the African trivalent meningitis vaccine discussed below, and for those parts of the vaccine development chain that are based on more standard forms of competitive tendering. Again, the key protagonists show hardly a hint of concern for these issues. Private financers would.

2.5. Capital Costs

There is both risk reduction and risk creation under APCs, and all risk has to be priced into the private capital costs of pharmaceutical firms and venture capital firms when investing their own resources. For currently extant vaccines or vaccines very close to development, an APC achieves practically *all* risk reduction, given that most of the risk is market risk, many other risk factors have fallen to zero, and the compounding of capital costs is relatively light. For current early-stage HIV vaccine research, there is next to no current value in market risk reduction (this is way too far off to have much of an impact now) and, indeed,

[147] For example, if the mechanism has specified a price of $15 for the first 200 million HIV treatments, if the treatment costs come it at $20, and there is a rich market prepared to pay $30 a treatment, the developer has a perfect right to sell to the richer market first, and an incentive to allow costs to drift above $15 per treatment to give them the right to do so.

market risk remains very high given the many forms of market-based crowding out and faults still in the mechanism described above. Meanwhile, all other risks (including that of the operation of the APC itself) are high. We therefore know that, to the extent it actually motivates *any* research, a sizeable chunk of an APC for an early-stage vaccine such as HIV will be taken up in the cost of finance. But exactly how much?

2.5.1. Emphasizing risk reduction: Downplaying risk creation

When it is stated that "by putting in place an advance purchase commitment, the overall risk, and hence the cost of capital that will need to be repaid, is lower"[148] or that a contract "does not call upon donors to spend more than they otherwise would; but it would increase the value of that spending"[149] the writers are emphasizing those parts of the R&D process where risk is reduced by purchase commitments, but they are completely ignoring those parts where risk is created. Indeed, they are essentially describing late-stage vaccines, even when applying the logic to early-stage vaccines. This is careless given that the capital cost component is likely to vary significantly across vaccines and according to the relative position of a purchase commitment in a chain of incentives, and given that it this a key piece of empirical evidence for working out how to use other instruments alongside purchase commitments, for optimally placing (and sizing) purchase commitments in the chain, and for evaluating their cost-effectiveness compared to the alternatives. Thought of another way, the overall aim of using a combination of instruments is to minimize risk and maximize impact, and this *cannot* be worked out without first knowing how each instrument either creates or removes risk. It is difficult to comprehend the argument that this approach is part of a package of measures[150], to create a chain that is strong, when, in this crucial respect, it is not modeled as such.

As the mechanism deals with longer and more cumulative processes, and potentially more complicated vaccines such as HIV, the cost of capital locked up in research rises *exponentially* because:

a) The lengths of time involved lead to very heavy compounding. For early-stage vaccines "*industry may still deem the commercial return to be too distant and uncertain to be worthwhile given the immediate, high-risk investments under consideration*"[151];
b) The private sources of capital are expensive[152];
c) The scientific risks are very high, including (amongst many other things) the risks of ever getting a vaccine, and the risks of not internalizing the results of privately-funded research for oneself (especially if data has to be

[148] Berndt, E.R. ibid.
[149] 'Making Markets' March 2005 p38.
[150] Berndt, E.R. ibid. made this claim although neither he nor the recent proposals made any concession to the position of other mechanisms, nor indeed to even their existence.
[151] Batson, A. 'The Vaccine Book', ibid. p 366.
[152] For some reason this has been interpreted as a 'criticism', when it merely refers to an empirical fact widely accepted within the industry. It is only reasonably to be expected that any APC would have to reflect this fact.

shared and the vaccine turns out not to be a pure preventative vaccine but instead a composite and therapeutic vaccine);

d) There is high perceived risks of the APC *itself* (that is of 'mechanism risk') especially relating to the many institutional layers, the tradeoff between credibility and discretion (described in the next section), and the very real possibility that the mechanism will not work remotely as initially proposed (the latter seems to generate no concern from leading advocates, though it is a serious risk when rushing to use a completely untried mechanism).
e) The 'Making Markets' report repeatedly asserts the centrality of long-term political commitment to make the program work, yet it is hard to imagine investors and senior executives in pharmaceutical firms making such political predictions and trusting multiple overlapping political administrations as far as the mid 2020's when launching major, very long-term, and expensive privately-funded R&D programs. This would add to the required risk premium, probably significantly.

Given this exponentiality, an instrument can be very powerful under a set of conditions only to find that power drop rapidly as those conditions are not met.

For an HIV APC to actually work – *all* of this capital cost needs to be *fully* repaid by taxpayers and philanthropic foundations through the APC, and this also has to be worked out in advance if the overall payment is not to be set too low.

Incidentally, when the NIH does highly 'risky' research, the main 'hidden' saving to industry is all the capital cost it saves by not feeding such research through firms, but by passing it on to the public sector. This cost saving is never measured though it really *ought* to be, to help in comparisons of mechanisms. Indeed, when one sees tables of spending on pharmaceutical research, the value of the contribution of the NIH and of others is always massively under-reported compared to the contributions of private industry on account of this data limitation. That these capital costs get passed away from firms and on to the public sector is recognized[153] but the leap is not made of arguing that this risk should be properly valued and that its correct evaluation would upset the relative evaluation of APCs against 'push' approaches (including, for example, the push parts of the 'Global HIV Vaccine Enterprise') and, indeed, that the appropriate distribution of the IP reward at the end of the whole process should be adjusted in the light of it.

The *core* justification for facing private investors and pharmaceutical firms with this risk is that APCs would so massively improve the choice of vaccine research leads and trial attrition rates for HIV, tuberculosis, and malaria over anything that the Global HIV Vaccine Enterprise or any other vaccine initiative, such as current PPPs, could possibly achieve, that this more than outweighs all of these extra capital costs. We would therefore like to know how much of an APC gets eaten up in these finance costs, rather than in real out-of-pocket research, thus reducing its 'pull' power, and exactly how this might offset any improvement in choice of

[153] See Kremer, M., Towse, A., and Williams, H. "Briefing Note on Advance Purchase Commitments," DFID Health Systems Resource Centre, May 2005.

research leads and trial attrition rates. Given the more recent acceptance that PPPs and sponsors would almost certainly do most of the choice over research leads and that PPPs could (and should) be greatly improved as selection mechanisms, it is even less clear that these extra capital costs would have much of a corresponding payoff.

One presumes these figures must be being calculated and fed into the current calculations of HIV and malaria APCs, but these figures are not to be found *anywhere* in recent pronouncements. Without them, one can only guess, something that will now be done for HIV. All figures below are nominal, i.e. not adjusted for inflation, and the author would welcome the figures being challenged and recalculated in light of the actual evidence[154].

2.4.2. Some vague figures

One would imagine that the stock market and venture capitalists would take the view that current HIV vaccine research is a particularly speculative investment – especially in the first five to ten years or so (and maybe even much longer) after an HIV APC might be fixed. It seems reasonable therefore to presume that the required rate of return on financial capital would be higher than, say, the required rate of return calculated by TUFTS for drug development – a nominal rate of 14%-16%, with a mean of about 15% – by the very same large pharmaceutical firms now being targeted with HIV vaccine APCs.

Let us presume for the moment that there is no crowding out in the workings of an HIV APC (though this is highly unlikely to be the case). If the required nominal rate of return to financial capital invested in current HIV vaccine R&D was 25-25% (not outrageously high compared to speculative investments that venture capital firms normally make, but is it too high for this case? Or, indeed, too low?) and the average expected horizon until repayment was 10-15 years[155], it follows that each dollar of early pull-induced private R&D would require approximately $4-$9 of eventual payment at a ten year horizon, and $8-$28 at a 15 year horizon, with the bias almost certainly in the direction of the higher figures. That is, if the expected horizon was ten years, each $1billion of promised nominal APC would pay for, say, about £100m-$200m of early out-of-pocket HIV research costs, and if the expected horizon grew to 15 years, each $1billion of promised nominal payment would pay for, say, about $35-$100m of early out-of-pocket research costs[156]. One can see that getting a hold on the figure for capital costs is quite important. It is all the more shocking not to find any of the likely private capital costs discussed in the APC literature.

---

[154] Though a previous request for this posted to the Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, received no reaction, except a repeat of the mantra that product market risk is lower with an APC (Berndt, E.R. ibid.), which we all know to be the case for a host of late-stage vaccines.

[155] Kremer talks of most of the repayment for a malaria vaccine being 15 years and more away 'Strong Medicine' p74. Given the state of HIV vaccine science, this may even be overly-generous for HIV (cf. Bill Gates's "eat my hat" quote) though it also depends on what is being done on the 'push' front and how much risk is being passed on to push funders.

[156] All these figures presume immediate payment at the end of ten or fifteen year, when in point of fact the mechanism is supposed to spread payment over several (if not many) years, even as capital costs are rocketing.

Adding in some 'crowding out'

If there was 'crowding out' too of, say, half (maybe push payments prove hard to remove from 'winners', and Russia, India and China cannot be barred from 'spoiling' markets for products later) then this would lead to $1billion of promised HIV payment paying for about $50-$100m of genuinely *additional* early out-of-pocket private R&D in the first case and about $15m-£50m in the second case. In this instance, given that something as small as perhaps $15-$50m of crowding out is capable of seriously harming – by halving – the effectiveness of a $1billion payment, there are, clearly, easily imaginable scenarios where *most* of the effectiveness is 'crowded out'. So, a notion of likely levels of crowding out would be very useful too. Again, one presumes the figure must be out there entering into current calculations[157]. But none of the literature even discusses the evidence, and it is hard to believe that it is therefore forming part of the decision-making process.

As one can imagine, increasing the likely horizon to discovery or increasing the required rates of return to private financial capital or increasing the levels of possible 'crowding out' creates increasingly dire-looking figures. Maybe this is why current levels of private funding are so low? Kremer claims it is 'no market'. Maybe, more likely, it is the very high risk and the high capital costs and crowding out?

In truth, capital costs would make up by far the largest portion of an early stage APC for a vaccine such as HIV. It is likely that the capital cost component would remain huge for a very long stretch of the process of development, starting off at close to 100% today declining to maybe still in the region of 50% at the late manufacturing stages within sight of vaccine development.

Would sponsors be happy with a mechanism that absorbed 80% or even more of the resources devoted to it just to make good on capital costs, thus reducing its pull power? Are the PPP alternatives so bad? Again, no evidence is provided in this literature to evaluate this.

It is important to get a handle on these figures, since if the ones above are even remotely correct, some of the current PPP-financed activity starts to look a much more cost-effective way to direct fresh government, G8, and foundation funding. Indeed, it is not clear why large pharmaceutical firms themselves would prefer to be stimulated in their HIV vaccine research in the current environment by an APC. They would be foolish to respond to the figures just described. Why would even a large pharmaceutical firm respond to a $6bn HIV APC that creates no more than a few months' worth of what those working on the Global HIV vaccine enterprise says is needed?[158] Surely they would have to be crazy to believe that a vaccine would be achieved?

---

[157] This is a rhetorical statement. There seems to be no interest taken whatsoever in these matters by those advocating the APC approach.

[158] As I finalise this, I discover that this has become obsolete yet again. Those controlling this particular research project at the Centre for Global Development say the cost has suddenly halved to $3bn. It is getting rather tiresome watching supposedly important policy initiatives constantly being manipulated for the interests of politicians rather than for the interests of getting a vaccine. The drop by half says everything about the ultimate vacuity of the proposal and the opportunism

So, why the rush?
If this is the view taken, then it becomes even less pressing to set the terms of an HIV APC any time in the near future before good information is available on how to fix terms – perhaps revealed by experience on earlier purchase commitments. It would be doing hardly any cost-effective pulling in the near-term yet it would impose higher costs by being prematurely and inefficiently set (there is an expensive option-price component to fixing the terms of an APC *now* before much of the information is available on how to efficiently and correctly set it[159]), and be open to later adjustment that itself would be very damaging to its credibility and hence later effectiveness.

All of this may be slightly 'academic'. If, for example, a $10billion[160] HIV APC were permanently fixed yet could currently only generate at the very most a year or so of genuinely additional privately-funded out-of-pocket R&D, then the most likely reaction of private firms and venture capitalists would be to hold off on their R&D anyway, and, indeed, to simply not trust that the mechanism would ever work to repay them anything they spent now. Throw in the fact that it cannot be guaranteed that the vaccine will not cost $5-$10 or more to manufacture ($2.5bn for 250m courses of treatment), and it is very easy to generate scenarios where it simply is not worth investors bothering. The notion that if the APC were made even bigger, enough firms would react by investing, does not obviously follow. All this simply indicates how wasteful such instruments are for paying for HIV vaccine development.

Of course, funders, via the IFF perhaps, would still be stuck with the $10bn commitment, unless they can find some way to wriggle out of it that does not generate too much litigation. And alternative approaches would have to work out how to get around it.

2.6. A Trade-Off: Rules Versus Discretion

Even if we presume that any practical application of APCs to early-stage vaccines will follow the tenets of the idealized benchmark case described above, with also the 'quality' issues and crowding-out issues dealt with (though from recent policy announcements, this looks highly unlikely), there is no guarantee of the quantity of vaccine sold by any developer nor any guarantee that they will get all of their expected risk-adjusted development costs back even if their vaccine is developed and used. This is all from the perspective of the firm's decision problem *before* they invest anything. At *that* point the required return is calculated on the basis of expected trial attrition rates, all capital costs, and the expected portion of the market and pricing structure allowed by the IAC to the firm, so that even if a firm gets its development costs back in the ex post sense, this may be totally insufficient in the ex ante sense to justify the initial investment. When 'Making Markets' discusses two-stage pricing to ensure that the "producer received a fair

---

of those pitching it. I've lost interest in trimming my figures yet again to a new lower pitch. The $6bn and $6.25bn figures stay; the 'new' $3bn pitch I leave to those making it.

[159] See Farlow, 2004, ibid. Chapter 6.

[160] Cut this figure by 70% to fit in with the current latest Centre for Global Development sales-pitch.

return on their investment" but that "once this return had been achieved" prices could fall, it must be fully understood by all firms, buyers, political commentators, and the general public that 'fair return' is being thought of from an ex ante perspective. It will *never look 'fair' ex post*, and it must be credibly fixed in advance that it will *always* be calculated ex post from an ex ante perspective.

Dynamic inconsistency persists

The big worry for firms is that there will be ex post bidding down of returns to make return *look* more 'fair' ex post. Instead of getting the full $6.25billion reward for a couple of hundred million dollars' worth of out-of-pocket research costs (and the general public will know all about these costs given the information revelation described above), the firm will instead get, say, only $3billion, and will still 'look' greedy, even though this is actually not a 'fair' return for the efforts and risks borne by the firm. This is a worry under a procurement system, but applies equally under an APC if there is any ex post discretion. Having a model that generates a fixed single value APC avoids such decision problems arising. Early proposals tended to concentrate on such outcomes (especially the No 10 policy unit material). However, this is a far cry from what would be needed in reality for vaccines for HIV, malaria, and tuberculosis.

Once the drastic simplifications described above are removed, and we get much nearer to a likely real world application, we face an elaborate trade-off between inflexible rules and discretion. The rules are based on expectations at the time the APC is set of the complexity of the science, expected publicly-funded research, expected technological improvement, expected 'qualities' of vaccines achievable, etc. Discretion would impinge on all of these features.

Fixed terms too difficult to know

'Making Markets' concedes that "it would be possible – though complicated – to agree to product requirements in advance," and that "a small number of public health experts were concerned that it would be difficult to establish in advance technical requirements that a vaccine would need to meet."[161] It is not clear whether this was a small *proportion* of public health experts, with a much larger proportion feeling otherwise, or whether it was most of the few public health experts who were asked[162]. In this author's sample of a 'small number of public health experts', *all* expressed extreme doubts about the ability to efficiently set technical requirements in advance for HIV, malaria, and TB. *Some* set of technical requirements can always be set for any mechanism, but 'efficiency' of those technical requirements (and the need not to intervene to change them later) requires some notion of the underlying feasibility of HIV and malaria science, the potential costs of manufacture and distribution, and a range of many other factors. And none of *these* public health experts felt *any* degree of confidence in knowing this.

The only way out, as 'Making Markets' concedes, is to have contracts "sufficiently fixed to ensure that the donors cannot renege on their commitment

[161] 'Making Markets' April 2005 p44. Incidentally, setting product requirements based on epidemiological factors is only part of the required solution.

[162] One suspects the latter. The philology of the APC literature would make an interesting study in its own right.

when a vaccine is developed, but still flexible enough to accommodate contingencies not foreseen when the rules were established"[163] But this simply shifts the problem to a different level – that of having a good notion of unforeseen *potential contingences* in order to set the flexible terms efficiently. On the one hand Barder says that "It would be important that the experts from industry, the public private partnerships, the sponsors, and the public health industry, work together to finalize the technical specification…the technical specification would be set in advance and included in the contract." But then he claims that "the difficulty of setting a rigid technical specification in advance is met, at least in part, by the flexibility built into the AdvancedMarkets proposal."[164] But this is, as it were, wanting to have one's cake and eat it.

A costly trade-off that cannot be avoided, and plenty of 'mechanism risk'

There is a trade-off. Non-flexible rules are needed for credibility but are inefficient and raise costs. But, discretion, and the other remedial features, generate risks for developers and a higher capital cost component of a given APC, more complicated contract terms, much stronger informational demands, and the dangers of institutional failure or capture (or costly mechanisms to prevent it).

For example, if a piece of contractual language is missing such that there is a 75% chance of purchasing at the agreed $6.25bn and a 25% chance of reneging and paying only half (which may still 'look' a very good deal from the public's perspective ex post), this yields an expected payment of $5.47billion[165]. If $6.25bn *was* the risk-adjusted figure required to generate optimal research intensity via this mechanism, and *if* we wish not for vaccine development to be slowed by this risk of underpayment, and *if* vaccine developers are risk-neutral, then the promised payment by the sponsor has to rise to $7.14bn[166] – that is a premium of $890m has to be added – to ensure the same intensity of research effort. If vaccine developers are risk-averse, the premium must be even higher[167].

The cost of this trade-off rises sharply, the more complicated and risky is the technology, and the longer the process being held together. In addition, small acts of reneging on one advance purchase contract have major damaging effects on other advance purchase contracts via the way the latter's probability structure over reneging will shift. By ignoring these issues, the terms of idealized early-stage APCs would always be set correctly, and would never be anything less than 100% efficient. This naturally maximizes their claimed 'strength' compared to alternative approaches.

---

[163] 'Making Markets' April 2005 p42.

[164] Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 19 November 2004. Why are such statements tolerated without a single financial economist brought in to evaluate the actual risks and capital costs being described?

[165] Farlow, 2004, ibid. Section 7 explains why situations like this are a very real possibility.

[166] x such that 0.75*x + .0.25*0.5x = $6.25bn.

[167] This calculation also presumes that the probabilities are not altered in the process of adjusting up to $7.14bn. This is unlikely to hold. The probability of reneging is likely to rise with the APC price, necessitating adjustment of the APC price *even further upwards* to compensate. Price would settle at the stationary point in this reasoning process. All of this would also have to be adjusted upwards in proportion to the degree of risk aversion, with some players much more disadvantaged than others.

Clearly this 'rules-versus-discretion' dilemma creates an awful lot of 'mechanism risk' for those relying on early-stage APCs. This is totally unmodeled in the literature promoting such contracts. Once we move away from the idealized setting, a picture develops of potentially huge levels of already (and sometimes long ago) sunk investment resting on the discretionary ex post decisions of a committee or committees[168]. The point of the original exercise was to get away from decision-makers having any power of discretion. At the same time, given the sunk costs build up under APCs, policymakers lose their ability to change the overall approach as they go along, since all ex post changes (after the costs are sunk) have to be somehow ruled out. A tension builds up between the need to modify the overall approach, but the inability to do so for reputation and credibility reasons.

Since we have no experience of operating such APCs, we have no evidence of how severe these problems with 'mechanism risk' might be, of how to cope with them, and whether the mechanism may even have to be radically overhauled (an act that in itself may generate litigation by any firm that operated, or claimed to have operated, under the original mechanism).

In summary, we find that we cannot set up product requirements. Yet, discretion is very, very bad. Why do those advocating early-stage APCs for complicated vaccines not talk about this much more openly? Probably because, yet again, the objective is the 'policy success' and not the policy. And besides, these issues are really not such an issue when the idea is to target, with all of the funds anyway, the one large firm that first appears with anything meeting the most minimal of conditions.

Ratchet effect: Costs can rise but they can't fall. Quality can fall but it can't rise.

There is also a natural tendency to one-sidedness in this flexibility too, putting excessive risk on any firm believing that the criteria would not be lowered. We are told that there should be "waivers from the stated eligibility guidelines"[169] and that there was "consensus that there should be a procedure to make the specifications *less onerous* in case a useful product were developed that did not completely meet specifications" (italics added)[170] If this was not clear enough already, Barder explains:

> "*The AdvancedMarkets proposal that the Working Group has put forward does allow the independent arbitration committee to lower the bar. This would enable a vaccine which substantively meets the desired criteria, but fails on a technicality, to be rewarded. (By contrast, the arbitration committee would NOT be allowed to raise the standard after it had been set, to reduce the risk that sponsors seek to renege on their commitment.)*"[171]

---

[168] Incidentally, in PPP models, at least more of the 'intervention' can take place before sunk costs are invested. This has a high risk-saving for firms. Again, why has the model not been run past some financially-trained economists able to get *some* sort of handle on the risk costs and savings?

[169] 'Making Markets' April 2005 p44.

[170] 'Making Markets' April 2005 p44. What exactly does "not completely meet" mean anyway?

[171] CIPIH Forum, 19 November 2004.

What does "fail on a technicality" mean? That the specifications were perfect to start with, and some minor detail was carelessly mis-specified? We see below, in the malaria vaccine case, the way the temptation to lower the bar easily creeps in once this reasoning process is tolerated. Lowering the bar – and risks about the ex post discretionary power to lower the bar – are a risk for those who might invest in vaccines that are likely to follow the first vaccines. A lower bar on the first vaccines will lead to much, if not all, of the available fund going on the early vaccines leaving none or little for these later vaccines, and it also gives those working on early, less efficacious, vaccines less incentive to share knowledge with later developers. Or do later vaccine developers lobby for the bar not to be lowered? If so, how does the committee adjudicate the likely success of the later vaccine(s)? Does the committee not simply end up having to judge the quality of research leads, something we were explicitly reassured the committee could not and should not be doing?

Incidentally, if the interaction between technology and quality changed such that much greater quality could be expected for small changes in costs, why could '*more onerous*' specifications not be instigated? What if everyone can see that the 'more onerous' specifications are justified? What if forthcoming results from the malaria genome project indicate that low specifications set for the GSK Biologicals malaria vaccine turn out to be too low? Would that classify as "failure on a technicality"?

2.7. Lessons from Bond Markets

APCs have been likened several times recently to Government bonds:

> "*It is not unusual for Governments to enter into legally binding contracts: think, for example, of issuing Government bonds (which are contracts to repay money at a future date): these are legally binding, and credible with the private sector.*"[172]

> "*One good example [of a long-term commitment] is the issues of Government bonds, which legally bind them (and their successors) to make payments in the future. Markets have no difficulty accepting these as binding contracts, even though future Governments could, in principle, renege on them.*"[173]

This is a highly misleading analogy, though the differences and similarities with bond markets also help us to understand just why APCs for HIV, malaria, and TB may face difficulties:

1) The value of bonds is fixed openly by millions of individuals on a *free market*. There are none of the central monitoring isssues (supposedly) found in the case of APCs in trying to work out what the true value of the commitment is. Price bubbles aside, the price is an accurate reflection of

[172] Barder, O., CIPIH Forum, 27 Nov 2004.
[173] Barder, O., CIPIH Forum, 19 November 2004.

the market value of the underlying payment stream. Bonds are hugely more easy to price in the first place;

2) Bonds are relatively simple contracts, dealing in a very simple underlying payment stream. The underlying payment in an APC (the value of, for example, HIV vaccine R&D to be repaid) is hugely more complicated to price;
3) It is quite useful to think of an APC as a bit like a bond, that is it has a face value of, say, $6.25b (or is it $3bn these days?) as set by the sponsor at the start, and a present discounted value now to the markets trading in such instruments (here, large pharmaceutical firms). One would imagine that the present discounted value of an APC for HIV would not be high. It might have a current face value of, say, $6.25billion, but (if there were a free market for such instruments to price it) would only trade for, say $200-$500 million[174]. Actually, it might be quite interesting to explore how such a market might work!
4) No one individual (or committee) has the power to manipulate the value of bonds in favour of or against the holders. Firms working under the incentive of an APC face a one-sided deal in favour of the issuer, unless somehow they can capture the issuer;
5) The government is able, on the open market, to issue fresh bonds to pay off old bonds, because the government has the power and sovereignty to tax. Indeed it is the only legal entitity with such powers. So long as the economy is sustainable there is never any problem getting buyers for fresh bonds, though it comes at a price that varies according to the state of the economy. It is the ability to tax future generations (heavily if needs be, even if such taxation is 'damaging') that reinforces the credibility of bonds. Who do the IAC go to raise more revenue from to defend a collapsing APC (i.e. to make it bigger to compensate investors for rising risks)?
6) The reason the US does not default on its previously issued bonds (with the US deficit so high at the moment, cancelling the previously issued bonds would remove the defecit at a stroke) is because the future costs of issuing bonds – that is future borrowing costs – would spiral massively; current interest rates would shoot up and there would be apalling consequences for the economy. This huge adverse consequence disciplines the government to repay, and this reassures bond holders;
7) Bond holders are still harmed by government acts. If governments behave in ways that send interest rates higher, the capital value of previously sold bonds falls. Similarly, the value of an APC depends on a whole range of government and funders' acts, including the push initiatives of government and expectations of expenditure on competing approaches, and expectations of how the faults discussed above will be dealt with;
8) Issuing fresh bonds does not affect, except trivially marginally, old bonds. If an individual non-coordinated APCs is in place with one company, issuing a new one with anther company will weaken the value of the first one;
9) Bond markets are one of the most highly developed financial markets in the world with over two hundred years' of history and many professional

[174] We don't know this. This is a purely speculative guess on a 10-15 year highly risky instrument.

players knowledgeable in the workings of the market. APCs have never been tried before for anything. They have no history and no lessons have been learned.

10) Once bonds are issued, the government is tied into issuing fresh bonds regularly (IOUs to make up for the fact that previous IOUs have come up for repayment). Similarly, once APCs are in place, they increase the incentive to issue fresh ones.
11) Countries *do* regulary default on bonds, leaving huge losses to those who had originally believed in, and held, the bonds. Think: Russia, Latin America, Asia, etc. And that is just in recent years. Indeed, even as this paper was being written Argentina was in the throes of finalizing 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[175]. Perhaps the views expressed above about the wonders of bonds say more about the US-centric view of the world of some of those working on the APC proposals than it does about their understanding of bond markets? Perhaps the experiences of Argentina, other countries, and a range of practical experiences should make them more soberly reflect on the allegorical claim that large APCs are akin to large bond issues[176]?
12) The chances of default lead to a higher required return on bonds. Russian bonds in the mid 1990s were returning 60% per year because of the default risk. In the case of an APC, the risk that the APC would be allowed to collapse would translate into very high required capital costs, and very low R&D power. If, once in existence, there are any worries about the APC, capital costs would start to go up, and the APC would become inceasingly less powerful. In such cases the incentive power of such an instrument would quickly grind to a halt. Developers would simply come not to believe in repayment of their R&D costs via the APC. Collapse becomes self-fulfilling;
13) Default is so damaging, that, short of default, one is essentially stuck with having to repay the bonds even if the resources they generated when they were originally issued have been completely wasted. Similarly, the cost of default on APCs, including litigation costs (even if they were set up so badly that they were bound to fail from the start), means being stuck with them, short of default, even if they stop working.
14) At some point, markets realise that the only rational thing is to default, and then default becomes self-fulfilling. At least in bond markets, the government can keep trying to issue fresh bonds to put off the moment of default. This would bite sooner for APCs. However, there would probably be a terrible delay before recognising it and 'bailing out'. Indeed, to avoid the embarrassment of having to 'bail out', the most likely trajectory is a period of non-reaction to the contract followed by the contract being left in place and all of the other incentive devices having to be ramped up. This is explained in detail in Farlow Section 8.7,

[175] And as it was being re-edited in the UK a few weeks later, before "going to press", one of the UK's largest car manufacturers was defaulting leaving at most one penny for every pound of debt owed to creditors.

[176] Hint: What is it that the US has that Argentina, Russia, a host of other Asian and Latin American countries (and car manufacturers) and APCs may not have?

Chapter 9, and 11.10. Viewing APCs as a financial contract clearly reveals their ability to suffer crises and collapse just like any other such financial contract.

15) Unlike bonds, the government or sponsor has no obligation to make good on investments sunk towards APCs at the 'Framework Stage'. Firms are stuck with any losses if the APC is abandoned. Or rather, if the APC is terminated early, to the extent firms could prove that they were operating under an implicit contract, they could (and should for the sake of their shareholders) sue, if they could prove that the Framework setters were at fault for the mechanism collapsing. It is, however, not clear to what extent worries about the very public PR consequences of suing would undermine the incentive to engage in the investment in the first place.
16) With defaulting bonds, the sellers (the government) gain something out of it in the shape of initial loans. With defaulting APCs, the sponsors gain the private expenditure on R&D up to the point they default, but they seem to have no obligation to make good on it. In both cases there are private sector losses.
17) You can engage in economic policy that risks bonds failing. But you can't set up bonds *to fail*. You *can* set up early-stage APCs to fail (incorporated in frameworks such as the IFF that also take some of the brunt of failure).
18) Repeatedly the APC literature alludes to cases where contracts are not honored: "The fact that these mechanisms have not been tested increases the risk, for example, that they will be subject to political 'changes of heart'. For manufacturers who must invest early and heavily, 'changes of heart' have serious financial implications."[177] Observe how, at very long horizons, small doubts are compounded very heavily into the value of the purchase commitment. Imagine what this would do to the value of a bond with an expected repayment in 15 years but with the niggling doubt that in any year between now and then there might be a decision to scrap the promise to repay the bond given the failure for it to work sufficiently well up to that point.
19) One would imagine that the fewer the existing bonds the less the penalty from reneging on those that exist, especially if it is clear that they are not working. Experimenting with HIV or malaria 'bonds' early could be a very risky way to explore the whole idea.
20) It ignores the huge range of problems listed above.

There are not many positive similarities with bonds. But there are plenty of negative ones. The analogy is more worrying than reassuring. Incidentally, if the APC is set low relative to the incentive needed, it may in effect collapse, have little or no incentive effect, rely on other approaches (such as PPPs and other funding) to drive everything, and then activate itself very late on to take all of the IP – and become a general nuisance at the end of the process. This seems to be the current proposal for the HIV APC.

[177] Batson, A. 'The Vaccine Book', ibid. p363.

2.8. Lessons from Standard Procurement Contracts

The contracts underlying 'Making Markets' are *not* standard procurement contracts, even though this is also sometimes suggested: "Goverments also enter into long term private finance contracts, and procurement contracts, that the private sector is happy to accept."[178]

Features of typical procurement contracts

We observe that, ordinarily, when private firms contract – *after* a competitive tender has taken place – to supply services or goods to a government at a fixed price, the government will subsequently turn out to have paid 'too much' or 'too little' (though usually there are terms in contracts to allow for unforeseen circumstance) depending on how complicated the technology turned out to be, but that the firm would still be *contractually obliged* in both circumstances *to provide* the promised services or goods. Under the fixed price contract, the technological risks fall onto the company (and onto financial markets where the risks are, in theory, diversified away). The justification for doing this is the usual requirement to create incentives (especially if there is asymmetric information), mostly the incentive to produce the goods or services cheaply (with plenty of contract terms to make sure that the quality is not sacrificed). Even then, if the risks are great, it may turn out 'expensive' for the firms (in financial contracting costs) to operate under a fixed contract, but this will be passed on to the government in the contract price. The government operating on a fixed price contract is, in a sense 'insured', and pays an 'insurance' premium as part of the price. The setting of the price and the premium require some knowledge of the distributions of possible outcomes (in analogy here to the need of those setting up the APC to have some notion of what the technological possibilities are). If the risks are great, the premium might have to be large. However, if there is an efficient competitive tender, all of this can be left to 'the market'. The 'premium' is set by competitive forces and there are incentives towards lower cost. None of this exists for early-stage APCs. We will shortly discover that the weakened ex post incentives to drive product prices lower is a particular ex ante worry for developers.

If the government is less risk averse than the private sector or (much the same thing) has much better access to credit markets, then even under a standard competitive tender it may make *more* sense for the government to bear the risks (or some of the risks) than for the private firms to bear all of the risks (in much the same analogy to the way that, under an APC, firms might rather prefer the less risk-averse government to bear the risks), but there is a tradeoff against the value of creating incentives.

Things are very different for commitment-style 'contracts'

Under an APC, things are theoretically slightly different, but in a way that has very significant practical repercussions. The 'Framework Agreement' *is the tender*. Firms don't bid for it *before* sinking expensive investments; they sink their investments *in order* to bid for it. The two are hugely different. All these risks and 'premiums' have to be 'paid', but, since there are no 'contracts' with private firms until a vaccine is developed, firms always have the option to pull out (including if they find other markets, say HIV markets, more lucrative for the

[178] Barder, O., CIPIH Forum 27 Nov 2004. Also 'Making Markets' March 2005 p8.

results of their investments) and they also always have to worry whether those operating the other side of the 'implicit' contract will renege. The scheme has to be adapted to avoid these eventualities – at a cost. And the costs are higher the more risky the technology and the more likely the mechanism itself will fail. Those 'players' able to take part are also different under the two approaches. Those who win the standard contract can use that fact to attract finance. Those seeking the APC must already have good access to finance and ability to sink possibly mostly irretrievable costs.

2.9. The Adjudicating Committee

Because of all of the issues above, the independence, credibility, financial veracity, and legal aegis of the IAC are, of paramount interest, both for policy-makers and for developers who are naturally worried about risks, and who will need to price all risks into their investments. Others express this problem better:

> "*Although the credibility of market assurances theoretically can be increased through legally binding commitments, in reality it is difficult to imagine how they would be enforced against public institutions like WHO, UNICEF, or the World Bank.*" [179]

> "*More attention needs to be paid to issues concerning the legal aegis under which this program would be conducted. Vaccine regulation and IP are sovereign nation issues. (I use the term sovereign" to include International Organizations such as WHO and the World Bank which must operate in accord with various treaties that have legal force. Foundations must operate according to the laws of the countries in which they are based.) A good beginning would be to specify the exact legal status of the IAC even though that specification may lead to complex political considerations*."[180]

> "*If the IAC is not an independent legal body, it would derive its legitimacy only through the legally established organizations that create it. Thus, one wonders how those organizations will deal with changing events, for example, without becoming directly involved in the operations of the IAC. The IAC could not, in my view, be intellectually and operationally independennt. The founding organizations could and should be involved in its operations, which means, de facto, it is not independent. They are paying for it; their reputations are at stake; and they have vital policy and financial interests that they must be able to exercise."*[181]

> *"As with all prize mechanisms, the potential for political rent-seeking is great, as the prize-awarding authority may be tempted to favour political or commercial allies. Senior individuals within the authority might even accept bribes. Furthermore, the donor's view of what constitutes a*

[179] Batson, A., 'The Vaccine Book', ibid. p 366.
[180] Malone, R. CIPIH Forum, 21 December 2004.
[181] Malone, R. CIPIH Forum 21 December 2004. It does not help to be told that contracts could only "legally be implemented by the US and members of the EU" Barder, O., CIPIH Forum 19 November 2004.

socially useful innovation will reflect their own priorities, and could result in areas being neglected or over-prioritised. Project choice, for example, might reflect the preferences of bureaucrats rather than those on the ground. Priority setting by outside agencies might result in R&D being directed only at one type of country, one region of the world, or one disease – with other equally needy causes missing out on the additional investment."[182]

The reason the legal aegis and credibility are issues is because of what the IAC is being expected to do at a very fundamental level. Essentially the committee is trying to take over the role of the IP system. Since, in the case of drugs and vaccines in poor countries, the IP system struggles to resist pressures to bid down the prices of drugs and vaccines, the IAC is being asked to do what the IP system cannot itself do. The problem is not avoided, but shifted elsewhere – on to the IAC[183]. Instead of winners and complicated patterns of IP ownership being dictated by a patent system, they are dictated by a committee. Current worries about the patent system are transferred into worries about a committee (as well as the patent system, since results are still strongly dependent on that).

Not really 'market-based' instruments in the case of complicated vaccines

It is claimed that APCs are 'market-based' instruments[184], indeed, that the mechanism is especially appropriate where there is wide "divergence of opinion on prospects for development."[185] such that policy-makers can avoid having to make difficult decisions about the underlying science. "Private firms, rather than funding agencies"[186] would make all the difficult decisions. We have just seen that this is simply not the case. APCs for early-stage vaccines like HIV turn out to be surprisingly interventionist, and much more radical than first presented. Instead of referring to anything unique, such commitments (if they are to work) end up involving variable quantities, prices, qualities, timing, and even the numbers of companies involved, with layers of institutions, committees and regulators with discretion, treaty-type arrangements (including across *potential* as well as actual sponsors and buyers), centralism of public research decisions, a very high degree of information processing and monitoring, and a very high willingness of firms to be 100% truthful, in a mechanism that is nevertheless still very heavily based on secrecy. Worse, and paradoxical, policy-makers have to have good scientific information even before the science exists that could have revealed it to them, and to have information about the 'quality' of potential vaccines to set up all the above features to reveal the quality of those vaccines! It seems, "divergence of

[182] International Policy Network "Incentivising research and development for the diseases of poverty" 2005 p15.

[183] With the added difficulty that the IAC has to monitor and, supposedly, be completely transparent about information flows with both firms and the general public (at least the patent system allows firms more ability to hide information until they have their patents in place, and has a legal system to back them up) and has to take all the pressures for ex post adjustment and discretion that now show up in pressures on the patent system.

[184] 'Strong Medicine' p64. Barder, O., "This particular proposal is in fact very market-oriented." CIPIH Forum 19 November 2004.

[185] 'Strong Medicine', p27.

[186] www.pupress.princeton.edu/titles/7830.html.

opinion"[187] is not so divergent as to aggravate these decisions and the setting up of, and gyrations in, all these ex post rules.

By assuming a static state of science that is perfectly known by policymakers, 'Strong Medicine' ensures that all of these problems never arise in first place. But by modeling on the basis that the quality and symmetry of information is unusually high – especially knowing in advance what *all* the probability distributions are – the mechanism cannot then claim that it solves the information difficulties that it has just ruled out. This all rather numbs the criticism that other mechanisms require some of these features. And it is not clear what the point is in criticizing vaccine scientists, PPPs, and 'institutional failure', given the heavy use of administrators, executives, layers of institutions, *and* vaccine scientists, in setting and constantly updating the terms of an HIV APC.

2.10. An Expensive 'Advance' Purchase Commitment to Compensate

The only way around these difficulties is to set the size of early-stage APCs for vaccines higher to achieve the same given impact on incentives. What if 70% or more of the payments for an APC for an early-stage HIV vaccine is absorbed purely in the costs of the financial capital wrapped up in that research, half of the rest is crowded out, and it proves impossible to set the size of the APC within a factor of two or three of the 'true' underlying terms? We do not know the magnitude of any of these imperfections; the literature does not enlighten us. We can say, however, that a mechanism that might use a dollar of funds to generate a few cents' worth of new research would hardly be described as 'strong'.

As a salutary indication of the low power of early-stage APCs, the only recent comparable example of such a mechanism is the $6bn budget for the US Project Bioshield. So far, no large pharmaceutical firm has shown any interest. For sure, this is partly because the legislation fails to commit to prices for particular products, so that producers are not guaranteed from the start larger markets. Once a product has been developed, the US Government would still have an incentive to bargain for a low price. But it is also partly because of the extreme uncertainty of such research, the huge expected capital costs, the difficulty of working on such projects in secrecy, and the fact that large pharmaceutical firms were not already active in the field. Failure to commit to prices, arguably, simply indicates the extreme difficulty of working out efficient terms of contracts for such very early-stage products. Meanwhile, the only firms to show any interest have been small companies. Given the dependence of these small companies on the large pharmaceutical firms for markets for their outputs, even their response has been weaker than it might have been under other mechanisms.

[187] 'Strong Medicine', p27.

2.11. Quality of Research Leads and Cost Effectiveness: Who is Targeted?

Of the total $430-$470 million of HIV vaccine research per year, a very small fraction, only $50-$70 million, comes from private-sector activity[188]. Even this may overestimate the size of privately-funded HIV vaccine research since much of this private activity was publicly-subsidized[189].

Only $60-$70 million of combined public and private expenditure is spent per year exploring a malaria vaccine. Only $4 million between 1997 and 2002 went into exploring a vaccine against schistosomiasis. Underlying the mechanism in 'Making Markets' and 'Strong Medicine' lies the notion that there will be a massive shift in the relative pattern of R&D expenditure away from one based on PPPs and other approaches towards one based on large pharmaceutical firms with 'deep pockets' financially, and the rôle of stock markets and – to eventually pay for all this – there will be a massive increase in public funding that is not being made available to other approaches to vaccine development. For example, there will be up to $6.25bn (plus co-payments), and maybe even a great deal more (once tax breaks, and other subsidies are factored in) made available to large pharmaceutical firms for a malaria vaccine[190], dwarfing by well over a hundredfold what is currently spent in total globally per year on malaria vaccine research and many hundredfold current privately-financed activity.

2.11.1. The mechanism favors[191] 'deep pocket' pharmaceutical firms – even if they don't want it

Given this shift in emphasis, and given the high cost of venture capital and the extreme forms of capital market failures that many would-be vaccine developers face[192], real-world (as opposed to idealized) applications of early-stage APCs will tend to favour those with large free cash-flows, good access to equity finance, those with 'deep pockets' as the finance literature describes it, i.e. large pharmaceutical firms in industrialized economies[193]. Indeed this was the original intent of the lead authors: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more."[194]

This would be even more the case if it were perceived that developed economy large pharmaceutical firms were more generously subsidized by push payments and, as we commented above, would not sufficiency have these removed from their pull rewards (after all, preventing this from taking place is a privately very valuable form of rent-seeking), or if developed country developers were able to

---

[188] 'Strong Medicine' p26.
[189] Updated by IAVI, "Scientific Blueprint: Acceleration global efforts in AIDS vaccine research and development', 2004, to $650m and $100m respectively: http://www.iavi.org/viewfile.cfm?fid=409.
[190] 'Making Markets' p61. Adjust all figures 50% or so downwards in light of recent pronouncements.
[191] There should be no need to put the word 'relatively' in front of this, since the word 'favours' includes this meaning.
[192] This is all explained in far more detail in Farlow Chapter 12, especially Section 12.2.
[193] These are not the only features biasing the mechanism in favour of large pharmaceutical firms. See, for example, Farlow, ibid, section 8.6.
[194] Kremer, M., No. 10 Policy Unit, Appendix 1, p9.

use patents, know-how, and other strategic assets more effectively than developing country competitors, or if developed economy developers were perceived more able to influence discretionary decisions of the IAC and other committees after research costs had been sunk. We saw above, in a very simple calculation, that the ability to influence discretionary decisions is hugely valuable, since it can add literally hundreds of millions or even billions to the value of a research project and force similar-sized losses on competitors.

It has been claimed that the approach "is deliberately neutral, allowing any company, small or large, North or South, biotech or pharmaceutical, to benefit from the contract"[195]. But this is a bit like saying that the top suites at the Savoy Hotel in London are 'available to anyone' regardless of their income – so long as they can afford to pay. Being technically available is not the same as being actually accessable. Incidentally, we will see later that – in contrast – well-designed late-stage purchase commitments *can* be made more accessible to all kinds of vaccine players.

This raises two questions.

First, whether these large pharmaceutical firms are the most productive receptacles of the bulk of research for vaccines, in particular of vaccine trials – instead of, for example, university-based researchers, small and new biotechs, not-for-profit and developing country researchers. For maximal impact, these *other* groups of researchers, to the extent that they rely on other forms of finance rather than equity or venture capital, will be *ineligible* for any eventual APC (it is supposed to be an 'enhancement' to other public or foundation funding, remember). Indeed, it would be much easier, compared to large pharmaceutical players, to strip out from the payments of these smaller players their use of *other* non-private forms of research funding.

Second, whether using 100% equity finance is the best form of finance for research of a very 'collaborative' nature. Farlow 2004 Chapter 12 finds plenty of reasons to justify equity finance[196], but we also find, in the context of developing complicated vaccines, that there are some losses and tradeoffs to be priced in too. Do these tradeoffs become too costly in some circumstances, such as, for example, HIV vaccine research?

There is also a bias in the way decisions are handled on large programs, that favors large developed economy pharmaceutical firms. The current handling of the Global HIV Vaccine Enterprise is through the G7 finance ministers (because it involves up-front cashflows), part of who's remit is to act in the interests of G7 domestic industries, and not to be thinking in terms of supporting emerging economy and developing economy vaccine developers to displace G7 domestic

[195] Berndt, E.R. ibid. One supposes that this refers to the case of early-stage HIV vaccine research as much as any other vaccine, including late-stage vaccines, since no distinction is made in the comment.

[196] For some reason, awkward questions like "What is the exact place of equity finance?" almost always gets used to imply that one is questioning entirely the role of equity finance, and, by extension, private players. Private equity-financed players themselves are not helped by this dismissal of the issue.

industries. Meanwhile the vaccine APC notion is being fed through the G8, because of the notion that payment is a long way off. This decision-making process is not likely to yield the overall most efficient result.

2.11.2. Others may be at least as well or better placed for vaccine R&D

The justification for the emphasis on large pharmaceutical firms is the claim that the most efficient vaccine research takes place there. However, there is growing evidence that this is not the case. For example, the most recent Financial Times Special Report into Biotechnology points out that while the pharmaceutical industry has the commercial machine, "much of the industry is suffering from poor productivity in research and development"[197], and quotes the finding of Ernst & Young that half the drugs in clinical development belong to biotechnology companies ("a testament to the sector's creativity"), many of whom are themselves a spin-off from publicly-funded and university-based research. However, most of these drugs are found in just a handful of biotech groups: "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"(italics added)[198].

As Erickson put it in a CIPIH Forum posting:

> "*Without sustained watering, the best potted plants will abort before they have had a chance to reach maturity."*

Referring to the many novel but 'one-off' drugs in development by biotechs:

> "*It is easy to predict that the vast majority of these will not make it to the end zone - for many reasons. Not to pick on any particular company, but the usual reasons for drug failure by biotechs include lack of appropriate financing, improper clinical development strategy, poor regulatory tactics, lack of effective marketing strategy to big pharma, or just plain bad luck. We don¹t usually hear or read about the numerous failures only the occasional successes that make good copy for the media and good advertising for stock brokers and analysts. Besides bad luck, none of these problems typically plague big pharma, which has all of these capabilities in spades and lots of cash and momentum to withstand multiple failures. Another big difference between Big Pharma and biotechs is that Big Pharma does not place the same emphasis for survival on innovation and execution as do biotechs, which are chock full of ideas and risk-takers, but too often run out of gas before they can get to their destination. What Big Pharma does best is manufacture and sell drugs. To wit with many notable exceptions, the vast majority of innovative drugs in Big Pharma pipelines were in-licensed from biotechs, academia, or competitors as opposed to having originated from their own research teams.*"[199]

---

[197] Lauren Mills, "Great science not all that matters", Financial Times Special Report into Biotechnology, 10 November 2004, p 5.
[198] Mills, ibid.
[199] 2 March 2005, CIPIH Forum. John Erickson is President and CEO Sequoia Pharmaceuticals, Inc. and Founder and Scientific Director Institute for Global Therapeutics and Drug Design,

Berkley quotes another:

> *"The pharmaceutical industry has virtually turned its back on HIV vaccine research, leaving the biotechnology industry as the gatekeepers of hope for a preventative vaccine, yet the number of biotechnology companies in the field is small and getting smaller."*[200]

If small innovative biotechs are already struggling to raise finance under the current 'blockbuster' regime, it is not obvious that a similar regime would work for early-stage vaccines if such work is highly dependent on small and new biotechs, not-for-profit, developing country, and university-based research. Analysis would be needed on devices to support *these*, and, indeed, such analysis should be done *before* instigating any large early-stage APC, since, to the extent that the situation of these other researchers can be improved, the size of the APC would turn out to be wrong. A key component of APCs is to hold back on finance in order to incentivize effort and quality – but this is self-defeating if it locks out those who already struggle most in their access to finance.

PPPs

Indeed, PPPs have better vaccine (and neglected drug) trial attrition rates than large pharmaceutical firms, since they are able to choose across a much wider field of IP, and not just what they happen to hold in-house. For example, Pfizer, is working on just one 'new' malaria drug based on its own in-house drug zithromax combined with off-patent chloroquine. Medicines for Malaria Venture[201], on the other hand, is working on 21 new malaria drugs and approaches based on IP from half a dozen companies, small and large, as well as academics, public domain and developing country IP (for example Chinese artemisinin discoveries). Being able to pick and choose across a field of IP is much more efficient than an approach based on narrowness and secrecy.

MMV

The Malaria Vaccine Initiative[202] has 20 vaccine candidates at various stages of pre- and clinical development (with 8 having entered phase-I and phase-II clinical trials), and all this has been achieved on resources of just $43m since 1999[203]; that is less than 0.007% of the $6.25bn (plus co-payments, subsides, foundation funding, and tax breaks, etc.) mentioned above as possibly being made available under the 'Strong Medicine' approach for a malaria vaccine. Again, why direct a hundred-and-fifty fold increase in funds to a small number of very large firms instead of creatively using it to fund other developers? The constant argument that

---

www.globaltherapeutics.org. We explore below in section 2.13 (on research 'bunching') more reasons for why such innovative activity is more likely to fall outside of the big pharmaceutical players.

[200] Berkeley, S. "The Need for a Vaccine" p588 in Chapter 38 in "AIDS in Africa" Second Edition, Kluwer Academic/Plenum Publishers, 2002, quoting Glaser V. "Number of biotechnology companies pursuing HIV vaccines begins to dwindle." Genetic Engineering News, 1997; 17:14,44.

[201] www.mmv.org/pages/page_main.htm.

[202] Set up in 1999 at the Program for Appropriate Technology in Health with funding from the Bill and Melinda Gates Foundation.

[203] See MVI website www.malariavaccine.org for details.

push funding "poses a challenge" to policy-makers "because funds are limited" and "not enough to bring the candidates through the pipeline" is not an argument *per se* favoring huge levels of advance purchase funding, though it is often made[204]. The issue is the relative impact of the last dollar spent on any particular funding route, and that is an empirical issue. Once that is settled, politicians have to bite the financial bullet.

Large pharmaceutical firms would similarly not appear to be well-positioned in other respects for APCs for many developing country early-stage vaccines, or, indeed, drugs. On top of the very high capital costs, they now have a very low level of in-house expertise in working on these types of diseases, no built up libraries of compounds active against neglected diseases targets, and little expertise in working with developing country patient needs and developing country regulatory authorities, or even on developing country drug trials (for example for TB). IAVI reports that compared to their marginal impact in 2000, developing countries are now "helping to lead the field". 'Making Markets' also recognizes that "Manufacturers in developing countries, which have lower cost structures, are building the capability to supply low-priced products in the long-term"[205]. It would make more sense to explore first how to extend funding to these 'neglected developers' before launching a mechanism that concentrates its financial impact on large, and often less willing, pharmaceutical firms. If "all these are having a positive impact on the structure of the vaccine market"[206], why not take care not to upset these positive trends?

Why base costs on high-cost developers?

And why, into the bargain, base the terms of APCs on the costs of large pharmaceutical companies?[207] There is evidence that so long as the volume is high enough, much lower profit margins (that is not 'blockbuster' margins) are attractive to emerging suppliers when they compete for procurement contracts even if they would not appeal to OECD firms, as the MVP project has highlighted[208]:

> "*We had assumed that a profit margin of about $0.50 per dose for 25 million doses per year would be a sufficient return on investment, if the public sector were providing the investment. However, if the costs of development also included opportunity costs that might be estimated at $200–500 million for a vaccine company with a promising research pipeline, then the return on investment from sales of the meningococcal vaccine would be perceived as insufficient.*"
>
> "*Finally, MVP negotiated a contract with a large manufacturer in Asia (Serum Institute of India, Pune, India)…willing to sell 25 million doses per year of group A meningococcal lyophilized conjugate vaccine in ten*

[204] 'Making Markets' March 2005 p26 and p27.
[205] 'Making Markets' arch 2005 7.
[206] 'Making Markets' March 2005 p7.
[207] All of the pull papers are based on US industry figures.
[208] See "Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries", Jódar, LaForce, Ceccarini, Aguado & Granoff, The Lancet, vol. 361, 31 May, 2003.

dose vials for less than $0.50 per dose, which includes cost of depreciation of facilities and an acceptable profit margin."

"*In short, what was viewed by established vaccine companies in Europe or the USA as an opportunity cost, was seen by the developing country manufacturer as an opportunity—[among other things]…the prospect of sales to Africa of many doses of vaccine at a low but profitable price for an estimated 10 years or more.*"

2.11.3. A proposal that puts most risk onto biotechs?

The CGD report states that biotechs engaging in research on early-stage vaccines expressed much less interest in APC programs compared to large pharmaceutical companies with vaccines coming to market soon. Yet, confusingly, the accompanying "Frequently Asked Questions" document claims that biotechs had been "particularly enthusiastic about this idea"[209]. The CGD report goes on to assert, without any evidence, that the program would initially motivate biotech companies while larger pharmaceutical firms would get involved after "further advances in the science…perhaps led by biotech firms". Indeed, it is this prospect of the taking over of the process by large pharmaceutical firms that is supposed to motivate the biotechs in the first place.

This initial reliance on the role of biotechs – even if ultimately it is large pharmaceutical firms who take over – is based on the claim that the expected decisions of the committee at the end of the process, in conjunction with the rules set at the start, and the interest of the large pharmaceutical firms – most of whom have abandoned the vaccine market, and are not likely to return for just one difficult early-stage vaccine – will work all the way back to very early rounds of biotech investment. But this is where the difference between a genuine market and a committee-driven program bites. 'Mechanism risk' is extremely high for early investors into such non-market based programs. The further away from the ultimate committee decision, the greater the chances that the program will not work as intended – or that it may even collapse. There is a large investment 'option price' to be priced in by venture capitalists when investing early, a price that is especially high if a program is highly uncertain.

If the program collapses – indeed, biotech investor reactions to just such a possibility may make this largely self-fulfilling – it is biotechs and their investors, and not large pharmaceutical firms, who will pay the heaviest price. Furthermore, given the huge degree of discretion at much later stages of the program, the risk of 'dynamic inconsistency' – of decision makers taking advantage of firms' already sunk investments to drive an even better ex post deal – is especially high for early

[209] The truth is that certain groups – such as "Bio Ventures for Global Health" – have been much more vocal than others. It would allay this author's concerns if these supporters would distinguish whether their support is based on early-stage vaccines such as HIV, malaria, or TB, or based on a range of late-stage and currently existing vaccines and products. If the former, the obvious reassuring step would be to muster all those private venture capitalists eager to start funding of HIV vaccine research as soon as an APC for HIV is in place, and get them to make public (and, if possible, legally binding) financial commitments *now* to fund the necessary research once a $3bn HIV APC is in place. If these sorts of investors cannot be found, then Bio Ventures for Global Health should reassess how vocal it wants to be in encouraging an APC for HIV.

investors. For these reasons – and also because of the greater difficulties in internalizing the value of early investments compared to later investments for such highly complex vaccines as HIV – early developers will have a very high required rate of return. At a fifteen to twenty-plus year horizon, with highly uncertain science, a $3bn APC for HIV (that proposed by CGD in its final report) starts to have extremely weak pulling power, if any at all.

The report presumes that biotechs would be prepared to take on board much more risk than any evidence suggests that they would be prepared to bear. Their rapid (and needed) reaction in order for the program to work is based more on hope than on any solid evidence. To reassure early investors that the program would not be wound up early, it might be thought that the program could be made 100% permanently fixed. However, it is not clear which would be worse – having a reversible program that is not motivating biotechs because of the possibility of reversal, or being stuck with a non-reversible program the terms of which are set badly such that biotechs are not motivated by it.

2.11.4. Milestones for biotechs

One might imagine that in normal 'market-based' situations, large pharmaceutical firms would set milestone payments into contracts (if there are any contracts in place[210]), and that only the 'size of the pot' would matter. However, if there are concerns about the riskiness of the surrogate-market mechanism, this clearly will not hold, and biotechs may wish to be protected against the risks of the *mechanism itself*. 'Making Markets' points out that biotech companies had, indeed, requested that the mechanism incorporate interim payments for achieving pre-determined milestones, "to create incentives for research and early-stage development activities and encourage venture capital investment in emerging companies committed to the Framework."[211]

The worry is that by putting all of the pot of funds at the end of the process, and *because of the risks of the mechanism itself*, financially-constrained biotechs may not be able to get hold of the resources to take part very early on, and that in a highly iterative research process with elements of public-good to some discoveries, biotechs may be unable to internalize the value of all that they do[212]. But milestone payments were deemed too difficult to incorporate in the initial 'Making Markets' proposal.

Very recently, however, the argument has swung the other way: "These types of interim pull payments would be particularly attractive to smaller biotechnology firms and could be *easily worked into* the AdvancedMarkets agreements" (italics added)[213]. Many things can be 'easily worked into' contracts. That the result would be pretty, efficient, or practical is a different issue altogether. Certainly, it

[210] The issue is complicated for early-stage vaccines by the fact that many biotechs are investing in the hope, rather the present reality, of large-firm pharmaceutical firm contracts, and therefore may not have access to 'milestone payments'.
[211] 'Making Markets' April 2005 p91.
[212] There is a standard patent problem too. The value to the biotechs of their research depends on much later users of their ideas. With a limited duration patent, any licensing fees generated by an interesting discovery may not materialise until late in the patent's lifetime.
[213] Barder, O, CIPIH Forum 27 November 2004.

is clearly very different if the mechanism organizers *themselves* are having to do something *within* contracts that, ordinarily, large pharmaceutical firms would do *given* the pre-set contracts. It has not been spelled out how this would to be done. For example, are milestone payments drawn from the eventual pot of funds? This would be the logical approach. But how then is the draw-down judged (a huge amount of underlying science would need to be understood in setting terms at the start), and what happens to the incentives of others as the pot shrinks (especially if the draw-down is badly carried out and not transparently clear)? When setting the terms of such interim agreements, one must worry that distortion and discretion at intermediary stages will distort incentives. It:

> "*seems not to take into account the extraordinarily complicated way in which vaccine R&D takes place. Milestones are built into donor contracts, venture capital investment agreements, and even internally within companies. If the AdvancedMarkets agreements were to incorporate additional milestones, the complexity of the overall agreement, in at least some cases, would be extraordinary and would require great expertise in vaccine R&D on the side of the AdvancedMarkets program. For example, who would adjudicate whether a milestone had been reached when there was disagreement?*"[214]

What if it was a tiny emerging economy biotech or a large developed economy pharmaceutical firm? What if there is rent-seeking over such decisions? What if this favors some (larger) players over others? Given the importance of expectations for investors, what if this was even just a 'worry'? What if an interim payment was made that turned out not to be justified? As with many other promised aspects of the application to HIV, malaria, and TB, no proof has been provided that this could at all be 'easy', and is, unfortunately, just another example of the way that certain parts of the audience (here, biotechs) are, expediently, and philogically soothed by the 'right-sounding' language. This is not to suggest that interim agreements might not have value as a way of reassuring investors, and keeping down the costs and the risks of the mechanism to them. Just that the ease of making such agreements work cannot be casually asserted, and must be proven.

The final version of the CGD report swung back the other way and dropped the idea of interim milestone payments altogether, stating that in spite of the issues discussed above: "We intend that intermediate incentives of this kind will be created by the commercial activities of developers in the expectation of being remunerated through sales of vaccines under the guarantee agreement."[215]

Nevertheless, biotechs have a high risk of failure, and venture capital is only interested in high-risk high-return activity with some notion of rapid gain and an exit strategy, so that investors can move on with their resources to the next opportunity[216]. Having achieved some useful interim step, venture capital would

[214] Mahoney, R, CIPIH Forum, 21 December 2004.
[215] 'Making Markets' April 2005 p91.
[216] If nothing else, they cannot prove success to backers quickly enough to attract more capital funding.

not want to have to be locked in for the 15-25 year lead times that might be typical of HIV vaccines.

It might be thought that success at early stages of vaccine development could be converted into contracts, but this raises a whole range of valuation issues and worries for the firm about internalizing the value of its research (say in a collaborative setting). And besides, we already just saw that such contracts are not working to create access to finance for the "hundreds of smaller biotech companies" with "great proposals". This provides no reassurance for even more complicated products, such as HIV vaccines, potentially very much longer timeframes, and mechanisms the workings of which are high risk.

As the proposals stand, APCs for early-stage vaccines are heavily dependent on those with free cash flow, a history, and a likely continued existence, even if they are not the most innovative recipients, and puts risk disproportionately onto the shoulders of biotechnology firms for early-stage vaccines.

2.11.5. The global state of vaccine manufacture

The approach also seriously misunderstands the global state and direction of vaccine manufacture, and, indeed, vaccine R&D. In the past, seven or eight leading industrial country manufactures would be working on five to six vaccine-related R&D projects each at any one time. The industry is now consolidated into just four major multinational manufacturers[217] and "R&D budgets have shrunk, and competition for capacity has become fierce"[218] with dramatically reduced numbers of vaccine R&D projects, especially for developing country markets. This is partly, but not exclusively, the result of reduced competition and 'replacement effects'.

All of these four firms have products against which any vaccines they might seek to develop would have to compete (including, for example, replacing relatively much more lucrative HIV drugs markets with cheaper one-off HIV vaccines[219]). With so few large players, any new R&D projects they initiate are more likely to destroy the value of projects they already have drugs for, and this raises risks and hence capital costs. This is not to cast aspersion on executives of such companies. Capital markets feed these higher capital costs onto firms if they work on such projects[220]. They are also much less likely to engage in multiple research leads as a result. The cost of an APC has to be higher to reflect all of this. Having more, and different, vaccine players is more valuable than having the same few players being enticed with ever-bigger payments.

---

[217] 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. This is based on 2000 market data, though this might also under-exaggerate the impact of domestic production in China, Brazil and India on account of government suppression of prices in these countries (See Batson et al, The Vaccine Book, p 349 for details).

[218] " Issues Paper: Accelerating new Vaccines", Glass, S.N., Batson, A, and Levine, R. Global Alliance for Vaccines and Immunization: Financing Task Force, 2001, p10.

[219] If these are therapeutic and not preventative then there are all the problems and costs of having to monitor for twenty years or more (for a product that has supposedly cost only a dollar or so to manufacture, and is supposedly then pitched at a very low cost after the first few hundred million doses). The sums may simply not add up.

[220] See Farlow 2004, ibid. Section 12.4.

Even as the number of developing country manufacturers with products on the WHO pre-approved list to supply UN vaccines has risen, the number of industrial market manufacturers supplying industrial countries has been falling precipitously, and so: "While new players are emerging to fill these voids, they have not replaced the multinational manufacturers, in some cases contributing to vaccine shortages"[221]. At the same time, "Smaller and emerging market manufacturers are less likely – *and financially less able* – to take on the risks of product development" (italics added)[222].

Why not target differently to increase the number of manufacturers?
Why, in such circumstances, adopt mechanisms that *deliberately* favour a very few large developed economy manufacturers? Why not, for example, formulate a mechanism that instead targets more funds at emerging market manufacturers and those willing to work with them, and that tries to increase the number of manufacturers? Arguments have been expressed against this, including problems caused by poor regulation and control that can lead to inconsistent vaccine quality and unreliable quantities, and problems with access to foreign exchange to purchase raw materials. However, the first problem is becoming ever less applicable given the rapid expansion of the pharmaceutical industry in both India and China (and is slightly self-reinforcing logic anyway). As to the second, if the problem is lack of access to foreign exchange, it makes no sense to deliberately further feed this problem, and it is hardly a reason for holding back global finance for vaccine research, given that the finance is to be spent anyway. The second point does suggest though that access to these global research funds will more likely need to be front-loaded through a global vaccine enterprise than end-loaded through an APC that will require dollar-denominated free cash-flows running into the billions in the meantime.

This does *not* mean that biotechs and others would not respond to early-stage APCs (though, for HIV, the figures suggested so far do not add up to suggest that they would respond). The argument being made here 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. The flip-side to this is that the APC for such vaccines is a more expensive instrument. Large pharmaceutical firms regularly express a lukewarm attitude to APCs for early-stage vaccines like HIV and malaria even though the logic seems to be favoring them. This does rather suggest that they are poorly-targeted instruments.

2.11.6. The need to expand the number of vaccine producers

The vaccine industry is dominated by a handful of companies. The share of the four major developers listed above has risen from 50% in 1988 to about 80%

[221] Glass et al. ibid. p5.
[222] Glass et al. ibid. p9.

today, and capacity has become constrained. There are only five ways for capacity to expand:

1) Increased construction of facilities by the four majors;
2) Partnerships between regional and major manufacturers;
3) The growth of biotechnology companies into major vaccine manufacturers;
4) The growth of regional small manufacturers in countries such as Brazil, Cuba, India, Korea, and Japan;
5) Development of new institutions to make vaccines (perhaps as part of the Global HIV Vaccine Enterprise).

APCs impact the relative likelihood of these outcomes, though not all purchase commitments would be equal in their impact. Given their emphasis on free cash-flows and access to developed economy equity markets, and the way in which APCs are heavily biased in favour of large players[223], the order of greatest impact for early-stage vaccines is approximately as listed above, with the first relatively most greatly favoured, and the fifth the least impacted. Is this the most appropriate response to expanding capacity for complicated vaccines? Given the competition that there already is for the vaccine capacity of the 'big four', is it sensible to have developing economy vaccine requirements having to compete against 'rich economy' vaccine requirements for the capacity of the 'big four'? As purchase commitments become more late-stage, and other instruments are used to support research (including the use of the sort of purchase contracts described in later sections) it could be that the order of impact on capacity is even reversed[224].

At the very least there should be more open discussion of whether 2), 3), 4) or 5) above offer the greatest hope, or whether sticking with 1), and pitching with APCs to a handful of large multinational companies, since they are currently most dominant, is the best approach.

Furthermore – and something woefully underexplored – it is clear that much recent legislation, including BioshieldII will intensify competition for the resources and the skills-base of the biotechnology sector, government researchers, and for any increase in vaccine production capacity. To offset this, would it be more sensible to seek to adopt strategies that emphasize the reverse order of the list above, rather than starting at the top and working down?

[223] See Farlow 2004, ibid. especially Chapters 10, 11, and 12, which all repeatedly suggest that there are inherent biases away from small, emerging economy, not-for profit, PPP and other players.

[224] The author would welcome counter-arguments on all of these points (that go a bit further than just restating that the approach is "open to all"), since these are observations based on an understanding of the underlying logic of the approach, not based on any empirical evidence. It is an interesting (and important) empirical issue however. For example, since domestic producers in developing countries often do not get prices high enough to do much R&D or create new production, could their access to finance be improved so that they could more easily compete for purchases? However, observe that their distance from research institutions, such as the NIH, mitigates against them too and a more open collaborative mechanism may enable them to acquire more of the necessary knowledge.

2.11.7. Contracts that risk locking out certain players

It was originally claimed that an open contract could be set up with no need for the APC sponsors to put financial resources aside to make good on the APC. It became clear that this could not be done. On the one hand, early developers would have too little hold over the APC wit fundshout a contract, and so this *would* necessitate resources being put into an escrow account to reassure them and, more importantly, their investors. On the other hand, the APC sponsors also needed some claim on the firms for the sake of monitoring and knowing if the program was actually even working. The contractual arrangements therefore now call for the sponsor(s) and for all actual and potential vaccine developers to sign-on to the 'framework' contract within 36 months of the initiation of the program, and for all developers to agree to be monitored by the committee running the program and to abide by its rules and its use of discretion when determining the distribution of the payments many years later at the end of the process.

To prevent firms 'cheating' by doing unmonitored, even largely 'hidden', research – and thereby taking advantage of that fact that others are being monitored and are having to give sensitive information over to a committee – those conducting current vaccine trials and failing to sign-on, and those initiating future vaccine trials without prior permission from the committee, will be penalized by being barred access to the 'eligible' markets controlled by the committee. Such 'cheating' also makes it hard for the sponsors to know what is going on, and for firms taking part in the program to know the expected value of what they are doing and hence 'how much' of it to do. Entry of later developers to the program – who unlike early entrants will not be allowed to have done any clinical trials – will be controlled through the committee[225].

However, the development, introduction, and manufacture of vaccines are extraordinarily complex processes that take place over many years and involve many organizations. In addition, the global state of the development and manufacture of vaccines is rapidly changing, with centers in developing and emerging countries such as India, China, and Cuba becoming increasingly important. At a very early stage in the development of a vaccine, it would not be possible to identify all those who may potentially take part in such a program in ten to twenty, or even more, years time. Nor is it clear why the incentives of later innovative research teams should be stymied by contractual arrangements that unnecessarily constrict competition by potentially forcing them to go through large multinational pharmaceutical companies[226].

[225] It is not clear how firms will be treated if they seek to enter the program later *based on* the results of clinical trials performed elsewhere or performed within the program by other players. In normal market circumstances one would expect that such firms could exploit any opportunity open to them, and would therefore have the incentive to invest in such opportunities. It is not so clear-cut under the contract-and-committee structure now being suggested.

[226] Incidentally, emerging firms who later seek to 'break' the program by compulsory licenses or me-too products based on vaccines developed under the program, may argue that the constricts of the system were 'unfair'.

2.11.8. The problems of competition through a committee and one point in time

Given that, unlike the current system for vaccine procurement, there would be very little competition in the end market, with competition essentially via IAC decisions relating to actions many years before, one naturally has to consider carefully whether the mechanism would achieve this 'virtual' competition, or whether large companies or developed economies could in any way stymie it (via suitable choice of patents or pressure for relaxation of strictures of the IAC on them, including weak monitoring of activity[227], failure of the IAC to shift product demands to emerging- or developing-economy vaccines, etc.).

It risks capture

One of the dangers of 'policing' all competition and quality through just one point in the development process and just one committee is that it risks the capture of the process, and higher risks and capital costs of those least likely to do the capturing. And fear of this by smaller players makes it self-fulfilling. For example, if the IAC had any degree of discretion, is it conceivable that the IAC would do something very financially 'damaging' to a dominant developed economy pharmaceutical company in favour of a developing country manufacturer, like entirely replacing the former with the developing country manufacturer? One doubts it. And so would developing and emerging country manufacturers who would struggle to believe, from 15-20 years out, that the IAC committee would be truly independent[228]. Regarding this independence, we are (somewhat ironically) told that: "The Working Group believes this is possible, and has set out a detailed proposal in the report which has had positive responses from senior industry figures."[229] The irony may not allude developing and emerging country manufacturers, and they would stay away in the first place.

The signs are already not looking good

'Making Markets' points out that there was "Strong opinion in favour of having current or recent industry experience represented on the committee"[230] but that most (and recently all) of those consulted on the proposal were in rich developed economy markets. However, the more we study the likely reality of a real-world early-stage APC, the clearer it becomes that being able to influence the discretionary decisions of the controlling committee (or indeed any of the layers of committees involved) is potentially hugely valuable. Yet, we are told that very little contact was made with developing country developers in trying to work out the terms of such a mechanism, with no input from, for example, Brazil, China, Cuba, and Korea (one of the major developers and suppliers of hepatitis B vaccine) and only one developer from India, the Serum Institute (that represents

[227] Comments on behalf of the Center for Global Development suggest that this is already pretty well accepted (Berndt, E.R. ibid.).

[228] Holding the launch party for the Center for Global Development's final report at the headquarters of one of the preeminent corporate law firms to 'big pharma', Covington and Burling in Washington (and not at CGD itself or somewhere more neutral), with the support of Merck, probably did not do much to encourage developing and emerging country developers to believe that the mechanism would be neutral, nor that the crucially-needed independence at a 20 year horizon was an automatic given.

[229] Barder, O., ibid. 19 November 2004.

[230] 'Making Markets' April 2005 p43.

less than 1% of the global vaccine market). If this cannot even be achieved during discussion at this stage of setting up such a mechanism, what are developing country developers to believe about later stages?

For example, we are told that the committee would have the power to terminate the entire agreement if "certain interim milestones are not achieved in a timely fashion" and "if the Framework does not appear to be stimulating productive research and development activities"[231] or "not enough is being done", but it is not clear what legal redress, or compensation, emerging economy developers would have if they disagreed with this and were forced to lose all their sunk investments. Developing and emerging countries would worry that the mechanism would be unfair to them if not enough vaccine research was simulated amongst the large pharmaceutical firms – something hardly the fault of developing and emerging country vaccine firms.

2.12. Advance Purchase Commitments Lose Power when Vaccines Replace Profitable Treatments

APCs pitched to the current big developers have to work *against* another serious problem[232]. The possible development of cheap, one-off, vaccines risks replacing profitable, long-term drug treatment programs. This generates less of an incentive to develop vaccines in the first place. Total (expected, discounted) *industry* profits will be lower if vaccines for HIV are developed[233]. This has nothing to do with the motives of the CEOs of large pharmaceutical companies. It is an effect that is being forced on them through the natural workings of equity-based finance – as well as being a function of the structure of the pharmaceutical industry and the nature of IPR. The issue is certainly controversial, but this should not prevent us from tackling it. If it turns out that 'replacement effects' are part of the problem in raising private finance for the R&D of vaccines, such as for HIV, then better policy will result from considering rather than from ignoring such effects – as the following section will hope to show.

How the replacement effect comes about

If equity markets correctly price all future expected discounted profit flows, then those firms working on projects with the mere *possibility* of reduced overall profit flows caused by the replacement of profitable programs (profitable in the expected sense, which may be an important sense for a growing treatment market like HIV/AIDS), will experience a depressing influence on their equity valuations, and this will increase their capital costs generally – not just for this research project but for other activities too[234]. This leads to firms requiring an even higher rate of return on projects. The figures are not inconsequential. Even at the currently much lower prices than a few years ago (one can imagine how the equations must have looked then) the costs of the drugs alone for life-time treatment of HIV/AIDS, generate a cost of nearly $1,200 per DALY saved in

[231] 'Making Markets' April 2005 p101.
[232] This is largely taken from Farlow, 2004, Section 12.4.
[233] Kremer, M., hints at something similar going on in the TB drugs market. Kremer No 10 Policy Unit Appendix 1 p2.
[234] Notice that it does not have to be 'actual' replacement; risk of replacement is sufficient.

developing countries[235] compared to a few dollars per DALY saved for a vaccine. If there is already a 'lack of a market' for HIV/AIDS vaccines, this simply reinforces this problem.

On the one hand equity finance has much to recommend itself as a method for driving pharmaceutical R&D incentives in a world of asymmetric information (see Farlow 2004, Chapter 12). The ponderings of this section do not alter this. But we should recognise that there is a tradeoff between the incentive effect of equity finance and other, less positive side-effects, such as, in this case, the replacement effect. A different configuration of financial markets and other sources of R&D funding and a different industrial structure would feed a different set of constraints. For example, the fewer the number of firms that are already being relied upon for *both* treatments and vaccines, the larger the 'replacement effect' and the lower the incentives to invest in vaccine R&D. Conversely, the more competitive the pharmaceutical industry then the stronger the incentive for firms to work on vaccine R&D, since success would replace the treatments of *other* companies.

But there may still be constraints on even this. In a competitive pharmaceutical industry (where, also, the IP system would allow entrant firms to acquire technology that might undermine current firms), one might expect that those companies developing vaccines would still have an incentive to do so, since vaccines would replace the treatments of *other* companies. But a system heavily dependent on the *same* few companies for both treatments and vaccines generates a much larger 'replacement effect' and less of an incentive to develop vaccines. This problem is reinforced if biotechs and not-for-profit firms cannot raise finance to take a vaccine 'all the way', since the only viable market for their output is created by firms that face a 'replacement effect', thus feeding the 'replacement effect' onto the biotechs. One of the solutions would be a mechanism that allows for more players in the market, not bigger incentives for the same few players. The 'replacement effect' is also stronger the more able are incumbents, through tight IPR, to restrict access to information that might undermine their competitive positions.

It follows that part of the reason for the collapse in global vaccine R&D is related to the structure of the industry. A research device such as an APC would have to devote a sizeable portion of its size to fighting against these structural issues (even as it risks making the problem worse) when really it would make more sense to tackle the structural issues head-on.

The problems of an aggregate condition

This is also complicated by the fact that the 'replacement effect' is an *aggregate* condition. Clearly, if the expenditure on HIV/AIDS treatments in Sub-Saharan Africa is already pitifully low, then vaccine developers might not expect much of a 'replacement effect' there. However, the HIV/AIDS treatment market also includes potentially very profitable segments, and the effect on *these* segments from vaccines developed for the *poor* segments (or from the discovery that a

[235] Based on approximately $430 per year of drug costs (No 10 Policy Unit Appendix 10). The author has no up-to-date (2005) figure for this based on $120-$140 per year drug costs, and would welcome a correct updated calculation (rather than improvising an approximate calculation).

vaccine working on a clade in a low-value market is cross-reactive against clades in richer-value markets) works against private incentives to research towards vaccines for the poorer, low 'replacement effect', segments. This is much the same logic as that found at work in anti-retroviral drugs markets, where firms have sometimes been very unwilling to price-discriminate (normally the profitable thing to do) by setting very low prices in very poor markets for fear that this will alert consumers in much richer markets to the potentially extremely low marginal costs of the drugs, risking agitation for prices to be set much lower there[236]. Given the one-off nature of vaccines, and the very low prices that could ever be expected from them in very poor countries, the effect need only be tiny to undermine the incentives to research vaccines.

'Replacement effects' might even be at work for vaccines that do not obviously compete with treatment programs – such as vaccines for diseases that affect mostly the poor and for which there is low current treatment – if cheap only-once-ever-used drugs (costing cents or a few dollars at most) weaken pricing power in profitable treatment markets[237]. This weakening only has to be tiny for vaccines – maybe even only fractions of a percentage, given the size and duration of the treatment market compared to the vaccine market (all compounded by the fact that the former market refers to multiple periods of future sales of treatments whereas the latter refers to one-off sales), and that the prices in the latter could never be very high at all. And the effect is strengthened further if there is any expectation that any resources being made available might otherwise go to treatments in the poor markets.

Similar logic affects how we view the consequences for the private finance costs of malaria vaccine R&D if we seek to encourage private finance into both malaria *drug* R&D as well as malaria vaccine R&D at the same time.

Reinforcing factors

There are three further financial mechanisms reinforcing this problem:

1) If the current system relies on 'small' firms (entrants, biotechs, not-for-profits, etc.) to work on vaccines to achieve this 'replacement', such entrants will need access to sources of finance[238]. If these firms are much more credit-constrained than large incumbents – Farlow 2004 Chapter 12 argues that they are – then their cost of researching vaccines is much higher and profitability much lower. Their ability to do the 'replacement' is much weakened as a result.

---

[236] Scherer and Watal 2002, "Post-TRIPS options for access to patented medicines in developing nations". Journal of International Economic Law, 5(4) contains a diagram showing the weak correlation found between price and country-level income for 15 antiretroviral drugs (They also point out that the empirical evidence is complicated by import duties, local tariffs, price controls, taxes and wholesale profits, etc.).

[237] Kremer points out that one of the advantages of APCs is that it enables firms not to have to be transparent about what it actually costs to manufacture drugs, for fear of these effects (though, we also found that firms have to reveal a great deal of information to those running the mechanism if an auction mechanisms cannot be used to set the size of payment, and this clearly sets up an efficiency trade-off).

[238] Observe that overall profits to all companies would be lower after replacement, illustrating again the low incentives to do such activities by any player other than a purely marginal player.

2) In addition, biotechs usually have to sell the promising discoveries they make onto large pharmaceutical firms since they lack access themselves to the large amounts of capital needed to take projects right the way through to an end product (and this may be especially so for something like an HIV/AIDS vaccine). Even if biotechs are marginal, competitive, players and might not suffer from the 'replacement effect' themselves, the need to turn to large pharmaceutical firms at late stages, feeds the 'replacement effect' onto them. Biotechs in turn find it more difficult to raise the finance to do early stage vaccine work since financial investors know that they will face less of a market for the results of such projects because of the 'replacement effect' of the buyers, and because of the risk that buyers will not be so interested in sinking heavy investments themselves to bring a project to completion.

3) Currently, not-for-profit firms and '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 all their unused tax-breaks as an asset reflected in their equity valuations until taken over). This is unfortunate given that more than 50% of current vaccine research takes place in biotechs. That their research needs to boost their share valuations in ways that appeal to large pharmaceutical firms, gives another route for the 'replacement effect' to enter. A mechanism that is less reliant on this feature may enable a greater number of firms to exist in equilibrium and a lower impact of the 'replacement effect'[239].

Incidentally, given the way the APC is designed to create 'additional' private finance, and incentives 'additional' to tax-breaks, it would supposedly have to find some way to exclude the value of the tax-breaks of biotechs when it was being allocated (at least that is the assumption running through the cost-effectiveness calculations).

The APC, since it is differentially more targeted at large pharmaceutical firms over small biotechs and not-for-profits firms, makes this problem worse where it exists[240]. It is also an ironic strategy to pitch towards large pharmaceutical firms, if the reason for low vaccine research is, in some cases, in part generated by a 'replacement effect' induced by just such an over-reliance on those large pharmaceutical firms.

'Replacement effect' crowding out effect reduces cost-effectiveness of advance purchase commitments

If there are replacement effects in the system, this may affect how we measure the cost-effectiveness of APCs. There is what might be called a 'replacement effect' crowding-out effect working against the APC. The APC has to be set sufficiently high that the marginal positive return on vaccine research minus the marginal negative return caused by the 'replacement effect' produces an overall return that equals that on all other research projects that the firm engages in. And this

[239] This observation affects other features of advance purchase precommitments including the auction mechanism and other strategic behaviours that drive up the advance purchase precommitment price.

[240] All of this section is under *ceteris paribus* assumptions, since clearly the APC could be set so high that these problems become insignificant.

crowding out effect is worse if the APC concentrates incentives even more in a few large pharmaceuticals firms and leads to a tightening of IPR in ways that make research more difficult and expensive for small firms[241].

'Replacement effect crowding in' effect boosts the alternatives – especially the value of vaccine purchases

If there is a 'replacement effect', it is not clear why an APC would be preferred over alternative finance mechanisms that more directly tackle the 'replacement effect' – for example, mechanisms that feed finance more directly towards biotechs and not-for-profit firms, enabling them to take projects further without needing to rely on large pharmaceutical firms, and measures that generally create more of a competitive industry with ease of entry and greater numbers of firms, and an IPR system that better works to allow firms to freely acquire technology that might undermine those firms experiencing (and causing) a 'replacement effect'. If there is a 'replacement effect' at work, there is what might be termed a 'replacement effect' 'crowding-in' effect boosting the effectiveness of these alternatives[242].

It may be that this 'replacement effect' 'crowding-in' effect can even be boosted further. The flip-side to the notion that overall (expected, discounted) industry profits are lower if vaccines are developed in areas with large 'replacement effects', is that large institutions who might otherwise spend heavily on treatment programs, like the World Bank and the WHO, would be better off. That this fact does not automatically lead vaccine developers (and their financiers) to reason that it is in their interests to develop vaccines *even if* they replace treatments, is at least in some part down to the previous under-purchase and under-use of vaccines by such institutions[243]. It is sometimes claimed that the simple purchase of currently-available vaccines (and, indeed, acts that enable their usage) by these institutions has little effect on vaccine research incentives[244]. However, once the 'replacement effect' is recognized, the 'demonstration effect' of the purchase of current vaccines is stronger. Quite literally, the purchase of current vaccines in part unlocks the credit constraints (i.e. makes finance cheaper) of biotechs and not-for-profits, and others by 'demonstrating' that the 'replacement effect' is now weaker. This also indicates the possibility of a 'demonstration effect' caused by investments into healthcare infrastructure too[245]. With a 'replacement effect' present, a stimulus package including expenditure on previous vaccines and on

[241] Observe that this refers to the 'crowding out' effect, not the overall effect, of a dollar of government finance.

[242] Looked at another way, it is *cheaper* to use other modes of support targeted at small biotechs/not-for-profit, etc, since they do not have to contain this extra cost.

[243] This indicates that part of the problem may refer to the lack of healthcare infrastructure, and again emphasises one of the arguments of a previous paper (Farlow 2004) that the APC price would need to be set higher as much on account of the lack of infrastructure as on account of the 'lack of a market'. The hepatitis B vaccine and the Hib vaccine discussed above are cases in point. After 13 years of being largely unavailable, even though the hepatitis B vaccine is supposedly now generally available, 40% of children in Sub-Saharan Africa still do not receive it. After 11 years of being largely unavailable, Hib vaccine usage even when supposedly generally available is heavily skewed towards rich countries, with only tiny percentages of coverage in poor countries. Millions of children do not get a yellow fever vaccine costing cents to manufacture.

[244] Kremer, M. No. 10 Policy Unit, Appendix 7 page 46.

[245] The unwinding of the 'replacement effect' boosts the marginal impact of investment in infrastructure.

health infrastructure might have the added externality benefit of 'crowding in' some privately-financed vaccine R&D[246]. This stimulus package would be strengthened further if finance mechanisms were set to give differentially greater impact to biotechs, not-for-profits, and all those working on 'replacement' projects, rather than to those suffering from and, indeed, creating the 'replacement effect' in the first place.

Clearly, this would alter the APC cost-comparison figures too.

2.13. The 'Bunching' of HIV Drug and Vaccine Research

Resistance to HIV/AIDS *drugs* is an increasing concern. Correspondence on this issue in the CIPIH Open Discussion Forum points in the direction of lessons for vaccine research too, and also suggests we should reevaluate APCs in the light of this phenomenon.

Harvey Bale[247] drew attention to a recent article by Gottlieb[248], which contains the following passages:

> "*It is now clear that the virus, which mutates rapidly to evade our best drugs, may be gaining an advantage over the research community that's trying to fight it…Nearly 18 years after the first HIV drug hit the market, all of the 20 distinct medicines we have address the same three targets on the same two HIV genes. In fact, 11 of the 20 drugs target proteins that are coded for the same exact gene in HIV, called pol, making it easy for the virus to alter a single gene in its genetic code and to evade most of our best medicines.*
>
> *The good news: There are nine HIV genes in all, and only one – pol – has been thoroughly picked over. Two of the other nine genes, gag and eng, have been worked on some, but the other seven remain un-drugged, giving researchers plenty of completely new turf on which to work. These include the regulatory genes named tat, rev, nef and vpr, which are all thought to regulate the speed by which HIV is able to replicate itself, and the "accessory" genes vif and vpu, which are less well understood, but believed to control its ability to infect people.*
>
> *Most of this novel development work is going on inside a few dozen small biotech companies with hardly household names.*"
>
> "*But the collective work of biotechs, however, is still no substitute for the deep resources of the big drugmakers.*"

---

[246] It is not clear what the size of the effect might be, and the effect will be reduced somewhat by the fact that investment on vaccine R&D could well be a ten year plus program, followed by returns over a further ten years, with an average time to repayment of maybe fifteen years. And developers may still worry about the commitment of large institutions to such programs.

[247] 1 March 2005. Harvey Bale, Director General, IFPMA, Geneva.

248 Gottlieb, S., "Let The Market Find A Cure For AIDS" Forbes Adviser Soapbax, 1 March 2005, www.forbes.com/2005/03/01/cz_sg_0301soapbox_inl.html.

This repeats the logic that though small pharma/biotech research-driven organizations are often more productive at generating good drug/vaccine leads and clinical candidates, nevertheless, because they do not financially have 'deep pockets', incentives should target those who *do* have 'deep pockets'.

At least as striking is the observation that previous research strategies have culminated in a situation where it is "easy for the virus to alter a single gene in its genetic code and to evade most of our best medicines." This – in the context of a virus long known to be especially prone to mutation – should make us sit up. It both suggests past R&D failures, and future &D failures to be avoided.

Erickson corrected the Gottlieb reference to the pol gene:

> "*This is jargon, for which he (Gottlieb) may be unaware and innocent…The pol gene actually specifies three separate protein targets: protease, reverse transcriptase, and integrase.* ***The first two are the targets of all but one of the 20 FDA-approved HIV/AIDS drugs****. Merck had an integrase inhibitor in clinical trials but recently halted its development due to undisclosed animal toxicity. It claims it has a backup on its way into Phase I…A minority of potential drug targets have been successfully exploited by drug makers, but this is generally true of the entire pharma/biotech industry.* ***However, it is instructive to note the degree to which drug R&D groups all bunched together to go after the same few targets in HIV over the same time frame.***" (emphasise added) [249]

So nine genes in all for HIV/AIDS, and all but one of the 20 HIV/AIDS drugs rely on two of the three targets on just one gene. According to the models underlying APCs (the Appendix 3 model) this 'bunching' behavior does not happen. The probability structure is such that firms naturally 'spread out' and pick over different parts of the research space to maximise their individual chances of winning and the size of the expected win. In the process, this speeds up aggregate rates of vaccine development and (not modelled in the APC literature) it would also increase the average quality of vaccines, especially their ability to resist mutation. So, in the Appendix 3 case, just make the pot bigger for the current 'big drugmakers.

But the above passages suggest that the 'big drugmakers' 'bunch'in the same 'tried-and-trusted' areas. Is this a failure of public funders narrowing the field down too much? Or is it that such firms don't do what the models say they should do? If so, why so? Is it less risky for big players to 'bunch' than to 'spread'? Or is it a joint failure of public funders and private investors? And how does this help us to assess proposals for stimulating research into the 'non-tried-and-trusted' areas, especially if biotechs are not bunching even as the all the big players are? Why do biotechs not bunch so much but large pharmaceutical firms do? What does this say about who we should target with fresh resources, and how we should do it? Don't APCs just make this problem worse?

[249] 2 March 2005, CIPIH Forum. Such debates and correspondences between such a wide variety of interested parties demonstrates just how extraordinarily valuable the CIPIH Forum and the whole CIPIH endeavor has turned out to be.

Several hypothesis suggest themselves for this 'bunching', or herding, behaviour. It would be interesting to hear of others. No doubt there are plenty of possibilities, and several may be at work together. Importantly, different incentive mechanisms will impact on this differentially, and it is not clear that the APC mechanism is not the worst at tackling the problem.

2.13.1. Financial herding

Models of financial market herding suggest that it is better to be wrong collectively than to be right individualy. For example, when a stock market is in a bubble, those investors[250] who correctly assess this and try to break the bubble by 'selling the market short' will find – if other investors do not also do this, and therefore the bubble persists – that they have to make expensive margin calls. Given that they rely on other investors' money to try to arbitrage the bubble, they will 'look wrong' even if they are actually correct in their views, and will lose their sources of finance, business and market share. Even their jobs. In such situations it is easier to attract funds by going with the herd than by taking a contrary position. Similarly, for drugs and vaccines, the 'safer' strategy (for CEOs and stock market investors) may be to invest in something *similar* to other big players.

This may also suggest why smaller 'biotech' players feel less need to herd. They have no portfolio of other drugs that might be harmed by the fallout of 'looking wrong' compared to the herd, and it is more of a one-way bet for them; if they turn out right, they make a large gain (via stock options and other venture capital devices), but if they turn out wrong, the downside is capped by. Similarly, holding a diversified portfolio of smaller players enables this sort of risk-taking to be diversified by VCs and others.

2.13.2. Large firms have less incentive to target multiple leads

Is there something about being 'large', other than herding, that causes lower risk-taking? Why do large pharmaceutical firms not *collectively* diversify their vaccine leads more? Are there economies of scale to a firm in following similar leads? Or is it because there is an inherent bias towards fewer leads per large firm anyway thus generating a less diversified set of leads? In the Appendix 3 model, although there is constant reference to targetting a few very large firms, the model presumes perfect competition in the choice of research leads. Once this competition is missing, there is less incentive for individual firms to target multiple leads since each lead partly risks crowding out, in the expected value sense, other leads that that firm is persuing. Using instruments that tend to target a few large firms is less good than using instruments (and finance) that allows many more players to take part.

2.13.3. The downside consequences of integrating upstream R&D and downstream manufacture and marketing

Or does a business model based on the integration of upstream R&D with large downstream investment in manufacturing and marketing capabilitiy, simply mean

[250] Investors are financially constrained in that they use the money of others and cannot take on bets large enough relative to the market to cause correction on their own.

lower risk-taking? Does the need to find the revenues to support the complementary downstream operations lead to conservatice research strategies and an overreliance on production and marketing to the detriment of R&D? The literature suggests it does:

> *"Integration may reduce the innovative potential of the firm, because the acquisition of the complementary assets inevitably increases the size of firms and induces important changes in the culture of the firms and in the speed and fluidity of information flows."*[251]

Levinthal and March[252] note the way that organisations divide their attention between the pursuit of new knowledge, 'exploration', and the use and development of what is already known, 'expolitation'. In this context 'exploration' is similar to R&D, while 'exploitation' refers to downstream production and marketing. March[253] and Levinthal and March[254] show that while a blend of exploration and exploitation are desirable, the internal dynamics of large firms may lead to exploitation driving out exploration. Learning processes driven by experience – the typical case for manufacturing and marketing – tend to favour exploitation since exploitation generates clearer, earlier feedback.

> *"These dynamics are hard to resist in larger organizations. Large organizations are unable to provide the high-powered incentives for exploration…Large organizations can try to encourage exploration by forming and nurturing small sub-units that are isolated from the rest of the organization. "Corporate ventures", however, have inherent limitations…they tend to yield modest returns at best. In sum, there are reasons to believe that as a research-intensive company converts itself into an integrated firm, with in-house manufacturing and marketing units, its research productivity is likely to decline."*[255]

This contrasts sharply with the incentives of bankruptcy and stock options that small exploratory start-ups face. Stiglitz and Weiss[256] show how limited liability means that smaller organizations with fewer fixed assets at stake, will be more willing to undertake more risks.

This would suggest that sticking with the current industrial structure and concentrating on incentivising large pharmaceutical firms is misplaced. Industry consolidation has made the vaccine industry a subset of the pharmaceutical industry and it must now compete in that marketplace, even as it is impacted by some of the dis-incentivizing effects of that restructuring. It might, for example,

---

[251] Arora, A., Fosfuri, A., and Gambardella, A., "Markets for Technology and Corporate Strategy", Chapter 4 (p94) of "Economics, Law and Intellectual Property" Ed. Granstrand, O., kluwer Academic Publishers, 2003.
[252] Levinthal, D.A., and March, J.G. "The Myopia of Learning", Strategic Management Journal 1993, Vol. 14, pp95-112.
[253] March J.G., "Exploration and Exploitation in Organizational Learning", Organization Science 1991, Vol. 2, pp 71-87.
[254] Levinthal and March, ibid.
[255] Arora, A., et al ibid p94.
[256] Stiglitz, J.E., and Weiss, A., "Credit Rationaling in Markets with Imperfect Infromation", American Economic Review 1981, Vol 71(3) pp393-410.

be better to use financial instruments more targeted at start-ups, adopt IP systems that allow them to undermine large incumbent players, and give them better access (maybe via a processes of competitive bidding) to manufacturing facilities (for trial vaccines) that are independent of any large pharmaceutical firm, and enable emerging and developing country developers to have access to the same support. Besides, if marketing is not part of the deal with HIV/malaria vaccines, we gain none of the 'advantages' of using companies with a large element of that in their constitution, even as they (and we) suffer all of the drawbacks.

2.13.4. Patent stringing

If the reward to R&D is a patent of limited duration, then the build-up of resistance and eventual replacement of earlier drugs with later drugs is, perversly, more valuable than 'killing the golden goose' by building a more resistant drug from the start. As with the case (discussed in section 2.12) where vaccines replace more lucrative treatments, the interest here is not with the motives of pharmaceutical CEOs but with the financial, especially equity, market pressures, however worthy might CEOs personal motives be, and, indeed, however worthy the motives of investors in equity markets might be. So long as there will be more, later, resources to support later higher drug prices for a new round of patents, finacial markets may feed incentives to go for the efficatious short-run HIV drug than for the long-run once-for-ever drug, that 15 or so years later falls out of the patent system and becomes widely, and cheaply, generically available. If the needed drug is composite and requires firms to coordinate to create it, the incentives to do this are weak, and less-compostie drugs come out of the research process, but these eventually hit resistance and need yet more more less-composite drugs to replace them in due course.

This affects our interpretation of the APC when applied to vaccines. It might seem that the pecommitment 'pot' could be irrevocably capped, such that when it runs out, that 'would be it' for vaccine R&D, and maybe that this would prevent 'bunching' and the less-resistant products it generates. However, no particularly convincing reason is given for why the knowledge of this would enforce development of the globally 'best' vaccine or vaccines. This is perhaps also compounded by very high capital costs concatinating the horizons of players. If vaccines are developed under such an APC, is it really credible to suggest that once the funds are gone, no fresh funds will be made available to develop better vaccines?

If markets come to understand that an expansion of the 'pot' will be allowed, how can a limit on the size of the 'pot' (and expected decisions through a committee late in the process) be used to discipline behaviour towards 'high quality' vaccines early on in the process? Conversely, if the mechanism has failed to achieve the desired quality, then the uncertainty that the 'pot' will be expanded becomes a risk for researchers (especially those without 'deep pockets'). This generates the worst of both worlds; a 'pot' that is not strictly fixed, but the possibility of further funds being highly uncertain. This author has long argued that the fixity of the APC 'pot' is a mirage. The APC literature has never really explained how the 'pot' could be permanently fixed in such an environment, and yet the fixity of the size of the 'pot' is a hugely important part of the disciplinary workings of the mechanism.

2.13.5. The bunching of public funders

Are firms simply responding to public funders bunching *their* research? Indeed, there may be a common feature to any mechanism that tends to reward previous 'good result' in that it becomes slightly self-fulfilling at supplying rewards to only a limited part of the research space – that is the part that produced 'good' results in the past! If one thinks of this as a dynamic optimization problem[257] the dynamic path leading to the highest quality vaccine is not a priori clear from the start. If one simply always pick off the stretch that has proved quickest at any point in time, the path thereby taken may not be the most optimal overall if the true optimal path involved slow or expensive stretches at any point. Incentives that always reward vis a vis progress on the most recent part of the path, are rarely globally the most optimal. Do any of the current proposals for incentivizing R&D achieve better reward for risk-taking behavior, in the sense of a wider variety of research leads? Does this suggest more need for a strategic overview and 'control', even if this does not fit easily into the ideological framework of some, including those driving the APC?[258]

2.13.6. Patent fees

Since patents have more value the greater the number of potential users, does this tend to reinforce the problem, especially in the early days of a new research direction? If most other firms are working in one area – and, indeed with the growth of others 'piling in' to this area – does this mean that the potential fees from discoveries are higher? Is there a standard coordination breakdown? If others are not working in a neglected area of vaccine leads are there lower incentives to do so too, in complete contradiction to the APC models?

2.13.7. Relative versus absolute performance

If there is no way of measuring actual quality relative to some benchmark of overall *optimal potential* quality (before much of the information is revealed, this is very difficult to know in advance for vaccines), and if financial disbursements are made relative to other developers rather than relative to some overall possible benchmark, one can see that a firm's position relative to others is what matters and this might weaken the collective incentive to get nearer to the benchmark. How do APC payments not become a victim to this?

2.13.8. Secrecy and lack of openness

Does lack of openess and secrecy cause 'bunching'? In a world of asymmetric information, one can imagine models where it is easier to signal 'quality' and attract funds if one is working on areas in the core of the area of current active research than from working completely 'out on one's own'. Does lack of transparancy, paradoxically perhaps, make 'spreading out' more costly and difficult, maybe because it is very difficult to signal good performance? Would more transparancy help? How does this conflict with the APC notion of tight IP and secrecy?

---

[257] See Farlow, 2004, ibid. Chapter 6.

[258] Though, we already saw just how heavily controlling an advance purchase precommitment would turn out to be if fully enacted. The contrast seems to be between a system that has more 'control' at the end (advance purchase arrangements) and one with more 'control' en route (the Global HIV Vaccine Enterprise perhaps).

Similarly, does bunching lower the incentive to *share* information (since research is more substitutible when firms bunch)? Or is the causation the other way around? Would some regimine that rewarded firms for 'spreading out', paradoxically also feed higher incentives to share information? The notion being that the ability to profit from a discovery in a highly dispersed research exercise is more likely to need discoveries elsewhere (say to produce a composite vaccine); i.e. discoveries are more likely to generate complementarities. Conversely, does the relative lack of reward from sharing, and indeed *lack of a structure for sharing*, encourage 'bunching'? By concentrating on guidance through an end committee, APCs (at least as currently constituted) have little interest in creating structures for sharing information. There is a fundamental conflict between, on the one hand, the transparency needed to help prevent bunching and, on the other hand, the heavy use of equity finance and the lack of sharing of information needed to make the APC work.

2.13.9. Low levels of current funding

Do low levels of available finance, and short investment horizons, encourage bunching, in the sense that research strategies *have* to become much more risk averse? With limited funds, is it better to stand the chance of a medium quality result than gamble on a better quality result that may also mean no result? Would higher levels of funding weaken this tradeoff? Would an investor with a longer horizon be more inclined to search new areas where the early positive externalities are low? Instead of one very long (end-market-based) horizon such as that found in an APC, would (non-end-market based?) rewards linked to much shorter horizons be better?

2.13.10. Positive research externalities

Are the chances of discovery, given positive externalites to similar research, simply higher from all firms concentrating on one area of research over all other areas (certainly in the horizons of interest to firms)? By spreading limited resources over more areas, are some of these externalities lost? Is this another reason for expanding levels of funding?

In summary

Far too little attention is being paid to how the various R&D mechanisms – and APCs are no exception – create incentives to deal with long-term drug resistance and creation of quality over time. Past, and ongoing, experience should be more sobering. We find again that while equity finance has much to recommend itself as a method for driving pharmaceutical R&D incentives in a world of asymmetric information (Farlow 2004, Chapter 12), there are tradeoffs. Here, it is between the incentive effect of equity finance and – especially when it interacts with an industrial structure dominated by a few big players – the less positive side-effect of short-termism and herding.

2.13.11. Vaccines: More need for diversity

We see similar 'bunching' going on in HIV vaccine development. So far industry has tended to concentrate on those vaccines based on subtypes of HIV-1 found in developed countries. The idea is to prove the efficacy of the first vaccine, with the notion that others will be developed afterwards feeding off that knowledge.

"However, because numerous scientific uncertainties remain about the ultimate approach to HIV vaccine development, the simultaneous design and testing of multiple empirical approaches will be a faster route to safe, effective, and inexpensive vaccines that are appropriate for widespread use." [259]

One side-effect of this concentration on subtypes of HIV-1 is that it restricts the sites where vaccines can be tested in clinical trials.

2.14. Can a HIV Vaccine be Manufactured for Less Than $1 per Treatment?

We are told that: "Manufacturing costs will not be an issue with respect to a qualified product for so long as it is subject to the price guarantee."[260] This turns out to reflect a major flaw of the whole approach. In reality "it is difficult to predict which technologies will succeed and thus to anticipate the cost of production."[261] We have no figures, but let us say that some of the figures discussed above are remotely correct and that, in the best-case scenario, a vaccine costing $25[262] allows about $1-$2 to cover manufacturing and distribution. This is far more generous than some have hypothesized[263]. Can a HIV vaccine be manufactured and distributed (and, in the case of therapeutic vaccines, monitored too for many years perhaps) for $1-$2 a treatment? Or, more precisely, can developers *expect* this? The cost of the recent meningitis conjugate C vaccine was $21 a dose, subsequently falling to $12-18 a dose. What hope is there that a HIV vaccine (or malaria vaccine) could be manufactured for a tenth or a twentieth of that?

2.14.1. Some simple sums

Since we have no access to data, we can only entertain simple sums[264]. It might be thought that if a firm develops a vaccine that costs $10 per course to manufacture and distribute (i.e. it may take multiple doses to achieve one course), it would still be a good deal for the firm to take the $25 per treatment deal. $6.25bn minus $2.5bn (250million at $10 a course) is, after all, still a healthy-sounding $3.75bn, and this is far more than, say, the firm's $200m or so on private out-of-pocket research costs (and even better if half of that was subsidy) and more than what is needed to cover the firm's capital costs too[265]. But it should be obvious that this is the completely wrong decision problem to worry about. What matters is the way things look when investment is sunk, before *any* firms know who will be the 'winner'. At *that* point the expectations of a $10 per treatment cost will take $2.5bn out of the $6.25 value of the available fund. Even if the $6.25bn was set

[259] Berkeley, S., ibid p593.
[260] John Hurvitz Forum 16 December 2004.
[261] 'Making Markets' April 2005 p51.
[262] The interested reader will have to redo all of this in light of the $15 per treatment costs ($3bn for 200 million treatments) of the latest CGD briefing (or $4bn of the more recent Gordon Brown announcement). Clearly it makes the logic bite even more harshly.
[263] Kremer and Sachs talk of 'less than a dollar a dose,' www.malaria.org/news125.html.
[264] The author would gladly be challenged, if only to get some possible data out into the open.
[265] Clearly, it completely falls to bits if $3bn is fed into the calculations.

correctly to start with, this leaves far too little to motivate firms to bother investing in the first place. If firms responded regardless, they would end up collectively *subsidizing* HIV production to the tune of $2bn. More likely they would not invest ex ante. This is why it was pointed out repeatedly above that expectations about a whole range of issues, *including possible manufacturing costs*, matter.

Maybe the IAC will subsidize at $8-$9 per treatment to get around this problem? But we are told that the whole point in announcing in advance what will be spent on vaccines once they are developed is that it "does not call upon donors to spend more than they otherwise would; but it would increase the value of that spending"[266]. If large cash injections to get the vaccine manufactured are going to be needed, surely the lack of any ex ante credible commitment that *these* levels of funding will be forthcoming gets us back into the very problem we were trying to avoid in the first place (aggravated by the pot being lighter to the tune of $6.25bn)? And, besides, bailing out in this way wrecks the incentives to drive towards lower production costs. We pointed out above that the underlying modeling (Kremer Appendix 3) totally ignores the need for this incentive anyway, so perhaps we should not be too surprised that it now causes a problem.

However, this is probably a pointless discussion. The firm winning the $6.25bn APC will have only spent in present discounted terms a couple of hundred million dollars on-out-of pocket costs (if there was genuine competition). Its requests for multiple billion dollar top ups, even as it enjoys its $6.25bn, entirely fair 'winnings', would surely 'look greedy' and not be worth the PR damage. If firms understand ex ante that asking for 'top-ups' is not a viable proposition, they won't invest ex ante.

Other systems put much more emphasis on manufacturing and distribution
Under other, much more competitive, tender systems (discussed below) with more emphasis on manufacturing and distribution, there is more drive to lower manufacturing costs (there is some incentive here but it is much lower). Here, if a firm has invested and has a vaccine, then ex post it is rational to manufacture at $10 a course and take the $6.25bn. Contrary to the claim that "the contract is intended to give developers the incentive to create a low cost vaccine that meets the technical specification, if at all possible"[267] there is reduced incentive to push towards lower manufacturing and distribution costs, particularly if it risks delaying the payback with capital costs growing rapidly, or of ever being rewarded at all because of taking too long. Besides, since it is crucial to the APC having additionality that the one or two firms holding the key IP must keep a tight hold over it, the firm is only competing 'against itself' in this cost-cutting problem.

2.14.3. Lack of confidence in a low vaccine price undermines R&D

The paradox is that the knowledge that this will be the case, and that there will be little competition between manufacturers to drive prices lower at the

[266] 'Making Markets' march 2005 p38.
[267] Hurvitz Forum 16 December 2004.

manufacturing stage, will reinforce the notion that vaccines will *not* cost $1-$2 to manufacture and distribute, which undermines by backwards induction the incentive to engage in research in the first place. Indeed, we will repeatedly see in real case studies below that access to technology and know-how and competition between firms has often been very important in driving production costs lower and in enabling access to vaccines for poor countries. Work on some recent 'pull' mechanisms (for pneumococcus and rotavirus) is all about getting the costs of an expensive product down. It is puzzling that when looking at potentially very much more complicated vaccines with likely expensive production costs (at least for the first few hundred million batches and if the IP stays in the original developers' hands) there is not much more concern about production costs.

In the context of the GSK Biologicals malaria contract, John Hurvitz argues[268] that:

> "*If a developer produces a vaccine that is more expensive than $15 per course, they are unlikely to want to avail themselves of the AdvancedMarkets 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 AdvancedMarkets commitment makes them no worse off than they would be in the absence of the commitment.*"

Not only, according to the analysis above, should developers stop bothering *way before* it looks as if it will cost $15 per course, but this is a very puzzling statement in other ways. The bygones-are-bygones nature of R&D is such that even if the overall costs including R&D are greater than $15, firms will still avail themselves of the contract so long as *manufacturing costs* are below $15 and they have no more lucrative markets elsewhere[269], 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 contracts entertain the notion that manufacturing costs per course of treatment could ever be 30 to 50 times the winning firm's out-of-pocket R&D costs?

Given the claim that a vaccine would be "available to all eligible countries at affordable prices"[270] both during *and after* the APC allocation is used up, and also in countries *outside* of the mechanism (Russia, India, China for HIV perhaps?) while the mechanism is operating, a great deal more attention needs to be paid to the incentives to achieve affordable manufacturing prices, especially for very complicated and possibly composite vaccines such as HIV.

Incidentally, this is all pretty obvious logic. Yet, in all the bru-ha-ha about getting an HIV APC in place, and the suppression of proper debate, important details

---

[268] Hurvitz Forum 16 December 2004.

[269] This hints at the possibilities of perverse incentives. If a firm has a HIV vaccine that meets the program's requirements but for which there are more lucrative sales to be made elsewhere (at least in the early days and given low production capacity), there may be little incentive to drive the production costs below the program's price if it means the firm will look at if it is keeping an eligible vaccine out of the program.

[270] 'Making Markets' April 2005 p38.

about major problems like this that might undermine the whole initiative, don't seem to be of any interest. Like a whole range of issues it seems that the strategy is that it is best not to look too close. This author happens to think that having something that works is more important than having 'something'.

2.15. Problems with Long-Term Price and with Secure Long-Term Supply

The final CGD contracts call for determining, at the time of signing, the 'guaranteed' long-term near-marginal-cost-of-production price or an ex ante methodology for determining it, and for the obligation of a company to supply *at that price* in the long-term, in return for having had the short-term advantage of initial sales at high, heavily subsidized, guaranteed prices. This is described in the CGD report as a "critical component of the advance market commitment"[271]. If it were possible to make computation of such a price or to lay down a methodology for determining such a price, the report would have referred to a proven, transparent methodology. The CGD Working Group heard expert advice that production costs could range anywhere between $0.50 to $15.00 per course, depending on the manufacturing complexity of the vaccine discovered, and that no such guarantee could therefore be inserted into contracts – but this advice was ignored. Instead, this "critical component" is missing from both the report and from the contract term sheets.

The Working Group should have reviewed the extensive exploration of this issue undertaken by the NIH in the early 1990s, which concluded that it was extraordinarily difficult to compute or even lay out a methodology for computing the price of an unknown product, and that competition policy and commercial law may well preclude engaging in activity that could be seen as price fixing and/or a subsidy to a favored firm.

A mechanism that relies on this presumption holding in order for it to work and in order to secure long-term vaccine supply, should be treated with a great deal of caution, indeed skepticism – even more so when one sees that the CGD contract term sheets have also left blank those sections specifying remedies in the event of a breach of this condition.

The risk is that all the sponsor's funding is absorbed by the first developer and the long-term low price is not achieved, or even that the long-term 'eligible' market is abandoned in preference for serving a more valuable 'non-eligible' market. Crucially, the design of the CGD model precludes competition among different suppliers to develop more efficient production methods and lower vaccine prices to poor nations, as happened in case of the Hepatitis B, as a back-up for any failure to supply the vaccine. Thus the central goal of an AMC to buy out an effective vaccine so that it becomes available thereafter at a low price cannot be achieved by the route suggested in the CGD report.

Furthermore, the contracts call for a supplier to turn over its IP for the market covered by the program (not the outside non-covered markets) to the sponsor if

[271] 'Making Markets' April 2005 p47.

the supplier "prefers" to abandon the 'eligible' market in the long-term. However, this does not take into account that the supplier may not have the right to sublicense all the IP it has obtained by license or that the production of a vaccine is as much, or more, a matter of know-how than of access to patented technologies. Similarly, it is not clear that the threat means a great deal given the lack of capacity, and the 5-7 years it might take to build this up. Alternative capacity could hardly be built up in advance of confiscation! Short of taking over the physical production facility of the IP holder and, somehow, forcing know-how out of the IP holder, the IP holder might argue that the outside markets are just as important as the inside market and are needed to recoup their R&D costs (in the ex ante sense) and refuse to hand capacity and know-how over. One can see the IP holders' ex ante dilemma too; they may not particularly wish to face this strategic situation ex post, and this may color their ex ante decision to invest at all[272].

Such threats are, therefore, not credible ways to discipline suppliers. It risks severe supply shortages and damaging delays in access to vaccines; and the very knowledge that such threats might actually be used would undermine incentives to invest in both vaccine R&D and vaccine delivery systems in the first place. The strategy also creates a huge range of conflicts and of further supply problems given that the supplier nevertheless retains IP rights to 'non-eligible' markets. Consideration of "other penalties"[273] is suggested in the contract term sheets attached to the CGD report. However, other than unspecified "liquidated damages provisions"[274], the details are left blank. Such "damages provisions" themselves inflict disincentives on firms to carry out R&D – even more so if the provisions are as vague as they are here. This author was advised by legal experts that including threats at 20 year horizons would be unrealistic and is simply not normally done.

IP and know-how barriers have been principal causes of delays in achieving flexible, cost-effective manufacturing and in getting vaccines to poor countries quickly in the past. Yet this practical issue is not addressed in the report either. All the emphasis is put on getting the $3bn to the supplier of the first 200m 'eligible' treatments. Long-term price, and indeed secure long-term supply of these vaccines, is thus left totally unresolved.

2.16. PPPs, IAVI, the Global HIV Vaccine Enterprise, and Advance Purchase Commitments: An Awkward Fit?

Since all *other* mechanisms for incentivizing the development of vaccines have been stripped out of the key APC models (Kremer Appendix 3), it is, so far, unclear how such commitments, and the new institutions built around them, will fit alongside other research support institutions such as PPPs, IAVI, the Global HIV Vaccine Enterprise, and other publicly-funded and foundation-funded bodies. A core part of an APC for HIV (at least, as modeled so far) is the way the

[272] A similar situation faces IAVI. If manufacturers contracted by IAVI do no provide the eventual successful vaccine in 'reasonable quantities at reasonable cost' (cost plus 'reasonable profit') to the public sectors in developing countries, then IAVI reserves the right to transfer production of its vaccine to another manufacturer.
[273] 'Making Markets' April 2005 p109.
[274] 'Making Markets' April 2005 p109.

HIV vaccine IP is structured. All IP ownership goes to the 'winning' vaccine developer[275] during the period of the first several hundred million high-price vaccine treatments, the follow-on period of lower-price vaccine treatments to those countries covered by the mechanism[276], and for *all* sales to *all* markets not covered by the commitment (possibly including Russia, China, India, etc.) for the full duration of monopoly patent rights for the vaccine. PPPs on the other hand tend to work on the basis of more of the IP rights being in shared ownership with the public and foundation sectors, and more firms with access to the IP. IAVI uses 'social venture capital'; instead of asking for return in terms of profit or intellectual property, 'return' is measured in terms of access of the poor to the product.

This all shows up in prices. In seeking to create access, APCs generate a very high price on the first few hundred million treatments in the eligible market (paid for by the sponsors of the mechanism), high prices in non-eligible markets till expiration of the IP, and (supposedly) low prices in eligible markets after the first few hundred million doses are gone (or no vaccines if this portion of the market is relinquished). PPPs and IAVI seek to achieve access to poor consumers (including in markets that may not be covered by APCs) through lower vaccine prices from the start.

How do PPPs and IAVI sacrifice *their* objectives in order to make room for APCs? Or, don't they? If not, then what does the (complicated) IP regime look like? How is it enforced? Is it predictable how IP owners will be treated and how much investors should therefore invest? What if markets that are not covered by the APC are nevertheless covered by PPPs (either current ones or future ones) or IAVI? How is the clash in such cases between the IP system underlying the APC (and high prices) and that underlying the PPPs and IAVI (and low prices) resolved? What if the commitment concentrates IP in one set of hands, and the PPP/IAVI route dictates IP spread into more hands along with technology transfer to emerging vaccine developers? If MVI or IAVI creates a vaccine, what if it wants to allow its IP to be freely transferred and used by emerging manufacturers? Again, where does legal jurisdiction lie in all of this?

What if PPPs are more efficient?

Matters get more complicated once one recognizes that PPPs or IAVI might turn out to be the more efficient approaches. Why should PPPs concede space to let the APC run its IP and pricing schemes in order to help it enforce itself, if the APC is proving to be the less efficient approach, and may even not be working? We remember that PPPs should be barred from taking APC payments since this would crowd out, that is 'spoil', the value of the APC for those private investors relying on the latter mechanism. It might be said that PPPs, if more efficient, *should* be allowed to crowd out less efficient approaches. However we must remember that the commitment is still locked in place, and PPPs are constrained in their access to funds compared to the level of funds needed. So, if it is understood that crowding out will be tolerated, the overall level of funds active in

[275] Or, more precisely, is split in a complicated fashion across 'winning' developers as described in section 2.3 above.

[276] That is if the vaccine developer does not simply relinquish these sales and concentrate on more profitable segments elsewhere, especially if the developer is capacity constrained.

vaccine research will be too low, yet the commitment can still be activated to take the IP, and therefore be a threat to the PPP.

How do the chances of this 'crowding out' not self-inflict the collapse on the APC in the first place or leave it as an expensive liability that is doing very little positive even if it is doing plenty that is negative? For the sake of 'credibility' and to prevent this self-fulfilling collapse, would irrevocable rules be set in stone to protect the APC for its full duration (30 + years)? How will the dilemma – of tight precommitted rules restricting PPPs and others in order to enforce an APC outcome, but the reality of a bad outcome – be viewed in policy circles in later years? How bad does the bad outcome have to be before abandoning the tight rules and reneging (given the litigation costs of doing so) on the APC?

Can PPPs really be excluded anyway? Or is there some sort of mechanism for feeding recipients of APCs through PPPs first and thus controlling some of their IP rights? But how does that alter the distinctiveness of the APC mechanism given the claim of leading advocates that such mechanisms are far superior to any alternatives? And what does it do to the clarity of the investment signals supposedly being generated by the APC?

Furthermore, if, in contrast to the original analysis of leading advocates, an APC is only *part* of an overall solution – say, in the case of a HIV vaccine, covering the last 10% or so of effort leading to a vaccine – why is the APC mechanism modeled as giving *all* of the IP rights as reward to the firm doing the last steps? In more realistic models, how is IP and the reward 'split' across all developers if the reward system is imposed on top of a complex playing field of PPP and other IP rights-holders? How does the APC begin to attempt any of the post-development adjustments and redistributions of the 'pot', as described above, that it would have to be capable of doing in order to enforce 'quality'? How would private investors know what was going on and how much to optimally invest in such a mixed system given such a messy pattern of IP? How would they be certain of 'fair treatment'? How is all this interaction monitored?

More reputation risk

If an HIV APC is reward for only that last few percent of the overall effort – with tens of billions of dollars of prior public and foundation funds sunk in vaccine R&D – why should the firm get all the vaccine IP rights to non-eligible markets such as India, Russia, and China anyway? What if those countries feel this is an outrage given the role of (and their part in, and funding for) the Global HIV Vaccine Enterprise? And how do those bearing all the risks at earlier stages of innovation get repaid? If the 'winning' firm represents only one of 20 firms[277] working on late parts of the innovation process, will they wish to be seen to be getting 100% of the IP for 1% of the overall effort *even if* this is the correct risk-adjusted reward viewed from an ex ante perspective? Remember that before they invest, firms adjudicate that they have only, say, a one in twenty chance of getting the commitment. So the expected value of the $6.25 billion is actually very low, and it is *this low figure*, and *not* the $6.25bn itself, that has to be assessed against

[277] It is repeatedly argued here that this is not the likely to be the case, but this paragraph shows that *even if it is the case* the news is not good for individual firms.

the PR consequences of winning. From an ex ante investment perspective, firms can easily be tipped into preferring a strategy, such as PPPs, that is much less risky for their long term reputation and their PR profile.

Problems in coexistence

If instead of accounting for the last 10% or so of the overall effort, what happens if the 10% represents *some* vaccines generated under an APC with others generated under a (mostly) PPP framework? Are the latter developers barred from markets 'meant' for the former developers? How does this aggravate the incentives of both groups of developers? If HIV vaccines prove cross-reactive, will the relevant parts of the IP of vaccines covered by an APC still be freely available to those working on other vaccines and under other mechanisms, including PPPs? Or will those IP rights 'reach through' to other vaccines and to other mechanisms? What are the implications of this for incentives (and the institutions) to create those other vaccines? What complicated web of IP rights and institutional arrangements, lack of transparency and poor investment signals, comes out of the attempt to make the various mechanisms coexist? How do they coexist?

We observe that removing all other funding mechanisms and IP schemes from all the APC modeling (Kremer Appendix 3 in particular), strips out an awful lot of knotty and interesting problems in practical applications. We need to know answers to all these practical issues before imposing new institutions on top of those currently active in stimulating vaccine R&D.

2.17. The Role of Developing Country Recipients

The CGD Working Group did not seek out the perspectives of countries that are supposed to benefit and implement the program. Neither do the current contractual arrangements include them as signatories. These countries would make their 'commitments' to the program, via purchases, only after a vaccine is cleared by the committee, and they would pay only about 10% of the initial procurement price. Such an arrangement provides them, in essence, with a veto over the success of the APC. Their small, marginal, contributions would be essential to make the whole program, involving billions of dollars, work, and therefore they could use their position to achieve additional benefits. In return, the supplier (or the supplier's country) would come to realize the value of rent-seeking behavior and of 'subsidies' to developing countries – in whatever forms those 'subsidies' might take – targeted at winning the $13.50 per-treatment subsidy on the first small tranche of treatments (if priced at $15 per treatment as most recently suggested). The system of long-term multi-institution and multi-country monitoring and policing of such behavior does not bear thinking about, even if investors would need to be reassured in advance that such monitoring and policing would actually take place. Farlow 2004 Chapter 7 looks at the issues in much more detail.

Meanwhile, 'non-eligible' countries, even if still very poor, pay much higher prices for much longer. Neither were the views of these countries especially sought.

2.18. The Problems of Vaccine Delivery

Huge practical difficulties beset the delivery of vaccines to millions of people in developing countries. Field reports to the Bill and Melinda Gates Foundation and others detail problems of organization, qualified personnel, political interests, cultural barriers, and knock-on costs. Tackling these practical difficulties is not taken up in the CGD report. Nor is the knowledge of such problems, and lessons from past delays, used in the report to help design more realistic, practical APCs that would help recipient countries to actually deliver vaccines. Indeed, many of these grave practical difficulties are deliberately fed back on to vaccine developers through the payment mechanism proposed in the CGD report. The Working Group did not contain a single person with hands-on practical experience in delivering vaccines in developing countries.

2.19. Liability Risk

Any program involving billions of dollars, large organizations, global institutions, and medical technologies must apportion and deal clearly and effectively with issues of liability risk from the start. The final CGD report calls for the sponsor(s) to fully "indemnify the members of the Committee for claims and losses arising out of the performance of their duties"[278] – even though the sponsor(s) lose all control over their funding to a committee with wide discretion – and then for the eventual designated supplier to "defend and indemnify"[279] the sponsor and members of the committee. The former is impossible to imagine; what firm would want the PR disaster of suing the World Bank, the Gates Foundation, or a PPP? The proposal with respect to the supplier is not an impossible requirement to fulfill, although it does mean that only the world's largest companies will be able to participate in the program.

Failure to contractually cover liability risk has doomed previous such proposals and indeed is an important component of private sector worries about investing in early-stage vaccines, such as those for HIV, malaria, and tuberculosis. The report even recognizes this in the case of Project Bioshield, a project that no longer treats liability risk in the fashion that the CGD report now proposes should be applied to developers of HIV, malaria, and tuberculosis vaccines.

Sponsors of any proposed APC also have a responsibility to undertake 'due diligence' to check if the proposed mechanisms are economically valid for the types of candidate vaccines they target and if they are in fact likely to have the claimed effects. If the APC collapses through no fault of those firms taking part in it but because of the negligene of those setting it up, the sponsors would have some obligation for the losses.

It is hard to imagine – supposedly in order to achieve 'credibility' of the program – that sponsors, especially foundations and their legal advisors, would permanently relinquish key decisions to a committee with wide discretion, fail to work out the exact legal status of these new institutions alongside already existing

[278] 'Making Markets' April 2005 p92.
[279] 'Making Markets' April 2005 p108

institutions, and yet leave the issue of liability risk entirely unresolved. The contract term sheets leave all these issues blank.

Since the final CGD report was released this attitude seems to have been modified somewhat, and issues of liability risk have been separated out, in discussion at least, from the actual APC itself. It will be interesting to see how this develops.

2.20. The Terms are Set by 'Rule of Thumb'

In truth, terms would be based on information provided by large pharmaceutical firms themselves or highly contentious data. Indeed, chapter nine of 'Strong Medicine' and the HIV and malaria figures being produced by the Center for Global Development do just this, based on data that has nothing to do with the vaccines at hand. Kremer himself admits elsewhere that the figures are based on "rule of thumb"[280], and Kremer and Glennerster observe that we should not "attach even a moderate degree of precision"[281] to their own figures (though they do not use the same language to discuss the relative cost-effectiveness material they once generated to compare mechanisms – that relies on the same figures – most of which has since been quietly buried[282]). The No. 10 Policy Unit website states: "There is a lack of clear evidence of the size of market needed to incentivize R&D. Estimates range between an annual market size of $100 million and $500 million (real terms) per product."[283] These hugely important caveats are omitted from the recent material and from all policy discussion. These, nevertheless, are the figures used to persuade policy-makers to set up HIV and malaria APCs. Repeatedly above we saw the importance of getting the size and terms right for efficiency to be achieved. Yet, it does not matter how sophisticated a framework is (though this one is *not* so in practice), if it has no reliable data on which to base itself, how can a claim to superior efficiency over other approaches be sustained?

This "rule of thumb" approach even applied to the recent GSK Biologicals announcement. Discussion involving a billion added or taken away here and there generated a politically acceptable figure. An outside observer might think that if there was any scientific basis to the calculations, a billion dollars here or there might matter, and that the ability to drop a billion dollars just to make the deal more politically palatable might suggest that there was no particular scientific basis to the deal in the first place. The eventual $3bn in the CGD report has since been described as purely illustrative…

This 'rule of thumb' approach is becoming ever more bizarrely core to recent policy pronouncements. We know that the APC for an HIV vaccine should be linked to the underlying costs and difficulties of developing such a vaccine (after

[280] Kremer, New Vaccine Markets II: Design Issues, NBER, Innovation Policy and the Economy, Vol.1. p76 and p94, also www.pm.gov.uk/files/pdf/Appendix%207.pdf, p 76 and p 94.
[281] http://www.pm.gov.uk/files/pdf/Appendix%204.pdf, "A Vaccine Purchase Commitment: Preliminary Cost-Effectiveness Estimates and Pricing", Kremer and Glennerster, p 17.
[282] Generating, whilst en route, such lines as "Our quantitative analysis suggests that an APC is the most cost-effective means of encouraging the development of new health products." www.number-10.gov.uk/su/health/06/default.htm.
[283] www.number-10.gov.uk/su/health/06/default.htm.

all, the winner of the contract gets to keep an awful lot of valuable IP, and they should be paying for it by paying the expected R&D costs of generating it) and yet the size of the HIV APC has been allowed to fall precipitously (to $3bn in recent pronouncements) since it was first announced, and now bears absolutely no correlation (it never did) with any obvious level of underlying R&D costs for developing a HIV vaccine.

Since most of the evidence presented in favour of APCs for early-stage vaccines, compared to alternatives, is based on the hopelessness of other mechanisms at discovering information, it is a paradox that so many parts of *this* mechanism then require so much front-loaded information and monitoring in order to set the mechanism even vaguely efficiently. Then we discover that even the information being used to set them does not have "even a moderate degree of precision," and is "rule of thumb" itself anyway.

2.21. The Failures of Command and Control

Despite its rhetoric of "making markets", the suggested CGD program has all the hallmarks of failed command and control mechanisms. Rather than being 'market-driven', the program is 'committee-driven', and should not be graced with language that suggests otherwise. The CGD report discusses the great difficulty of monitoring the performance of the program – particularly with respect to early development – in the absence of periodic reporting by developers over very long stretches of time. However, this heavy dependence on monitoring, evaluating, and approving activities creates clear incentives to distort evidence and to corrupt the decision-making process, and it seems somewhat ironic given that one of the initial arguments made in support of APCs over alternatives was that APCs would avoid many of these interventions.

The report proposes reliance on a potentially very small committee making critical decisions at a few key points in time, with the opportunity for large mistakes. Indeed, it is suggested that important decisions about specifications and eligibility of vaccines be taken out of the hands of the sponsors themselves and put into the hands of as few as two or three individuals[284]. An alternative approach that spreads power and decision-making through time and puts decisions into more hands in a more democratic process would allow for more checks and balances, and for greater chances for mistakes to be discovered and averaged out. Giving to a few members of an already small committee the power to make or break an expensive research strategy is a big risk to many firms – especially if such firms are unable to influence the committee.

Such top-down, committee-driven, approaches are incapable of the subtle, complex, adaptive adjustments required for developing vaccines for HIV, malaria, and tuberculosis. Past experience teaches us that such highly-centralized, and heavily-discretionary, systems do not incentivize private efforts, and would work against private competition to produce a diverse range of vaccines, which improve over time.

284

The report also concedes that "it would be extremely costly"[285] to create a committee that was fully capable of doing all that would be required of it, and hence allows the committee to rely on third parties, such as the WHO and its procedures. Yet, it is not clear why the WHO or others, including PPPs, would perform such acts and yet relinquish all decision-making power, with all of its consequences for liability, to such a committee. And it is not clear why there is need for yet more layers of committees and decision-makers with potential conflicts of responsibility and consequentially complicated IP, institutional, and legal tangles of unclear jurisdiction.

2.20. Let's Not "Just Try It"

Given these many layers of unexplored and unquantified inefficiency, and potential dangers, it is very irresponsible to argue that, since the social value of vaccines *themselves* is so very high, our attitude should be "Let's just try it!"[286], and that we should just throw everything at a particular mechanism and just "see what happens". Unfortunately, the excessive costs of developing a vaccine for one disease show up in the loss of new vaccines and drugs and treatment programs (and clean water and housing and education, etc.[287]) that then cannot be afforded[288]. In the context of an International Financing Facility, IFF, these excessive costs show up as large commitments for the IFF to deal with at later times just as the IFF may be winding down and being repaid. Given that the IFF already has plenty of risks of its own to contend with, it is not clear that it should be burdened with a pile more. This "let's just try it" attitude would be especially dangerous if a particular APC for one of the vaccines being targeted turned out to be a great deal more expensive than initially thought (and indeed initially pitched) and also imposed extra research costs on other drug and vaccine projects or was even damaging to that vaccine itself.

The funds going into the research and development of many early-stage vaccines may be desperately short of what is needed, but this is no excuse for desperate, and ignorant, calls to throw huge sums of money into a mechanism without first checking that it will work and not just generate waste and hidden dangers.

---

[285] 'Making Markets' April 2005 p95.
[286] Pierre Chirac, Nature 2004;431:629-630.
[287] And the deadweight loss of all the needed tax revenues, and the loss of foundation-funded projects elsewhere.
[288] Go to www.cambridge.org/uk/economics/globalcrises for some notion of the competition for resources.

PART 3. THE VALUE OF LATE-STAGE VACCINE COMMITMENTS AND OF CURRENT PURCHASES

By concentrating so heavily on early-stage vaccines and the notion that APCs are the main driving force for their development[289], the danger with 'Making Markets' and 'Strong Medicine', is that the proverbial baby gets thoroughly lost in the bathwater. This is unfortunate since many of the problems and extra costs listed above fall – in many cases quite dramatically – as the mechanism concentrates on access to already available vaccines and the development of late-stage vaccines – such as some of those currently being worked on by CGD, including pneumococcus and rotavirus[290]. There are various reasons why late-stage purchase commitments might be useful instruments, even if a mechanism might not be based on such instruments as the principle driving force for complicated early-stage vaccine R&D, and vaccine prices need not cover large proportions of the total development and finance costs of such vaccines. Even late-stage vaccines create extreme challenges for purchase commitments, and in some cases it may not be clear what the exact form should take. The following section hopes to offer some pointers.

3.1. Lessons from Past Slow Vaccine Introductions

3.1.1. Hepatitis B

The first Hepatitis B vaccine[291] was developed in the 1970s at the New York Blood Center in New York City (based on research done at the US National Institutes of Health in the 1960s) under the direction of Dr. Alfred Prince and Dr. Barry Blumberg using the plasma from infected individuals. Merck & Co. was the first to commercially produce the plasma-derived hepatitis B vaccine, followed by companies in France, several institutes in China (with technology through the WHO and the Kitasato Institute in Japan) and two companies in Korea (Cheil Sugar Co. and Korea Green Cross Co.). The Cheil technology was obtained from Dr. Prince and the Green Cross Technology from an expatriate Korean living in Canada.

---

[289] Recently, there has been some back-tracking on this. In early December, reading all the promotional material for 'Strong Medicine', describing the "simple solution" within (www.pupress.princeton.edu/titles/7830.html), a solution "that has been so desperately lacking" (www.cid.harvard.edu/books/kremer04_strongmedicine.html), and listening to UK Treasury announcements, the distinct impression created was that APCs were '*the* answer' and 'just what was needed' to tackle the lack of an HIV vaccine. Recent announcements, thank goodness, have been more realistic and much more accepting of the overall collaborative approach required: "I also see an enormous opportunity for pushing forward the initiative to create a worldwide infrastructure – or platform – for sharing and coordinating research in AIDS, and then for encouraging the development of viable drugs. But it is generally recognized that the sums of money required involve at least a doubling of research money for AIDS", Gordan Brown, Council on Foreign Relations, New York, December 17, 2004.

[290] These kill 1.1 million, and 0.8 million a year each.

[291] This section draws heavily from 'Public-Private Partnership in the Development of Hepatitis B Vaccine in Korea' Mahoney, R.T. in "Science, Technology and Society" Vol. 10 No. 1, April 2005. I also thank Professor Richard Mahoney for giving me an insider account of what happened in the Hepatitis B case. See also 'Making Markets' penultimate draft version p105. This was removed in the final version.

Reasons for limited use
However, there was only limited use of this vaccine – in Europe and the United States and also in Taiwan, China, and Korea – for several reasons.

First, and most importantly, policymakers were simply unaware of the true extent of disease caused by the hepatitis B virus and there were problems in creating a case for vaccines in vaccine programs. For example, in several Asian countries, it had been shown that the leading cause of death among adult males was liver cancer caused by hepatitis B virus but this was not widely known. As information became more widely available, support for hepatitis B programs grew:

> "*With hepatitis B, the long period between prevention of infection and the improved health outcome*[292] *still made cost-effectiveness studies of this intervention difficult to conduct and interpret. Furthermore, the notion of vaccinating an infant to prevent an adult disease proved difficult for some agencies, such as UNICEF, to accept*."[293]

Second, the price of the vaccine was high. Initially, it was $54 per three-dose course plus the cost of the visits to the physician.

Third, plasma derived hepatitis B vaccine was derived from human blood, just at the time when concern about injecting anything derived from human blood was at its height because of the HIV crisis (it turned out that plasma-derived hepatitis B vaccine is an extremely safe product and that this risk was unfounded).

A new form of hepatitis B vaccine
In the mid-1980s a new form of hepatitis B vaccine was developed using recombinant DNA technologies[294] that was just as effective as the plasma-derived vaccine. Initially it was produced by three international companies: Merck, SmithKline, and Pasteur. Pasteur abandoned the marketplace because its production methodology used E. coli cells and proved inefficient. Merck and SmithKline used yeast cells and improved the efficiency of production. However the cost of their vaccine remained very high and was unaffordable to developing countries. The cost of the plasma derived hepatitis B vaccine produced in China was low, however most developing countries were reluctant to import because there were not adequate national regulatory control systems in China to guarantee the safety and efficacy of the product.

The approach taken
In the late 1980s, James Maynard, Alfred Prince, and Richard Mahoney formed the International Task Force on Hepatitis B Immunization with funding from the Rockefeller Foundation and the James S. McDonnell Foundation. The first priority was to lower the cost of plasma derived hepatitis B vaccine, mostly by bulk purchasing it for use in developing countries. In the first purchase this

[292] The real burden of hepatitis B is in chronic liver disease and liver cancer in later life.
[293] Mulholland, E.K., and Bjorvatin, B., 'The Vaccine Book' ibid., p392.
[294] A gene for the hepatitis B surface antigen is inserted into the chromosome of yeast cells which then subsequently synthesize the surface antigen. The surface antigen was purified from the fermentation mixture, and it provided an excellent vaccine.

bought the cost down to less than $1 per dose, with two manufacturers offering at this price, the Korean companies Cheil and Green Cross. This was part of a global strategy by the Task Force[295] with five key elements:

i) Defining the burden of disease and computing cost effectiveness;
ii) Conducting demonstration programs in developing countries, to show that the product could be integrated into immunization programs, to prove that "demand could exist at the right price." This created the incentive to create supply at that price;
iii) Building global and national consensus for use of the vaccine;
iv) Stimulating competition among manufacturers to reduce prices;
v) Stimulating the creation of international procurement funds for vaccine purchase.

Three Korean vaccine manufacturing companies – Cheil, Green Cross, and LG Chem – spotted the large international marketplace for hepatitis B vaccine and set about developing the new recombinant DNA hepatitis B vaccine. LG Chem and Korea Green Cross were successful in different ways. LG Chem decided to establish its own in-house R&D program to develop the vaccine from scratch. Green Cross obtained patented technology from a European biotech company, Rhein Biotech of Germany, who took a controlling interest in Green Cross.

In the late 1990s, the Bill and Melinda Gates Foundation made a contribution of $750 million to establish the Global Fund for Children's Vaccines, with a substantial amount of these funds set aside for the purchase of hepatitis B vaccine. With this level of funding, the Fund was able to procure recombinant hepatitis B vaccine at less than 25 cents per dose, a price considered almost impossible even a few years earlier. It was known that plasma derived hepatitis B vaccine could be produced at this price but it was not certain that the same applied to recombinant DNA vaccines.

From the mid 1980s to the mid-1990s, Merck and SmithKline were the world's largest producers and distributors of recombinant DNA hepatitis B vaccine. Mahoney argues[296] that though there was concern that Merck and SmithKline held important intellectual property rights which might have blocked other companies from marketing, and that neither Merck nor SmithKline were interested in supplying low-cost hepatitis B vaccine for use in developing countries, neither of these concerns seems to have been justified. Both LG Chem and Korea Green Cross developed their vaccines without infringing the patent rights of Merck and SmithKline (though they could not market in the United States and Europe for fear of infringing patents). And, in the late 1980s, SmithKline had committed itself to sales of the recombinant hepatitis B vaccine for about $1 per dose given sufficient procurement quantities.

Key ingredients
The key ingredients to innovation of the cheaper product were:

[295] Mahoney, R. and J. Maynard (1999). 'The Introduction of New Vaccines into Developing Countries'. *Vaccine* 17, No. 7-8, 646-52.
[296] Mahoney ibid.

i) The creation of a market by the funding from the Bill and Melinda Gates Foundation, enabling manufacturers large enough quantities to offer low enough prices;
ii) The upgrading of the Korean food and drug administration (KFDA) under the aegis of the Korean government and the World Health Organization;
iii) The design, execution, and evaluation of high quality clinical trials. The fact that the Korean manufacturers could provide these data greatly facilitated the acceptance of these vaccines in developing countries.

India and other developing countries such as Brazil and Cuba have emulated the success of Korean manufacturers in producing rDNA hepatitis B vaccine, even further helping to drive down prices. By 2000 more than 100 countries had introduced hepatitis B, mumps, and rubella vaccines into their routine infant immunization programs.

If a program such as that currently being proposed for HIV, malaria, and tuberculosis had been in place for the development of the hepatitis B vaccine, it would have led to the payment of $3 billion to one or two developed country producers who are not today major suppliers of hepatitis B vaccine for developing countries. Such a program would certainly not have been favorable for China, India, and Korea, who are today's suppliers. The hepatitis B case was included in draft versions of the CGD report but was removed in the final report perhaps because, as a case-study, it shows that the original vaccine developers were not the ones who developed and maintained the lower price market, and because the competitive situation for hepatitis B today – a key component in achieving long-term sustainable low prices and secure supply – reflects poorly on the non-competitive model being put forward in current proposals.

3.1.2. Haemophilus influenzae type B (Hib)

There has been a highly-effective Hib vaccine since the late 1980s used widely in developed countries, but largely unused in the developing world, where half a million children die every year from lower respiratory tract infections caused by Hib. As with HepB, cost is cited as a factor, even at just $2 per three-dose schedule. This is far below those charged in developed countries, but at prices higher than traditional products at $0.05-$0.15/dose.

Another factor holding back usage was the lack of conviction on the part of developing countries that there was a problem, since Hib-related pneumonia is observationally equivalent to other forms of pneumonia. The first efforts therefore were to demonstrate that there was in fact a problem. Use was also hampered by various other barriers including: "weak delivery systems, inadequate national disease burden data, and the unwillingness of governments and donors to increase investments in immunization"[297]. More recently GAVI set itself the target of vaccinating 50% of high-burden, low-income countries by 2005.

[297] Batson, A. 'The Vaccine Book', ibid. p350.

3.1.3. Smallpox

We can go even further back in history to look at previous examples of slowness of vaccine introduction. After development of a cowpox-derived vaccine, smallpox transmission was greatly reduced in Europe after WWI and virtually eradicated in Europe and North America after WWII. However, it continued to ravage populations in the developing world because of the much greater difficulty (and costs) of keeping the vaccine viable in field settings, something only resolved with the development of a stable, freeze-dried vaccine. Then it took from 1950 until 1967 to eradicate smallpox in the western hemisphere (with the exception of Brazil). In 1958 the World Health Assembly resolved global eradication, but nothing happened until 1967 when the WHA infused huge resources into the initiative. Ten years later eradication was achieved and in May 1980 the world was declared smallpox free: "The huge operational obstacles that were overcome to achieve the eradication goal cannot be overstated – mostly related to management, supervision, reaching displaced or mobile populations, cultural beliefs, vaccine shortages, and insufficient funds."[298]

In the 20th century alone, smallpox killed more than 300 million people, more than three times the number killed in all of that century's wars, and many times the 22 million who have died from AIDS so far. This is not a story about incentives to create vaccines in the first place, but much more about their production and use once they had been derived.

3.2. Recent Purchase Arrangements

There are not many cases of the use of purchase commitments (let alone advance purchase precommitments) and even those there are, don't remotely match anything described in Part 2 above. Nor do any of the products begin to match HIV or malaria vaccines in the extreme challenges that they pose.

3.2.1. African trivalent meningitis vaccine

One recent 'successful' late-stage vaccine purchase commitment is the WHO/MSF/GSK Biologicals commitment which helped to spur development of GSK's trivalent meningitis vaccine (African A, C, W135 strain). But this is also a perfect example of our lopsided attitude to vaccines (hence the quote marks)[299].

Until recently, African meningitis outbreaks were mostly caused by the A strain. Untreated it kills about half who get it[300] and leaves others suffering long-term neurological damage such as deafness or mental retardation. But in 2002, the W135 strain of *Neisseria meningitidis* infected 13,000 people and killed over 1,500 in Burkina Faso. The WHO, the affected African countries, and non-governmental organizations such as MSF mounted an international response. Traditional vaccines used in Africa thus far had only included the A and C strains. At US$4.50 per dose depending on where it is sold, the existing quadrivalent

[298] Birmingham, M., and Stein, C., "The Vaccine Book" Chapter 1.
[299] See e.g. www.accessmed-msf.org/campaign/men01.shtm.
[300] When diagnosed early and treated with appropriate drugs (such as oily chlorampenicol or ceftriaxone) the fatality rate remains at 5-10%.

vaccine (A, C, Y and W135) was deemed unaffordable for most African countries.

After months of WHO-led negotiations, GlaxoSmithKline Biologicals agreed to develop and license a new, trivalent (A C W135) vaccine for use in the 2003 epidemic season through the International Coordinating Group (ICG) on meningitis vaccine provision. Delivered in record time, the first round of production was largely funded by the Bill and Melinda Gates Foundation. Two million doses of the new vaccine were used in Burkina Faso for epidemic control in 2003.

By mid-2003 six million doses were agreed at one euro per dose, a price low enough for most African governments. MSF has committed to purchasing one million doses of the vaccine itself, and some funding is available from the ICG from previous years. However, donor countries have not responded to an emergency appeal launched by the World Health Organization (WHO). The UK government has donated £1million (approximately 1.7 million euros) and the Norwegian government has financed some 200,000 doses, but a funding gap of approximately 2 million euros remains for the target of 6 million doses estimated as needed for the short term. Despite promises by the European Union and agencies such as UNICEF, the epidemic response may still fall short of cash and there might be a shortage of vaccine if a large-scale epidemic occurs.

The enthusiastic response to multi-billion dollar largely ineffectual APCs for dim-and-distant vaccines contrasts sharply with the hopelessness in providing even the few hundreds of thousands of euros needed for this already existent trivalent meningitis vaccine, at what the developers themseves describe as a 'symbolic' price[301].

3.2.2. Meningitis conjugate C

Another recent 'success' is the quasi APC for a meningitis conjugate C vaccine. 'Quasi' since there was no signed contract, but an initial tender followed by verbal senior-level commitments. Along with trial support and expedited regulatory reviews, this led to several firms producing a vaccine that was subsequently purchased by the UK government. All those firms who took part in the bidding process got something out of the Meningitis conjugate C process. This is in complete contrast to the strict 'Making Markets' interpretation for HIV or malaria, which in effect has many firms (supposedly) sinking resources in the bid process (the Framework Agreement) but very few, if any, getting anything.

The sums involved are also much smaller than recent proposals; the initial 18 million doses (split three ways) of meningitis conjugate C vaccine were priced at $21 a dose, making a total of $378m. Capital costs were not the majority of the payments. The science was already there. All companies who accepted the initial tender produced a viable vaccine, suggesting no major gamble on the science. There were no problems (or, ex ante, likely problems) with later developers generating products so much better than the first products – such that the first products might have to be discontinued, as would happen with HIV/malaria

[301] www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379.

vaccines –, nor any problems with the need to create incentives to generate follow-on innovation. Subsequent tenders have still generated prices of $12-18 a dose, something probably unmanageable for an HIV vaccine.

3.3. Some Lessons: What Purchase Commitments Can and Cannot Do

We can learn lessons about purchase commitments and contracting generally from these cases.

3.3.1. None of these matches the mechanism proposed for HIV, malaria or TB

The most obvious first observation is that none of these cases even remotely matches the model for an APC for HIV and malaria as described in Parts 1 and 2 above. Many of the above cases describe vaccines that already existed, and the problem for them was underuse and not the incentives to do the original development, and in many cases the real breakthrough was achieving lower production costs. One, amongst many, keys to achieving low production costs and wide use was the creation of large procurement funds.

In the case of Hib, it was not 'lack of a market' leading to too little early-stage vaccine development, but a mixture of high dose cost and lack of decent diagnosis and problems with demand prediction and access of an already existing vaccine. Indeed, the Hib vaccine was developed, according to Kremer and Glennerster, "without any expectation of realizing substantial profits in poor countries."[302] The crucial requirement was creating incentive to improve production costs of the vaccine once it existed, and there, for sure, large sources of procurement funds – along with competition between suppliers – were important. Early-stage APCs along the lines of 'Strong Medicine' have nothing to say about this. In fact they would have got in the way.

Then there is a range of vaccines in need of R&D funding, at one end of which we find cases, including several above, that are helped by a commitment, and at the other extreme end of which we find HIV, malaria, and tuberculosis.

Indeed, in the cases above (and in upcoming purchases under the IFFIm), we have tested none of the underlying principles of such an APC model and have learnt next to nothing about its practical operation even for much more basic vaccines. For example, what if the 'Framework-Agreement-as-tender' approach can't be made to work and has to be abandoned? Would this not be better to do before, rather than after, initiating an HIV APC? What if lack of competition (indeed the expectation of low competition) in later stages undermines creation of cheaply manufactured vaccines, and manufacturing costs are expected to 'eat up' too much of any 'pot' of funds, and firms therefore lose the incentive to do R&D? What if capital costs are too high? Given the role of credibility, what if the mechanism cannot be constantly changed as faults become clearer because it destroys credibility and inflicts too much risk on developers? Or, will the mechanism have to stay the way it was set up (to avoid litigation) however

[302] 'Strong Medicine' p74.

inefficiently it may turn out to have been set up? Is the latter situation just as bad for credibility? With no data on performance, terms have to be set on the basis of a set of hoped-for relationships. Is this the right way to set such terms?

3.3.2. Current short-run contracts are inefficient: A stable market matters

It really is quite ridiculous that UNICEF and other organizations be constrained in their ability to sign multi-year purchase agreements simply because their funding streams are usually only guaranteed annually. It makes sense to either amend the rules governing UNICEF so that it can enter into long-term contracts, or look for new financing mechanisms such as underwriting agreements or promissory notes to help overcome the constraint, or, indeed large injections of fresh cash such as those announced recently by the Bill and Melinda Gates Foundation and the UK government. It is clear that unnecessary delay in access to already existing vaccines due to supply or demand creation was, and is, unacceptable in these cases. But none of this is about APCs like those being proposed for HIV and malaria.

With lack of reliable and predictable demand, the potential revenue stream is unpredictable and it is difficult to correlate production plans with effective disease burden estimation. Long-run contracts ensure long-run sustainability both for countries and donors. Both supplier and demander can be made better off than with a system based on short-run contracts. With lower uncertainty on both sides, overall potential profits and revenue are greater, so the seller is potentially better off. But the buyer is better off too since the number of immunizations is greater at lower average cost.

Observe how the benefit of this ‘certainty’ is ‘fungible’, and equally beneficial *whatever* the source of funding for the original vaccine R&D and for purchases. There is none of the ‘crowding out’ and lack of additionality described above.

3.3.3. Removal of market risk

Most of these practical cases indicate that vaccines can be in existence and yet there are a wealth of distribution and delivery problems that hold back their usage. Major access failures happened that were totally separate from the R&D problem. Clearly some kind of commitment to purchase (maybe via tender-based systems) is valuable in terms of ensuring access, even if not driving much earlier periods of R&D. The ‘Strong Medicine’ and ‘Making Markets’ proposal puts *all* of the emphasis on creating a large pot of funds to entice large pharmaceutical firms. There is no reference to this wealth of other practical problems that would need to be tackled once a vaccine existed, and, indeed during its development. There is no reference to a potentially much stronger commitment to ‘Advance Distribution’ contracts. Worse, the proposal even suggests that developers should be responsible for overcoming such practical problems. For example, in the case of HIV and malaria, the mechanism, in order to supposedly incentivize ‘quality’ (though we found that it struggled to do so), forces most of this risk of distribution and weak delivery systems back on to the developers.

Industry concern about the market risk of advance purchase commitments

Indeed, industry representatives have expressed grave concerns over the operation of advanced purchase schemes of the sort described in part 2 above because, in its bias towards creating large pots of funds – probably because of the motives of most of those framing the thinking – to entice large pharmaceutical firms, they fail to tackle these problems:

> "*Weaknesses in the current system of procurement and delivery of vaccines for the developing world are a major deterrent to investment. Most firms supplying developing country markets through public procurement are frustrated with inefficiencies in the current system – the lack of long-term credible contracts, unreliable demand forecasts, under-use of existing vaccines – and this reality colors their view of future promises from the public sector. The public sector can improve its credibility by increasing use of existing products and by improving demand forecasts.*"[303]

It seems highly ironic that late-stage vaccine purchase commitments are totally about removing such market risks, only for early-stage APCs to work them in as a key driving force.

3.3.4. Commitments are coordination devices

Countries can add to their immunization schemes since they know they will be affordable in the long-run and they will not have to reverse programs later. Such commitments, especially 'advance distribution' commitments, are also *coordination devices* helping to overcome "the uncertainty about the willingness or ability of governments to buy and deliver medicines through less advanced health systems"[304]. The value of a vaccine's development is lower the less likely it is that there will be vaccination infrastructure to use it. At the same time the investment in the vaccination infrastructure may be lower if those carrying out such investment (both privately- and publicly-funded) feel that investment in vaccine development and manufacture is low. In the case of HIV, coordination of these two activities would also include better demand forecasting[305], accelerated approval, and studies of the impact of, for example, an AIDS vaccine in varied epidemiological and country settings. Reduction of this uncertainty would help not just manufacturers but also low-income countries who would be more able to add vaccines to their immunization programs if they could be sure of reliable access.

3.3.5. The Importance of manufacturing scale and of low product prices, and the dangers of *not* supplying the 'eligible' market first

The short-run nature of many of the current contracts for vaccine purchases for low- and middle-income countries creates unnecessary uncertainty that shows up in vaccine shortages, unused capacity, and higher than necessary prices. The lack

[303] Trevor Jones, Forum 29 November 2004.
[304] 'Making Markets' March 2005 p20.
[305] Better demand forecasting alone removes significant, and totally unnecessary, risk to all sides involved in both vaccine development and use, whatever the source of funding. See, for example, the Accelerated Development and Introduction Plans (ADIPs) for Pneumococcus and Rotavirus vaccines.

of procurement funds to buy vaccines, the lack of infrastructure, and the lack of disease burden surveillance means that production capacity is not large enough and scale economies cannot operate. Manufacturers demand higher price from smaller production runs and have difficulty in scaling up later. Bulk purchasing is a traditional and highly effective way to overcome some of these issues.

In truth there are as many, if not more, issues *after* R&D of the initial vaccine product. Product price is still very important, even more so are *incentives* to improve the technology of production, to make the vaccine easier and cheaper to manufacture, and to cheapen the product price. The WHO/UNICEF/World Bank study "State of the World's Vaccines and Immunization"[306] worried that "new life-saving vaccines have become available – at prices that most low-income countries could not afford," not that such vaccines were not "becoming available." One reason that the Hepatitis B vaccine was not perceived at the start as viable was the very high price. From 1981 to 1987 there were no viable courses of vaccine for under $50-$60. The current pneumococcal vaccines are still way too expensive for most developing country settings. There is little point in engaging in the sunk cost of setting up immunization programs at such high prices.

Part of the Hepatitis B problem was the nature of IP ownership and control, and the location of manufacturing. Key to the Hepatitis B success was the creation of low-cost production in emerging economies, using a finance tool suited to that environment, and access to underlying technology for those wishing to mount a bid. Clearly, "means will need to be found, within the patent system and outside it, to generate the competitive environment that will help offset the adverse price effect of patents on developing countries"[307]. Tightening patents and concentrating manufacturing into the 'big' players, creates way too little of this much-needed competition.

Price is still a big barrier

One of the more surprising lines CGD lines is that "price has continued to be a major barrier to the introduction of Hepatitis B vaccine in the developing world (even as low of $0.30 per dose for the monovalent vaccine, it was 3-5 times more expensive than older vaccines)" (bracketed terms in the original, though the passage was removed from the final report). As of 2001, still more than 60% of the world's children were not getting the vaccine. Nevertheless, if even at prices as low as $0.30 this was deemed a "major barrier", especially to the very poor; it suggests that even practically given-away vaccines may not be taken up due to the large costs of usage that politicians and health systems may struggle to muster in very resource-poor settings. If developers of HIV vaccines are supposed to be paid "according to demand" this would seem to indicate that even at very low prices, developers would, ex ante, expect still to face a great deal of market risk, and this would have to reflect in the APC price. In the case of smallpox for example, a commitment of funds to roll out vaccine programs would obviously have been useful, but that the "huge operational obstacles" described above should have been placed on the heads of developers via the 'reward' structure is

[306] 'State of the World's Vaccines and Immunization', a joint report by WHO (World Health Organization), UNICEF, (United Nations Children's Fund) and the World Bank, 2002.
[307] The CIPR report p38.

much less obvious (and that's why R&D wasn't done that way). The "according to demand" thinking in the CGD report illustrates the limited mind-set of the framers of such proposals; developing country markets are deemed much the same as rich economy markets – just without the money.

Competition to drive production costs lower

Incentives to improve technology are to be found *nowhere* in the APC literature (they are stripped out of the Appendix 3 model for example). The current 'Making Markets' and 'Strong Medicine' proposal for early-stage vaccines does not even put any importance on the nature of competition at the manufacturing end of the process to drive prices down, and yet it presumes that HIV vaccines will cost (or, rather, be *expected* to cost) as little as $1-$2 per course of treatment to manufacture and distribute (and even monitor in the case of therapeutic vaccines). In the practical cases above, many of the advantages were driven by ccompetition at a very late stage of development and manufacture and via the use of competitive tendering, and the ability to switch technology from high to low cost producers. In the case of Hepatitis B, for example, bids that were perfectly profitable for the firms making them were as low as a dollar or less per dose. And we will shortly see that a large part of the rotavirus APC will be about getting manufacturing costs down. Yet, one of the prices of using APCs for *early-stage* vaccines is tight control over IP and know-how in a few hands and much less competition at late stages – and a paradox we described above where this is ex post optimal given the mechanism, but not ex ante optimal, thus undermining the mechanism from the start. It is not clear that this is a price worth paying.

A dangerous incentive *not* to supply the 'eligible' market first

If production costs cannot come in low enough, it might turn out to even make sense for firms to supply the non-eligible markets first before seeking the eligible market. This would be especially so for HIV vacines. Indeed, this is part of the general problem we discussed earlier caused by the fact that an APC has an 'option value' such that the commitment might motivate research even if those relying on the purchase commitment for their vaccines either do not get vaccines, or are not the first to get vaccines, or get them with delay.[308] The interaction of this problem with the problems of creating low enough production costs for developing economies needs to be explored further, especially for HIV[309], but also for TB and malaria. One possible scenario might be that there is an HIV vaccine, but it is much more profitable (given capacity constraints and production prices) to supply rich markets first at a price higher than the APC price, but there is no incentive to license and encourage competition to drive production costs down for the poor markets earlier rather than later (the APC mechanism has no

[308] See Farlow, 2004, ibid. Section 7.16.1. This argument was accepted as valid and a serious problem in private conversations with some of those heavily involved in the pull research agenda, but nothing has been done since. The only interpretation I can put on this is that like so many other parts of the advance purchase proposal for early-stage vaccines, it is deemed better to ignore knotty practical problems for fear of drawing too much attention to them and weakening the proposal in the eyes of politicians. But, instigating mechanisms still replete with hidden dangers is hardly a sensible way to enact practical policy.

[309] The option value is more valuable for HIV. Given the more widespread nature of malaria than was once believed (it is not just an African problem) this option logic would apply to malaria too, but may be less so than for HIV. The problem is that we simply do not know, since analysis of this, just like every other problem, is completely suppressed.

independent rights over the IP since the IP has been 'paid for' by private finance and the firm can choose not to use the APC mechanism).

If current production costs are greater than the APC price, why should firms be bound to the APC mechanism or denied it later? Could they be forced to push production costs down to get under the bar and *have to* supply the poor eligible markets? Or should they have their technology voluntarily licensed to dozens of firms to push the price down? Would not the APC, especially the IP aspects of it, not forbid this anyway? Or, having spent 'only' $200m or so on out of pocket research costs[310], could the firm hold up the culmination of a research process that has cost many times that? Would this (even just the expectation of it) not destroy this and other APCs? None of this is explored in 'Making Markets'. Farlow 2004 Chapter 10 explores some industrial organization aspects to the problem, and the concern that other developers may still be dissuaded from investing further in vaccines even as the first vaccine picks off the richer market first, and the poorer market later.

It is all because the Framework Agreement *is the tender*

This is all because the HIV Framework Agreement "is the tender". Competition is not 'real' between firms like a normal tender. Instead, ex ante competition is controlled ex post through a committee, the IAC, based on whatever information it can garner from firms. Worse, it is controlled in the 'virtual reality' of the *expectations* 10-20 years out of this ex post control. We find the notion that this can be done is an unproven and dubious claim. It's main fault is that unlike a traditional tender, all the faults of the tender mechanism (and of the IAC) and the layers of 'mechanism risk' created, are passed through to vaccine developers, to funders, and thence to taxpayers and foundations. To the extent that these risks are high (they are not in the case of late-stage vaccines, but they *are* very high for early-stage vaccines) it becomes very risky for firms to use such a tender, and a very expensive way to discipline behavior. In particular, the levels of sunk cost being risked on the workings of a mechanism and a committee at a far-off future period are far greater for a currently-set HIV APC than in any of the examples above.

One of the reasons that the recently announced Bill and Melinda Gates Foundation and UK government finance can potentially impact health through vaccines is because of pressures driving production costs down. It would be ironic to use these successes to argue for an approach that would have undermined this success had it been in place. And ironic given that such 'purchases' had always been regarded as one of the least credible ways to generate fresh R&D by those most pushing HIV APCs!

3.3.6. Access to technology, patents, 'know-how', and TRIPS

Since low-cost technology and competition from multiple potential vaccine manufacturers were major factors in price and hence access, easy (even free) access to some of the underlying technology, know-how and patents, and imaginative and creative IP management were key to this. One of the costs of using an APC for early-stage vaccines is the loss of IP. This may turn out to be a

[310] To repeat, this is just a rough illustrative figure.

high price to pay once the practicalities of production and access are fully considered.

In many of the cases above, issues surrounding patents were an important part of the delay, and indeed their relaxation or creative management a part of the solution. Traditionally, we have had to wait for patents to expire before other vaccine manufacturers have been free to produce vaccines without payment of royalties. Over time this leads to competition. In the meantime, millions of childrens' lives have been lost in developing countries, where governments are unable to afford the new vaccines until the price is reduced, 10-20 years later. Incidentally, given the rate of discounting, these sales 10-20 years out have practically no incentive effect on vaccine development.

In the cases of the practical 'purchase commitments'[311] described above, most of the IP issues were just 'end-point' issues anyway (that is the way they are modeled in Kremer Appendix 3 too), with relatively few problems modeled (or even considered likely) at intervening stages. Issues of highly-collaborative research and development did not arise. Being workable on such vaccine problems suggests nothing about the workability of APCs along the lines of 'Making Markets' for complicated vaccines such as those for HIV that require much more collaborative research. It would be ironic if patent failures in the past were rewarded with even higher patent failures in the future via aggravating these collaborative approaches.

Competitive tender-driven manufacturing contracts require fair access by competing manufacturers and 'potential' competitors to the underlying technology, and, especially in the case of vaccines, to know-how. An APC, of the sort suggested in 'Making Markets' and 'Strong Medicine', would rely on heavily-enforced patents and monopoly control over vaccine know-how. The Term Sheet for Guaranty Agreement (in Appendix C of 'Making Markets') specifies that: "The Designated Supplier shall own all right, title and interest in and to the Approved Vaccine,"[312] even, it would seem, if most of the cost of developing the vaccine had been borne publicly and via vaccine enterprises, and even by countries (including, perhaps, Russia, China, and Latin American countries) that then find themselves classed as non-eligible countries with respect to the vaccine now totally owned by the 'winning' developer.

The Hepatitis B case shows the importance of competition. How easy, for example, will it be to mount sealed bid tenders of the sort undertaken by the Hepatitis B Task Force in any APC HIV vaccine market, if there are very few suppliers and monopoly rights over important parts of the technology and know-how? Post TRIPS, this is already a much-weakened mechanism as it is. Will it be made even more difficult?

Technology and 'know-how' transfer

It is not clear what these cases say about the likelihood that patent-holding OECD companies would, under large-value APCs, allow technological transfer to

[311] In quotes since we have never had a pure APC or precommitment yet.
[312] 'Making Markets' April 2005 p108.

developing country emerging manufacturers so that they could grow and become competitors to OECD companies. This needs more exploration. One possibility might be voluntary licensing, but licensing is inherently less competitive than market competition. Licensing is a managed relationship between licensor and licensee. As Garrison points out, Cipla would not have been able to offer the sorts of massive price reductions we have seen for antiretroviral drugs had Cipla simply been a licensee of GSK, and Cheil or Korean Green Cross could not have offered similarly huge price reductions had they simply been licensees of Merck. This does not mean that all countries should have their own manufacturing capacity[313]. The key is to encourage international competition, and not to lock in an industrial structure but to allow it to evolve.

Incidentally, it is not clear to what degree the 'Making Markets' approach might be possible anyway, since such intellectual property rights are granted by sovereign governments and can only be protected or voided in the courts of sovereign governments[314]. The IAC would need to come with an international treaty attached wherein the member countries agreed to pass over to the IAC their sovereignty with respect to patents. How likely is this?

Neither is it clear what would happen if the inventor (say funded by a foundation or governments) of one vaccine chose not to overly-tightly enforce patent protection in various countries of interest (maybe to speed up dissemination and production capacity along the lines of the Hepatitis B case above). Incidentally, there are potentially profitable strategic reasons for doing this as well as philanthropic reasons, so we cannot even rule it out by some of the private players. It would totally mess up the workings for those relying on the APC, but should it be banned from the start? In order to make a high IP dependent mechanism work, should those who wish to share their discoveries for free or at very low costs be barred from doing so?

The dominant role of the IAC

Clearly, too, the IAC has such a dominant role – in place of traditional competition – that less 'powerful' developers must surely worry about capture of the IAC, especially as the days of hugely valuable decisions (15 to 20 years after investment was sunk) draw near. To the extent this worry is held *now*, the structure of the vaccine industry will fail to expand as hoped. In none of the practical cases above was control over the structure of the industry such an important issue. Though many of these issues are irrelevant to the main

[313] For some sense of the debate with respect to medicines, see "Is Local Production of Pharmaceuticals a Way to Improve Pharmaceutical Access in Developing and Transitional Countries? Setting a Research Agenda", Kaplan, Laing, Waning, Levison & Foster, Boston University School of Health, available at: www.worldbank.org/hnp/hsd/documents/LOCALPRODUCTION.pdf. This argues that for medicines there is no reason per se to produce medicines domestically since it makes it much more difficult to achieve economies of scale, though it also stresses potential data limitations underlying this finding and other positive side effects of domestic production. For vaccines, scale is probably more important, suggesting that international competition with rapid distribution of products is more viable than technology transfer to all affected countries.

[314] See Richard Mahoney Forum 21 December 2004.

protagonists of HIV APCs, who visualize all of the R&D being done in the current few large firms anyway.[315]

TRIPS

The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) will apply to all countries that are members of the World Trade Organization. In terms of vaccine development a particularly pertinent feature is that developing countries will have to recognize product patents as well as process patents, making it much more difficult for developing countries to reverse engineer products that are first developed in wealthy countries and then to produce those products by different processes[316]. It is already the case that large developed economy pharmaceutical firms will be able to obtain product patents in a great many countries, thus reducing the number of countries in which emerging market developers are able to market a similar product. It is not immediately obvious that, instead of more innovative finance directed at emerging market vaccine developers, a large early-stage APC, together with the financial advantages of 'deep pocket' pharmaceutical companies, and the new uses of tighter IPR, will not instead disincentivize these emerging developers.

3.3.7. Support to biotechs and developing country developers

We saw in several places above (but also in Farlow 2004, especially Chapters 10, 11, and 12) that 'Making Market'-style early-stage APCs tend to reinforce the financial problems of firms who are already struggling in their access to finance and tend to benefit those with already strong access to financial flows, whether they respond to the APC or not.

> "*Daunting new hurdles are being erected. Will the increasing difficulties of vaccine development, the increasing costs of obtaining regulatory approval, and the new system of international IP represent insuperable barriers to biotechnology innovation for developing countries? Will these countries primarily be licensees of developed country pharmaceutical companies and serve the role solely of toll manufacturers for the license owners? Or will the new regulatory and IP systems spur government investment in R&D and the formation of international joint ventures that will lead to heightened levels of national biotechnology innovation in developing countries?*"[317]

One of the arguments of the current paper is that we should not approach the issue of creating finance for vaccine development without first considering the *types* of players who will relatively benefit the most from the mechanisms chosen and how these mechanisms might interact with other parts of the overall bundle of problems that are creating hurdles for developing and emerging economy vaccine developers.

---

[315] As Kremer (Appendix 1 p9) put it: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more."

[316] Scherer, F.M. and J. Watal ,2002, ibid. pp. 913-39. A recent case going through is India.

[317] Garrison. C. "Background paper for WHO workshop Intellectual Property Rights and Vaccines in Developing countries," Geneva 19th-20th April 2004.

3.3.8. PPPs, not-for-profit firms, government, institutional and regulatory issues

The hepatitis B case involved multiple layers of institutional involvement including the original initiative of a non-profit organization, PATH, and its donors to launch a global effort to accelerate the introduction of hepatitis B vaccine into developing countries, the support of the Korean government for a first-class Food and Drug Administration, the interest and ability of international organizations such as the WHO to work with the Korean government to upgrade its FDA, and a combination of private and public sector effort. This case shows that emerging and developing countries can play a critical role in developing health products for the poor, but the importance of financial instruments that work in their favour rather than financial instruments with an emphasis on the big players.

Many agencies are involved in efforts to generate new vaccines, including the Global Alliance for Tuberculosis Drug Development (GATB), the International AIDS Vaccine Initiative (IAVI), the International Vaccine Institute (IVI), and the Malaria Vaccine Initiative (MVI) of the Program for the Appropriate Technology in Health (PATH). These organizations are already facing a series of challenges including R&D management, IPR management, regulatory considerations, access to manufacturing facilities, and many others (see Kettler, et al. 2003[318]). It is not immediately clear that these sorts of organizations are particularly helped by an APC promised for 15-20 years' time.

Regulation

The increasingly higher regulatory hurdles that are being developed by agencies such as United States FDA are tending to lead to a worldwide increase in regulatory standards and greater burdens in terms of both the financial and human resources needed to create a sufficiently capable clinical research capacity. In combination with increased IP protection this is central to understanding the future of vaccine research and development[319]. In this context large scale early-stage APCs have very different consequences to the instruments described in later parts of this paper.

3.3.9. The importance of incentives to install capacity quickly and for use quickly

In the most successful breakthroughs in demand creation above, the time between capacity creation and capacity utilization was relatively short, and utilization was almost totally certain. In the time-frame of interest, the *net* present value of revenue streams was much greater than it would have been with a much longer time-frame such as for HIV.

Neither was their much investment in capacity that stood a high chance of never being used because of a replacement vaccine coming along, for example to

[318] Kettler H., K. White, and S. Jordon S, 2003, 'Valuing industry contributions to public-private partnerships for health product development'. The Initiative on Public-Private Partnerships for Health, Global Forum for Health Research. http://www.ippph.org. Geneva. http://www.globalforumhealth.org/filesupld/valuing.pdf.

[319] Mahoney, R., A. Pablos-Mendez, and S. Ramachandran, 2004, 'The introduction of new vaccines into developing countries III: the role of intellectual property'. "Vaccine". Vol. 22/5-6 pp. 786-92.

replace the meningitis conjugate C vaccine (all three 'winning' firms got something and went on to tender for more of the same vaccine). We discussed HIV cases earlier where capacity for complicated vaccines may need to be put in place even if not used because it is replaced.

In none of the practical cases above is there commitment to purchase if a better product comes along after the first vaccine is developed, but neither was this much of a risk to firms in these cases. The ability to 'target' higher quality is much greater in all of the practical cases above than for complicated (and potentially 'only' therapeutic in some cases) vaccines such as HIV/malaria, and the costs and risks of doing so are much lower. One of the key differences is the use of the 'Framework Agreement' and ex ante perceived decisions of an IAC to drive quality. None of the practical cases faced this.

In all these practical cases supply and demand were created near simultaneously. In contrast, in an APC for an HIV vaccine, most of the 'demand creation' happens, supposedly, long after much of the R&D costs have been sunk. This affects, to a much higher degree than in any of these practical cases, assessment of credibility, and, hence, ultimately the cost-effectiveness of the mechanism.

3.3.10. Product differentiation and vaccine market distortions

Many of these purchase commitment mechanisms are, in a sense, about creating product differentiation of drugs and vaccines, most of the science for which is already known. The WHO/MSF/GSK trivalent meningitis vaccine (African A, C, W135 strain) above is a case in point. The end product in this case was extremely cheap and therefore more accessible to these markets. Compared to a HIV vaccine, very little market uncertainty or developmental capital costs were absorbed in the product price. Similarly, the Hepatitis B vaccine already existed, so contracts were not about high levels of sunk R&D costs, covering large levels of capital costs going back ten or twenty years with huge risks from the science and the cost of the mechanisms all needing to be incorporated into the price. The fact that all three developers in the meningitis conjugate C case managed to develop a product demonstrates that, relatively speaking, the science was hugely more simple than it would be in the case of HIV.

A number of features, especially in the US, have been pushing in the direction of higher vaccine production costs, and these too can also be partly offset, as part of a package of measures, by purchase commitments. First, more stringent regulation. Second, new techniques – including complex conjugate procedures, purification, and aseptic filling without preservatives – that require expensive equipment that adds greatly to the difficulty and cost of production, while also reducing the potential for economies of scale. Third, the banning of thimerosal in the United States. This is a mercury-based preservative that enabled multiple dose vials. Its removal forced US manufacturers to supply the US market with more expensive single-dose vials. Since developing countries feed off the same sources of vaccines, their costs have been rising heavily too[320]. Fourth, at the same time

[320] The economic logic goes as follows: Drugs are used on sick US children. Some side-effects are tolerated. Vaccines are used on healthy US children. Tiny probabilities of severe reactions lead to multi-billion dollar litigation. Developing country children are much more likely to die anyway without the vaccine. The tiny probability bad event is swamped by the lives saved (and they don't

there is a growing divergence between the sorts of vaccine products demanded in the industrialized world and those demanded in the developing world. The emphasis in developing countries is on "heat stability, safety and affordability" while in developing countries it is "absolute risk free vaccines at almost any cost". Developing countries can no longer rely on the residual supply from developed markets, at tiered prices (though we have also seen the lack of tiered prices often in reality).

Of course, these are all arguments as much for creating better access to alternative forms of finance – including front-loaded finance – for other vaccine developers and manufacturers, as they are for large APCs in the hands of a few industrialized nation manufacturers. Some forms of purchase promise also sit perfectly happily in a framework that incorporates the new public sector institutions described by some as providing vaccine development and production skills in cases where the private sector will not or cannot provide the necessary skills (perhaps because of the high opportunity cost), even if such promises are not being set massively high in the hope of generating incentives way back in the R&D process.

3.3.11. Competitive tenders and accurate information discovery

Not only is continuous competition and reward more possible, but also price is relatively easy to set in most of these cases (compared to HIV, malaria and TB), the more so the more late-stage the case. Everything in the Hepatitis B case was done through competitive tender and – with plenty of competition (10 companies) – this was capable of revealing very accurately the underlying production costs without the need for heroic assumptions 10 or 20 years in advance. The 'Making Markets' alternative to these tenders as a way for extracting information, is to monitor everything all firms do throughout history (keeping some sort of tally), with a side instrument to somehow extract APC payment in proportion to R&D expenditure that was not stimulated by the APC, and to set up an IAC to act ex post (but also whilst information is being acquired) on the basis of that information. This works 'as if' it is a tender, but it is clearly radically different from an actual tender. It is also much more open to being corrupted by pressures that lower competition, and, as in the case of 'standard' tenders, thereby undermining its ability to function efficiently[321]. And it is ironic, to say the least, that while tenders are usually used to extract information, in this case they end up *requiring* this information in order to work!

3.3.12. Relatively low capital costs

Capital costs are a *relatively* minor component of practically all of the above case-studies, and, in many cases, the overall impact on risk (incorporating the impact of 'mechanism risk') is to *reduce* it. In all cases the proportion of the allocation going to the costs of finance is completely the opposite of that for an early-stage HIV APC. In the HIV case, all the early stage risk being fed through the mechanism, along with all the new 'mechanism' risk being created, together

---

have access to lawyers). But the vaccine manufacturing capacity for the multi-dose vials is not in place.

[321] Farlow, 2004, ibid. Chapters 10 and 11 describes in much more detail the strategic possibilities leading to insufficient competition in this mechanism compared to others. In a 'standard' tender it is also much easier to spot and police corruption and strategic behaviour that narrows the state of competition.

swamp any later risks being reduced. Ironically, we even discovered that in its current set-up a great number of market risks are still very much fed into the HIV mechanism, completely contrary to many of the current APCs being discussed.

It is not obvious that making the size of the APC greater to try to overcome mechanism risk would work if one of the problems intensified by ever-higher APCs is mechanism risk itself (e.g. the 'pot' can be set higher to combat the risk of reneging by making payments high enough to compensate winners in the ex ante sense; but the problem of reneging probably just gets even worse with a bigger 'pot').

We seek a mechanism imposing as little of its own 'mechanism' risk on developers as possible, and with as much market risk removed as possible, and not the other way around.

> "*If the risks are linked to uncertainty about the science, as in the case of HIV-AIDS vaccine, then push mechanisms may prove more valuable than pull mechanism, which are too far in the future and too low probability. If the risks are linked to the market with little uncertainty about the science, as in the case of meningococcal A conjugate vaccine, then pull mechanisms become most important*."[322]

The current HIV and malaria APCs turn this all on its head.

3.3.13. Low crowding out

All of these 'purchase commitments' created a number of routes for efficiency gains that were equally transferable in their impact across public and private funders. There were none of the layers of 'crowding out' discussed in Part 2, particularly those forms of crowding out that require large amounts of information gathering to correct. In particular, the tendering systems used are more capable of setting the fresh funding to match the fresh private finance needed. In contrast, the 'tender' underlying an HIV APC has to find some other way to do this (monitoring all firm expenditure for all history and then extracting in a side contract from payments a multiple of any funding not incentivized by the APC). Thus, the HIV APC is much more informationally demanding, and paradoxically, interventionist, than any other tender-based systems.

Clearly even early-stage vaccines such as HIV should have purchase commitments, but there is no a priori reason why these should be pre-set in size nor cover more than manufacturing and late-stage development costs, and be set so high that they end up mostly having to fight against high capital costs, crowding out, problems with late-stage manufacturing incentives, and so forth. Besides, just a casual perusal of basic data suggests extreme weakness using them on early-stage R&D.

[322] Batson, A., 'The Vaccine Book', ibid. p361.

3.3.14. Purchase commitments can ease the last hurdle, but it is still risky

Late stages of vaccine development usually necessitate large investments in sunk production capacity based on a mix of hoped-for sales and of the need for quantities of vaccine for heavily scaled-up trials. Manufacturing issues are generally much more problematic for vaccines than for drugs. Being biological products, vaccines require complex, large, and early investment often many years before data showing the effectiveness of the product. Capacity decisions are often needed before a vaccine's potential market is even assured, or its efficacy and safety established to a level sufficient for licensure. Capacity is then often relatively fixed. It is difficult to quickly scale-up production of an existing vaccine – it can take anything from two to four years to scale up a filling line for example – and even more difficult to refocus a facility, since changes in the process have to be validated. Industry tends to build single-use production facilities, but these take more than 5-7 years to plan, build, validate and certify. Without knowing exactly what will prove effective in a vaccine it is impossible to know the best approach to ensure adequate levels of production.

There is also a risk that once vaccines are developed, buyers will use their buying power to bid prices lower than would be needed to repay manufacturing costs and the portion of late stage development costs that were paid for privately. Some guarantee on sales might help attract finance (both private and public) for such late-stage activities, though, again we must stress, it is not the only way to ensure finance. However, the return on investment need only cover the expected costs (including any private capital costs) of these stages of development.

There are also many problems specific to HIV and malaria that even casts some doubt on this 'late' stage of the process. These will become much clearer in the next two sections, but they largely pertain to the range of 'quality' issues discussed above, the need for composite vaccines, the much higher likelihood of only achieving a therapeutic vaccine, the much greater likelihood that products (and capacity to produce such products) *should* be totally replaced, and some likely special problems in arranging the distribution of purchase commitment funds and post-development problems linked to the vaccine being 'only' therapeutic. The ability for APCs, set very much in advance, to even be the last hurdle starts to look stretched. If all the risks have to be embedded in the terms of APCs many years in advance, firms might prefer alternative ways to insure themselves, for example through PPPs.

Besides, the problem of buying-power driving prices much lower (indeed even just the expectation of this) and thus undermining late-stage investment, is much greater when $25 is being charged for drugs and vaccines with a production cost of a dollar or so, than if prices are already close to a dollar (we saw that there might still be worries of pressures for the IAC to drive prices down to 'look fairer' ex post, even if this was not ex ante efficient).

Goodhart's Law for vaccines based on quality inefficiency?

However, in reality, the buying power inefficiency found in the current system will more likely metamorphose into quality inefficiency in an early-stage APC.

This is a sort of "Goodhart's law" for vaccines[323]; the notion of that law is that as one tries to control some economic variable based on some past observed statistical regularity (for example, a particular measure of the money supply based on its supposed link to inflation), policy makers will find that this statistical regularity will break down and the effect will show up somewhere else (for example, the targeted measure of the money supply may indeed be controlled but the link to the original problem, inflation, now lies somewhere else as agents work around the control). In the vaccine case, we might get rid of the ex post inefficiency to bid prices lower, but in exchange we create greater inefficiency, ceteris paribus, in the level of 'quality'. In the former case, matters are driven by the buyers in response to the producers. In the latter case, matters are driven by the producers in response to the buyers (the IAC and any country co-payment scheme in place[324]). This 'law' bites much less in late-stage or tender–driven processes than in mostly IAC-driven processes.

Late-stage APCs may not only speed access, but also lower the level of risk and capital costs. This is totally consistent with the notion that APCs would generate very high capital costs when used to stimulate early-stage vaccine R&D. Again, everything boils down to the relative positioning of the purchase commitment in the R&D process and the terms set. The terms of late-stage commitments are not being set to cover huge amounts of the overall previous development costs, just the bits that matter for late-stage risk.

The fact that one should have to go though all of these pretty obvious reasons for why some sort of commitment to purchase vaccines is valuable even if it may not be particularly strong for overcoming the problems particular to early-stage vaccines such as HIV, shows just how confused and conflated the different vaccine problems have become. This section has shown that many of these features are very different from those underlying the currently proposed APCs for HIV, malaria, and TB vaccines.

3.3.15. Purchases are said to not matter, but they do

The paradox is that the mass purchase of currently-available vaccines (and, indeed, acts that enable their usage) by institutions such as the WHO and World Bank is argued to have little impact on vaccine research incentives by key advocates of APCs: "Increased coverage of existing vaccines, while desirable in its own right, will by itself be inadequate to convince potential vaccine developers that there will be a market for new vaccines when they are developed."[325] And yet in many of the case-studies above, large scale procurement-style contracts for already existing vaccines were able to stimulate a great deal of investment in both capacity but also in innovation targeted at getting the price of vaccines down and access up. For example, the funding of the Rockefeller Foundation, the James S. McDonnell Foundation and the Bill and Melinda Gates Foundation were crucial in driving down the price of the Hepatitis B vaccine – a huge part of the success

[323] 'That any observed statistical regularity will tend to collapse once pressure is placed upon it for control purposes,' in "Monetary Theory and Practice," Goodhart, C.A.E., 1984, p96.
[324] Problems with the latter group are covered in much more detail in Farlow 2004 Chapter 7.
[325] Kremer, M. 'Creating Markets for New Vaccines Part II: Design Issues' p46, www.pm.gov.uk/files/pdf/Appendix%207.pdf. If actual purchases have such little impact, quite how an entirely inadequate $3bn HIV APC is supposed to do it is anyone's guess.

of that program. We also saw, earlier, the great importance of vaccine purchases in sending signals to biotechs, and in overcoming the negative impact of the way vaccines tend to replace the lucrative treatment markets of large pharmaceutical firms. Furthermore, the use of current vaccines not only increases credibility that any new vaccines will be used, but it also improves the vaccine delivery and managements systems that will eventually be needed for HIV, malaria, and TB.

3.4. Future Vaccines

The Center for Global Development originally set its sights on two vaccines, streptococcus pneumoniae (pneumococcus) and rotavirus. The emphasis was not at first on HIV or malaria vaccines, nor was there much notion that these were obvious targets for impending APCs, in spite of heavy lobbying by a tiny handful of voices. Of those involved in promoting pull approaches it is probably fair to say that many have gone along rather than actively promoted the HIV and malaria application. Like a virus itself, the recent emphasis on early-stage vaccines has exploited the understandable interest shown in these late-stage vaccines and the weakened immune response of those riding that particular policy wave.

3.4.1. Pneumococcus

A leading cause of bacterial pneumonia deaths is a bacterium called streptococcus pneumoniae (pneumococcus[326]), and it is preventable by a vaccine similar to the Hib vaccine. Like the Hib conjugate vaccine it has proved to be safe and very effective in randomized clinical trials. In studies in the US and Finland it has been shown to reduce the incidence of severe pneumococcal infections such as meningitis, pneumonia, and septicemia, and to prevent ear infections. Since 2000, it has been in regular use in the US and other wealthy countries, but not in the developed world. The four recommended doses cost more than $200 on the private retail market. Yet again we find that: “Although the vaccine is highly efficacious, reluctance to use it arose because of the price”[327].

Widespread use of an efficacious pneumococcal vaccine could help to alleviate an estimated 1 million deaths a year, mostly in developing countries[328]. Development and availability is even more urgent given the increasing antimicrobial resistance of streptococcus pneumoniae.

An advance purchase commitment, if carefully designed, potentially fulfils most of the qualities claimed in this case:

i) First-generation products get tested in the populations that need it;
ii) Suppliers get fed sufficient incentives to supply sufficient quantities for the developing world;
iii) The contracts influence the presentation and characteristics of products so as to better fit the needs of developing countries;
iv) Contracts can be set to influence the long-term pricing of the product;

[326] See www.pneumoadip.org.
[327] Plotkin, S. A., ‘The Vaccine Book’, ibid, p 186.
[328] WHO, 1998, Global Programme for Vaccines and Immunization (GPV). The WHO position paper on Haemophilus influenzae type B conjugate vaccines, Weekly Epidemiol, Record Vol. 73(10) pp64-68.

v) Sticking to the contracts will reduce wasteful investment in 'me too' products (which itself reduces risk to other products and hence costs of development).

These demand-side measures may help to overcome the problems that were caused by the slow use of Hepatitis B and Hib vaccine, impact positively on vaccine supply, and even impact some of the late-stage development needed to make the products more suitable for use. Competitive tender-type arrangements mean that crowding out can be largely avoided, and capital costs are also a potentially smaller part of the overall costs. Observe how, contrary to the HIV/malaria cases where it is simply presumed that treatment cost will be a dollar per head (without any thoughts for how this would actually be made the case) here the entire issue revolves around the currently high production cost and ways to get this down.

3.4.2. Rotavirus[329]

Worldwide, rotavirus infection is the leading cause of severe diarrhea and vomiting in infants and young children between 6 and 36 months old. If untreated, the virus can rapidly kill, since 10 to 20 episodes of diarrhea in a single day rapidly dehydrates the sickest children. Globally, rotavirus infections account for approximately 138 million cases per year of infantile gastroenteritis and are responsible for approximately 450,000 to 650,000 deaths of children - one child a minute. 85% of these are in low-income countries, accounting globally for about 5% of all deaths in children under 5 years old. This disease affects both rich and poor countries. 95% of children worldwide will experience an episode of rotavirus disease by the time they reach 3-5 years of age, irrespective of race or economic status. Rotavirus infection is the most common cause of hospitalization worldwide for diarrhea and vomiting and is responsible for one third of cases of severe diarrhea globally every year.[3] The big difference is that in developed countries the rate of death is much lower and hospitalization and clinic visits take the brunt of 'costs'. Indeed it is one of the leading causes of hospitalization and clinic visits in such countries with between 1 in 19 to 1 in 72 hospitalized in the first five years of life[330].

It might be argued that one of the reasons that the death rate is the level it is in developing countries is because of poor sanitation and hygiene and lack of oral rehydration, and that if these can be improved a vaccine becomes much less of a priority. However, it can also be argued that given that natural infection gives protection, a vaccine is much more clearly possible than for, say, HIV, and that, furthermore, in spite of pushes to encourage oral rehydration and improve sanitation and hygiene, rotavirus remains a major cause of childhood morbidity and mortality. In the US, for example, there has been minimal improvement in the

[329] The case of Rotavirus is described in 'Making Markets' p88, and rotavirus issues in general are covered in Bresee, J. S., Glass, R.I., Parashar, U, and Gentsch, J., 'The Vaccine Book', Chapter 6E.

[330] De Wit, M.A.S., Koopmans, M.P.G., van der Blig, J.F., and van Duynhoven, Y.T.H.P. 2000. Hospital admissions for rotavirus infection in the Netherland. *Clin. Infect. Dis*. 32:698-704. Ryan, M.J., Ramsay, M., Brown, D., Gay, N.J., Farington, C.P., and Wall, P.G. , 1996, Hospital admissions attributable to rotavirus infection in England and Wales. J. Infect. Dis. Vol. 174 (Suppl. 1):S12-S18.

rate of rotavirus hospitalization in the past 15 years. It is estimated that 326,000 rotavirus deaths in developing countries could be prevented by a vaccine with features close to those in current development[331].

Many challenges

There are still many challenges. There are two first generation products licensed or close to being licensed for rotavirus (and a third product that was previously withdrawn that had been sold in the US market), at least one of which will be on the market in the next year or so. The GSK Biologicals vaccine – originally developed at the Children's Hospital of Cincinnati by Dr Richard Ward – has, for example, been in development since 1997 when it was in-licensed from AVANT Immunotherapeutics. More than 70,000 infants were enrolled in the global clinical development program, with studies conducted in Europe, the US, Latin America, Africa and Asia. The Phase III clinical study has already seen over 60,000 infants aged 6 weeks to 6 months use the product, and involved 11 Latin American[332] countries and Finland, with the product described as safe and well tolerated, with efficacy of up to 73% protection against any rotavirus diarrhea and up to 90% against severe rotavirus diarrhea over the first rotavirus epidemic season, with a clinical protection maintained over two consecutive seasons, and, its makers claim, no increased risk of intussusception.

This does not begin to compare with HIV

This does not even begin to compare with the situation facing a HIV APC of the sort being proposed by CGD. It would be absurd to even suggest similarities. Rotavirus vaccine development is way down the path of development. In particular: "The comforting point is that the efficacy of repeated infection on the intestine with attenuated strains against wild viruses is beyond doubt, and *one can be optimistic about the eventual availability of a rotavirus vaccine*"(italics added)[333]. Very unlike HIV we know that candidate vaccines based on attenuated live strains are possible (the source of most candidate vaccines), both human and animal rotavirus, and that various other more novel approaches are being pursued (including DNA vaccines, inactivated parentally administered vaccines, vaccine-like particles, etc.)[334]; indeed there already is one nonhuman strain vaccine[335]. Nevertheless "Although natural or vaccine-induced infection clearly protects against subsequent disease…the lack of clear immune correlates has made vaccine development problematic, because large trials are necessary to examine the efficacy of each candidate vaccine."[336]

The challenge is to make any rotavirus vaccine rapidly accessible, and *affordable* in predictable quantities, to developing countries. Rotavirus vaccines for

---

[331] Bresse et al The Vaccine Book, p230.

[332] Incidentally, this may be why not one of the XXX PAHO representatives who sat on the CGD Working Group at various times never stayed around to sign off on the final document. Whilst Latin American countries were hugely important in clinical trials, they would not have come off well in the pricing under the eventual APC, and would probably be better advised to strike deals outside of any APC.

[333] Plotkin, S.A. Vaccine Book, p181.

[334] Bresse, J.S., Glass, R.I., Parashar, U, and Gentsch, J., ibid.

[335] Lanzhou Lamb Rotavirus lincensed in China in 2000 for use in children, undergoing post-licence evaluations (see Bresse, J.S., Glass, R.I., Parashar, U, and Gentsch, J., ibid, p 233).

[336] Bresse, J.S., Glass, R.I., Parashar, U, and Gentsch, J., 'The Vaccine Book', p 226.

developing countries settings, and hence APCs for them, face a number of particular challenges, including: 1) The high cost of manufacture. 2) important issues regarding safety with respect to intussusception; 3) big differences in rotavirus epidemiology between developed and developing countries. We will briefly look at these in turn:

3.4.2.1. Cost of manufacture

It might seem strange to recognize that the greatest problem with rotavirus vaccine is manufacturing costs, only then to *trust for no explicit evidence-based reason* on $1-$2 or so manufacturing costs for HIV vaccines, yet find that the HIV APC currently being pursued tackles none of the design issues that might help achieve these low production cost (competition amongst multiple manufacturers; access to technology and know-how, IP issues generally, competitive tenders, etc.).

3.4.2.2. Safety issues

Intussusception is a relatively common cause of bowel obstruction in children. Following licensure of the RRV-TV vaccine, 15 cases were reported in just under a year in the US. Various studies showed a slightly increased risk, though further studies are less suggestive. The vaccine was withdrawn, and the path of future vaccine candidates is unclear until further studies have been done into issues such as: i) whether other live oral rotavirus vaccines lead to intussusception (this will require good post-license surveillance of any new vaccine); ii) the pathogenesis of intussusception in general, and RRV-TV- related intussusception in particular; iii) whether naturally acquired rotavirus or other enteric pathogens are associated with intussusception, so as to determine whether intussusception is likely specific to rhesus strain infections or a more general reaction to a broader set of gut infections; iv) given that the risk and benefits vary greatly across developed and developing countries, more on the exact risk-benefit in various settings.

3.4.2.3. Epidemiology

Big differences in seasonality, strain prevalence, age distribution, and outcomes, will influence the optimal composition, schedule, dose and priority between developed and developing countries. For example, it may make more sense to include a neonatal dose in the vaccine schedules in developing countries since the age of first infection and severe disease is lower than in developed countries, and it may be necessary to use higher doses to overcome the inhibitory effects of competing gut flora, use of OPV, and high levels of maternal antibodies against rotavirus. Vaccines protecting against strains prevalent in the US are likely to perform poorly in developing countries. Clearly this indicates the need for more trials on more vaccine candidates in developing countries alongside the studies of the epidemiology of rotavirus disease.

Rotavirus vaccine trials have yielded poor and variable efficacy results in developing country settings[337] because of differences in host factors, viriologic characteristics, and disease epidemiology. Most trials used a single- or two-dose schedule, when in fact additional and/or larger doses may be needed (observe how

[337] See Bresse, J.S., Glass, R.I., Parashar, U., and Gentsch, J., ibid., p239.

this raises cost), and, indeed there is even doubt that live oral rotavirus vaccines in vaccine programs will be effective in such settings. The science is not exactly easy, and there will be great challenge in creating vaccines that will be effective and safe in multiple settings, and even where purchase commitments can be set to motivate trials, it will be very difficult to set terms efficiently, suggesting the importance of other mechanisms for uncovering information. Nevertheless, the informational assumptions are a lot less heroic than for HIV or malaria, and there is potentially the benefit of using tenders to extract information. The description of vaccines as being a form of product differentiation may be apt in this case.

Some of the challenges facing rotavirus are potentially part of an advance purchase solution including: programmatic issues regarding addition of a new vaccine to EPI programs, ability to produce enough to meet demand, and obtaining data to evaluate need and demand in countries in interested in buying, and so forth. But it is clearly more of a challenge than simple APC notions might suggest, and such purchase commitments are much more likely to need, just like meningitis conjugate C vaccine, a myriad of non-APC devices too. Since repeatedly we find that many of the problems are about access to drugs and vaccines once developed and cheapness of manufacture, there are many potential lessons to be learnt from this case that might help in the design of much more challenging purchase commitments.

3.4.3. These are all very different from HIV, malaria, and tuberculosis

The vaccines being emphasized in 'Strong Medicine' in particular, are, however, many streets away from pneumococcus and rotavirus. It really is not very helpful to constantly conflate APCs for late-stage and currently existing vaccines with APCs for early-stage vaccines – so that one minute we are reviewing ways to solve a flu shot shortage (of a flu vaccine already in existence), and the next we are being told that developing an AIDS vaccine works on pretty similar principles[338].

The evidence of our hopelessness at procuring cheap vaccines that we currently have, is good reason for guaranteeing procurement for vaccines, but not per se for justifying the use of a poorly-understood APC mechanism for the much more expensive and difficult task of developing complicated vaccines such as those for HIV, malaria and TB. This is a separate issue and needs to be independently

[338] This analogy has been used to argue for early-stage HIV APC, but I will not draw attention to any specific author of the argument. Another analogy used is that of the $10 million "X Prize" for the first private flight into space (100km) and back twice within a defined period. The problem with this is that the top competing firms between them knowingly spent several times the prize fund to try to win it! So either they were irrational, or they each had an over-exaggerated sense of their chances of winning (and were not disciplined by financial markets) or something else was at work. In truth, many of the (very rich) backers saw it as an inexpensive way to garner a great deal of kudos. The sums did not run into the multi-billions as would be required to develop vaccines. The players could use their own private funds without any need to attract private finance. And the true 'prize' was a great deal more than the $10 million for the winning developers, who in the expected value sense would view the expected intangible asset of the prize (being first and getting a leading position in the emerging industry, etc.) at a great deal more than just the $10million. Add this to the value of kudos, and the size of the prize was a great deal lower than its true value. No similar arguments apply to any vaccine.

proven. Planning ahead in this way would help to avoid access delays once a HIV vaccine is developed, though it may well also need public sector investment, and it is not the same as suggesting that an HIV vaccine could be largely (or even much) driven by such purchase commitments. And even if APCs were chosen to stimulate part of the development of HIV vaccines, they would still need many of the above problems sorted out in order to enable the level of the APC to be credibly set anyway.

Future vaccines will be expensive to develop

There is another way in which many of these cases may not be typical, that is in their cost of development. The development of recombinant DNA hepatitis B vaccine was a "stroke of luck"[339]. Nobody anticipated that genetically modified yeast cells would produce hepatitis B surface antigen that was identical in all important biomedical respects to that produced by the human body itself. Like many things in science, it was serendipitous. Since then no further recombinant DNA vaccines have been licensed, although a vaccine against human papilloma virus using this approach may soon be available. Hepatitis B vaccine may turn out not particularly typical of the vaccines to be developed in the future. As Bloom points out: 'The easy vaccines have been made.'[340] Is this good or bad news for APC advocates? This author would suggest that it would be bad news. Given the dangers discussed above of setting the size of an APC too low, this would seem to suggest that policy makers should err on the side of making them too big, But if so, and given that they are already expensive devices, this serves only to make them even more expensive on average, and less efficient, ceteris paribus, than instruments that can adapt much more to future costs. Besides, policy makers, if anything, will be encouraged to go for the lowest-sized APCs that advocates think they can get away with[341]. The reality of this becomes ever more clear as time goes by.

3.5. Lessons for the International Financing Facility (IFF)

Britain, France, GAVI and the Gates Foundation have drawn up proposals to apply the principles of the International Finance Facility (IFF) to the area of immunization – an 'IFF Immunization Initiative' (IFFIm). This would create a framework for donor funding of vaccines over the next 25 years that is pre-committed that would enable many of the above benefits to be picked off. Funding would be better planned, sequenced, prioritized, more predictable and delivered sooner. With greater market certainty it would be easier to develop health-systems with capacity for vaccine delivery, and to tackle important parts of the R&D problem.

There is no time here to discuss the IFF itself in detail, accept to recognize that there is a vibrant debate about it. The IFF notion is that legally binding commitments today help to eliminate uncertainty about future behavior, and that this reduces risk and hence raises the productivity of current spending. The IFF is,

---

[339] Mahone, R. 2005 ibid.

[340] Bloom, B., 2003, Quoted in "Vaccines for the Coming Epidemic" *Howard Hughes Medical Institute News.* http://www.hhmi.org/news/bloom.html.

[341] I wrote this before I saw the precipitous drops in the size of APCs now being pitched by the Centre for Global Development compared to even just a few months ago.

in that sense, a risk-reduction tool. The one detail that is frequently observed as still in need of much clarification is what will happen when repayments fall due and future aid budgets are impacted. The mechanism rather relies on the current upfront funding bringing about the need for lower aid budgets much further off in the future, otherwise currently reduced risk is simply offset by more risk much further out. At some point worries about *that* risk even start to affect current behavior. This paper leaves others to clarify this. However, a few points are worth making in the context of 'purchase commitments' for vaccines:

1) Stability of flows is good for vaccine researchers, manufacturers and developers whatever the method of funding of those flows and whoever the vaccine researchers and developers are. This is a separate issue from the IFF initiative, and, indeed from 'APCs' too. Even if the IFF fails to take off, a Vaccine Fund should still be a practically achievable reality. It will just require taxpayers to bite the bullet sooner. For example, Gordon Brown[342] says:

   > "*Let me give an illustration of what - because of the IFF model - is already possible…The Global Alliance for Vaccines and Immunisation…is interested in applying the principles of the IFF to the immunisation sector - donors making long term commitments that can be securitised in order to frontload the funding available to tackle disease. If, by these means, GAVI could increase the funding for its immunisation programme by an additional $4 billion over ten years, then it would be possible that their work could save the lives of an additional 5 million people between now and 2015.*"

   But none of this *requires* the IFF model. In economic parlance, the IFFIm is a sufficient but not a necessary condtion. The key issue is to have sufficient and stable flows. The novely of the IFF is to delay payment (and the taxes to cover it) – and pay, via interest, for doing so. In this case the presumption is that the funding that would have gone on activities in ten years time can be brought forward to now. This creates a lasting effect if there is a backlog of immunization that needs clearing sooner and because immunization will prevent health costs and losses later, but there will still be need for yet more funding given that immunization (especially child immunization) is an ongoing and long-term phenomenon.

   According to the statement above, increasing GAVI funding by about $400m a year could save five million lives by by 2015. So, why not just commit more funding for GAVI? The IFF is not the most obvious way to do it nor the cheapest. Purchasing vaccines via an IFF-type instrument should not be seen as a way to just, somehow, prove the 'virtues' of the IFF, although it may provide a low-risk way to test the instrument out.

2) Using fresh funds, IFF or otherwise, to launch vaccine purchases will yield a huge initial payoff. Clearly there is a spectrum of impact, with

[342] www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_105_2004.cfm.

some currently existing vaccines so hopelessly under-used that the impact will be great, and other vaccines much further out in the pipeline. There are so many 'low-hanging' fruit, that the Vaccine Fund is likely to be very successful in the early days. Unfortunately, this says nothing about the application of the APC notion to complicated vaccine R&D;

3) Similarly, success on the Vaccine Fund, especially in the first few years, would say relatively little about the potential success of the IFF in general. Extrapolation from 'low-hanging' vaccine fruit to other developmental goals would not make for sound analysis;

4) The IFF is about bringing funding forward. The APC proposal for HIV is all about pushing funding back. If anything, IFF funding is more suitable for current purchases and front-loaded research, which is hardly the point of APCs for HIV. Furthermore, as currently proposed, any commitment issued by the IFFIm could only be outstanding for a period of 10-15 years – way too short to be of any use for early-stage vaccine APCs which would need 20-30 year horizons. Given the dangers to investors of 'sunset clauses', the funding route for early-stage vaccines would have to be much more open-ended.

5) Where IFFIm funds are used to speed up the introduction of two vaccines – for rotavirus and for pneumococcus[343] – that are in late-stage development, the funding will be used for a variety of both "push" and "pull" activities. It will therefore be difficult to determine the independent impact of any APCs present, though, again, it should allow lessons to be learned. However, because of this mix, it is less clear the extent to which any lessons learned will extend to early-stage vaccine APCs.

6) Nevertheless, given the need to create sufficient impact such that future aid flows can be reduced and the IFF paid back, it is still awkward to use IFF flows to pay for front-loaded HIV vaccine work, given that the outcome is highly uncertain, and may not impact development for a decade or even much more (or never), and the improvements in health outcomes may therefore be too far off to help the IFF project to 'repay';

7) On the other hand, if APCs *are* used instead and turn out to be a great deal more expensive than proposed (with large chunks of capital costs, crowding out, problems of high manufacturing costs needing yet more injections of funds, large amounts of so far uncosted front-loaded funding, great problems dealing with quality issues, etc.) they potentially amplify the risks of the IFF, since the much higher level of repayment and associated costs will hit in future periods when the IFF is coming up for repayment. If, for example, a $6.25bn APC for HIV is only capable of generating (on the basis of the calculations of the Global HIV Vaccine Enterprise of the levels of funding needed) just a few months or so of fresh current vaccine research (and the impact shrivels to nothing based on the

[343] However, at the time of going to press, it seems to be the case that the IFFIm will be too small to allow room to fund APCs for rotavirus and for pneumococcus.

current $3bn figure), then even if the APC worked (it probably would not in these circumstances), it would leave a liability of $6.25 behind to hit the IFF at a much later date in exchange for little current impact.

In addition, there may be yet greater needs for end-loaded funding to achieve maximum impact of a series of therapeutic vaccines, currently the most likely outcome of the HIV Vaccine Enterprise. Politicians seem to have lost sight of the fact that if 'only' a therapeutic HIV vaccine is derived, prevention and treatment budgets will remain very high way after any HIV vaccines are on the market, and those vaccines may themselves require a stream of yet further-out vaccines. The APC literature has tended to treat the treatment budget as being replaced by the vaccine budget at horizons of ten to twenty years. The risks of the IFF and the risks of APCs need to be properly analyzed together. Neither is a panacea to the funding problems.

8) Since the IFF is paid from future aid flows, it is not an excuse just to throw large sums of money at problems, including vaccine R&D. Such behavior jeopardizes the whole IFF enterprise. With so many other developmental goals, and given the risk of failure to pay back the loans later and associated financial penalties to this, there *is* a binding financial constraint, and the efficiency of the projects that the IFF will fund will matter greatly. If APCs for HIV end up being a great deal more expensive and less powerful than originally claimed, that is a risk for the *whole* IFF enterprise.

9) Global agriculture subsides are running at $1bn per day. Military spending in Iraq at $1bn-$2bn per week. IFFIm would be a ten-year $4bn dollar program, or roughly 4 days of the former subsidies and less than a month of the later military spending. What might it suggest about priorities that only immunizations get a borrowing instrument like IFF (that has to be repaid too) rather than simply being paid for? Would it have been better to have gone for a no-strings stream of payment?

10) What if the IFF proves problematic to set up? Should the success or timing of an immunization program be linked to the timely and continued success of something entirely different, and much more risky?

11) Immunization is an emotive issue, the IFF a more controversial issue. Should controversy about the latter be allowed to be associated in any way with the former? How do those who wish to be critical about the former not end up harming, or sullying, the latter?[344] Or is the hope that – by virtue of its emotive content – the link to immunizations protects the IFF somewhat? Given the sensitivity of the issues, policy makers need to make very sure that, in all their public pronouncements, the IFF is there to support the immunizations and never the other way around.

[344] See, for example, "Mr Bush opposes Gordon Brown's plan to help Africa using an international finance facility to fund vaccinations." http://news.bbc.co.uk/1/hi/uk_politics/4613987.stm.

PART 4. A COLLABORATIVE GLOBAL HIV VACCINE ENTERPRISE

The main problem with the emphasis of APCs on early-stage vaccines for HIV, malaria, and tuberculosis – and the greatest cause of their excess cost compared to alternatives – is that it misunderstands the nature of the vaccine research process. Let us examine this in the context of one of the major vaccines currently being heavily emphasized, HIV[345], a vaccine facing "daunting scientific hurdles"[346]. While we may concentrate on HIV, it is worth pointing out that for parasitic diseases, like malaria for example, high-quality vaccines are also especially difficult to develop, in that case because of the difficulty of determining which portion of the multi-stage lifecycle to target. Currently three types of malaria vaccine are in development targeting different portions of the lifecycle: pre-erythrocytic, blood stage and transmission stage. We will return to malaria in Part 6 below.

4.1. The Scientific Challenges of HIV

Klausner et al.[347] point out that many of the fundamental scientific challenges impeding HIV vaccine development remain unsolved very many years after the identification of HIV as the etiologic agent responsible for AIDS. These include:

i) The inability of current vaccine designs to elicit effective neutralizing antibodies against the circulating strains of HIV;

ii) The inability of current designs to prevent HIV from establishing persistent infection;

iii) The extensive global variability of HIV and the fact that in the process of replication in an infected individual it mutates rapidly producing genetically distinct viruses such that a vaccine protecting against one particular type of the virus may be ineffective against another. There is "a population of viruses in a single individual that is so heterogeneous that an antibody that binds to one virus and blocks its ability to infect a cell may not be able to bind to another of these viruses"[348]. Of particular current relevance, a high degree of HIV-1C diversity poses a significant challenge for the development of an efficacious HIV vaccine for southern Africa and the horn of Africa where the HIV-1C subtype is the main subtype causing HIV epidemics. The full-length

[345] For illustrative purposes we use HIV and malaria as examples, but one of the dangers of doing this is to forget that other appalling diseases are equally desperately in need of vaccines. Tuberculosis has also, unfortunately, tended to attract disproportionately lower attention.

[346] Birmingham, M., and Stein, C., 'The Vaccine Book', p15.

[347] 'The Need for a Global HIV Vaccine Enterprise', Richard D. Klausner, Anthony S. Fauci, Lawrence Corey, Gary J. Nabel, Helene Gayle, Seth Berkley, Barton F. Haynes, David Baltimore, Chris Collins, R. Gordon Douglas, Jose Esparza, Donald P. Francis, N. K. Ganguly, Julie Louise Gerberding, Margaret I. Johnston, Michel D. Kazatchkine, Andrew J. McMichael, Malegapuru W. Makgoba, Giuseppe Pantaleo, Peter Piot, Yiming Shao, Edmund Tramont, Harold Varmus, Judith N.Wasserheit, Science 300:2036, 2003, Vol. 300, 27 June 2003, www.aidscience.org/Science/Science--Klausner_et_al_300(5628)2036.htm.

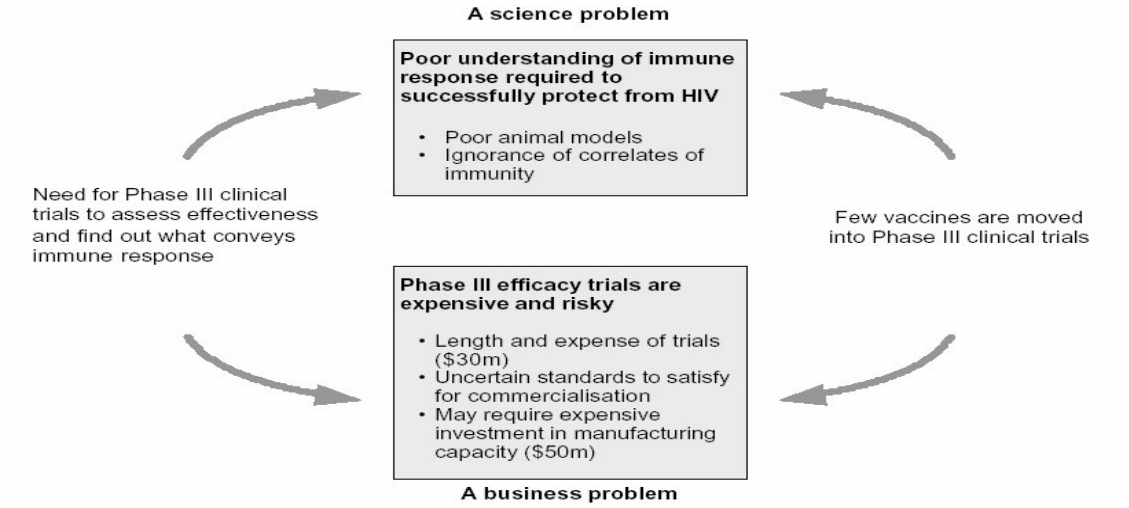
[348] Choi, E.I, and Letvin, N, 'The Vaccine Book', ibid. p 246.

genome sequence so far comprised finds 73 non-recombinant HIV-1C isolates;

iv) The lack of understanding regarding the mechanisms of protection in the most effective HIV vaccine animal model system – the live attenuated approach;

v) The lack of understanding of which HIV antigens induce protective immunity and which immune effector mechanisms are responsible for protection.

The problem is also circular:



"Why is the process of developing an HV vaccine so drawn-out and complicated? The answer to this question lies primarily in the fact that natural immunity does not appear to have a strong impact on the final outcome of HIV infection. In fact, without chemotherapeutic intervention, HIV infection is responsible for an extremely high mortality rate. Because studies of natural selection have not guided scientists in understanding what constitutes protective immunity, it has not been possible to identify the critical viral sequences to include in an HIV vaccine."[349]

"A lack of knowledge about protective immunity has hindered HIV vaccine development. This obstacle is to some extent offset by the knowledge researchers in the field have gained about HIV diversity, the structure of some key HIV proteins, the events surrounding HIV entry into its target cells, and host responses to HIV antigens. Even though many of these scientific gains have been, and will continue to be translated into HIV vaccine designs, it should be recognized that only through clinical trials will it be possible to evaluate the effectiveness of an intended immune response that is elicited by a candidate vaccine. ***HIV vaccine development needs to be an empirical process, involving repeated rounds of clinical testing of a large array of candidate HIV vaccines.*** *An efficacious HIV vaccine developed from such a process is our best hope of*

[349] Lee, T-H. and Novitsky "HIV Vaccines: Design and Development" Chapter 39 in "AIDS in Africa" Second Edition, Ed, Essex, M. et al. p596.

arresting the growing AIDS epidemic both in sub-Saharan Africa and in other regions of the world."[350](emphasis added)

HIV vaccine research has the structure much more of cumulative and reflexive research, not the linear unidirectional research presumed in the key APC models (Kremer Appendix 3); trial-discovered knowledge links back to basic knowledge and helps to uncover other trial-discovered knowledge, and so on. Much of the information revealed has public good features to it, quite unlike the properties presumed in the basic APC models, that the result of *all* research is a pure private good. The mechanism to solve this highly complex scientific challenge is, so we are told, "simple" and "easy to understand."[351] But how likely is it that simple economic models that do not match the highly complicated scientific reality will be able to guide scientific policy in a rational direction?

4.2. Combination and Therapeutic Vaccines

The scientific evidence also indicates that combination vaccine regimens will be needed to achieve a broad spectrum of immune response and the optimal balance of efficacy, safety, and cost for all regions of the world. On the one hand, with more and more recombinant strains around the world, and with more and more people traveling, there is a need for a globally applicable vaccine. On the other hand, it is possible that specific vaccines (made for locally circulating strains of HIV) based on the genetic makeup of specific ethnic groups or to cope with the needs of specific geographical regions will be required. Again, this contradicts the Appendix 3 assumptions. By dealing in only pure vaccines, such awkward issues as 'coordination' are not an issue, and by thinking largely in terms of '*the* HIV vaccine' it conveniently fixes the size of the pot of subsidy (and uses the fixity to discipline developers), in a situation where the bounds on the needed funds are highly unclear. When the pot of subsidy is gone, will more funds be made available to cater for the ethnic groups left out (and on the basis of who's ownership of vaccine IP will such R&D take place)? Indeed, our lack of understanding of the significance of HIV genetic subtypes for vaccine design is a constraint on vaccine design but also on any APC set up to incentivize vaccine design and research. But these knotty scientific difficulties are mere inconveniences to the creation of neat, simple, economic models. Better to dispense with then than to spend much time dwelling on them.

Just for one example, HIV can be transmitted either by cells infected with the virus or by cell-free virus. The type of immune response is very different in both cases. Virus in a cell can be recognized and eliminated by cytotoxic or killer T lymphocytes, but free virus can only be controlled by antibodies. The vaccines eliciting such different immune responses are very distinct, one cellular and the other humoral, and some coordination is needed to make sure that both are optimally present:

"*One of the main obstacles facing investigators in the field of HIV vaccine research has been the difficulty in constructing a single protein that is able to elicit an antibody response with activity against a diversity of HIV*

[350] Lee, T-H., and Novisky, V., ibid p604.
[351] Barder, O., CIPIH Forum, 19 November 2004

viruses…experimentation suggests that a combination of two complementary vaccine strategies will likely generate a more potent cytotoxic T-lymphocyte response than any single vaccine modality."[352]

In consequence:

"*The ultimate vaccine, therefore, will likely make use of a combination of strategies, an approach that radically departs from any vaccines that have previously been developed*."[353]

"From the perspective of both viral escape and HLA restrictions, the inclusion of multiple variants of key immunodominant CTL epitopes in an HIV vaccine could prove a more effective protection."[354]

Needless to say, this is completely at odds with the modeling underlying 'Strong Medicine', the No 10 Policy Unit material, and 'Making Markets', which all presume multiple competing *distinct* non-combination vaccines, and do not even pay lip-service to the notion that HIV vaccines will "radically depart from any vaccines that have previously been developed". The underlying model is based on 'vaccines as usual'. It does not help to rule out from the start one of the main drivers of the problem of developing HIV vaccines.

These combination vaccines would need to be developed and tested early with systematic evaluation of the strains and antigens used. This is complicated by the fact that gender, diversity in viral strains, duration, and magnitude of the ongoing epidemic are likely to influence vaccine efficacy, making the optimum vaccine regime something of a moving target. Only a system of collaborating vaccine developers (this does *not* mean that they do not compete) – based on an intellectual property regime that allows, and indeed encourages, sharing – would allow those working on cross-cutting technologies, such as novel adjuvant development or mucosal delivery, to work with the most promising antigens so that each component of a candidate vaccine would be optimized. This is currently lacking in HIV vaccine development. Early-stage APCs would not only fail to encourage it, but, as constituted in 'Strong Medicine' and 'Making Markets', would even make it much more difficult to achieve.

The problems of therapeutic vaccines

It may be that given the safety concerns about the use of 'killed' or attenuated virus methods (i.e. worries that a defective vaccine could in fact infect recipients), it may not be possible to develop vaccines that prevent infection, but instead 'only' therapeutic vaccines that slow the progress of AIDS. This is further complicated by the fact that for ethical reasons the efficacy of a vaccine alone, without prevention interventions, will be unmeasured in trials (in any clinical HIV trial, vaccine efficacy will be measured by comparing incidence among those who receive maximum prevention education alone with that among those who receive both maximum prevention education and the vaccine). Monitoring the efficacy of

[352] Choi, E.I., and Letvin, N. L., 'The Vaccine Book', p252.
[353] Choi, E.I., and Letvin, N. L., 'The Vaccine Book', p252.
[354] Lee, T-H., and Novisky, V., ibid p603.

a vaccine used on its own, will have to wait till after vaccine development and the vaccine is in regular usage.

An APC would have to take into account all of the possible variations in the epidemiology and treatment of HIV, as well as the question of whether the search is for a therapeutic vaccine or a prophylactic vaccine. The delivery of a therapeutic vaccine would be fundamentally different than for a prophylactic vaccine. For example, a therapeutic vaccine would be delivered to a population of infected individuals among mainly adults, whereas a prophylactic vaccine might be administered to all individuals at an early stage of life. The two markets would be very different.

Quite how the structure of an APC of the sort currently being advocated could possibly reward such vaccine developments is not at all obvious. Imagine trying to do some of the 'quality' adjustments – or, more to the point, trying to credibly commit to doing such adjustments – with therapeutic vaccines. Payment (and, meanwhile, the racking up of very high capital costs) could hardly be delayed to see how much delay is being achieved in the progress of HIV and the onset of AIDS in populations using 'only' therapeutic vaccines. And, what if most of the APC subsidy is used up and it becomes clear that fresh vaccines are needed because the first are not achieving enough delay? And, unlike previous vaccines, what if other treatment and health provisions would impact on effectiveness and hence the reward to developers? Should they have this extra risk added to the risks they already face? We also, again, spot the moral hazard and extra costs caused by having the same firms dependent on income from drugs for treatment, also investing in developing therapeutic products that undermine the market for such treatments.

4.3. Overlap and the Need for Expanded Focus

Even given the paucity of prototype antigens in clinical trials, there is nevertheless significant overlap in the current portfolio of HIV candidates. IAVI comments that only recently have major stakeholders started to grasp the nettle that global efforts on HIV vaccine research and development "are fragmented, lack effective collaboration and are unnecessarily duplicative"[355]. 'Strong Medicine' schools itself in this outdated thinking – embodied in its probability distributions. It presumes that a very large APC is the best way to encourage diversity of approaches and incentive not to overlap. However, no empirical evidence is provided that this is what in fact would happen. Indeed, given the highly cumulative and interactive nature of much HIV vaccine research, the importance of information spillovers in real-world applications (both cross-sectionally and over time), and the importance of push efforts (pharmaceutical firms stay well clear of areas of pharmaceutical research with little or no 'push' effort going on), it would in reality be difficult to prevent private finance from concentrating in those areas of vaccine research that are *already* well covered. In

[355] IAVI ibid. p18. For example there are multiple poxvector candidates at various stages of development, but since they have not been compared with standardised assays it is not actually clear which is the most promising to develop. This needs coordination.

section 2.13 above we saw that research 'bunching' is an ever-present problem that APCs tend also to encourage.

Several HIV vaccine concepts are yet to enter clinical trials, due largely to the focus of the global research community on the single scientific hypothesis of cell-mediated immunity. The 'neglected HIV vaccine' concepts include:

i) Whole-inactivated vaccines;
ii) Virus-like particles;
iii) Complex vaccines including host and viral antigens;
iv) Jennerian vaccines such as the potential for SIV-HIV chimeras to serve as immunogens;
v) Bacterial delivery systems targeting mucosal compartments;
vi) Vaccines specifically designed to target dendritic and other antigen-presenting cells;
vii) Safer next generation live-attenuated vaccines.

One hypothesis might be that APCs would broaden research to cover this wider set of possible leads. But this is an illusion. Rather than it being less risky to adopt a contrary approach to others, it is in reality *more risky*[356] and it would be extremely difficult, if not impossible, to use the ex post reward structure of an APC (in place of the guiding of activity ex ante) to compensate for all the risks incurred in exploring leads in highly unexplored research space.

While it may appear that setting an ever-more expensive APC may overcome waste, overlap, secrecy, and an overly-narrow focus, it is not obvious that it would. At some point, perhaps, the early-stage APC would become *so* large that research *would* be stimulated, but it would then struggle to prevent firms from following anyway the comparatively less risky routes dictated by the current research emphasis. All the failures that prevented early-stage research on the current area of maximum interest would bite just as severely, if not more so. The result would be a slower speed of vaccine discovery and weaker vaccines than would have been the case under a more collaborative approach (if the APC did not collapse first given worries of vaccine players about its size). Again, this failing raises the costs of this approach compared to others.

This obsession with one or two large players[357] also contradicts the HIV science somewhat:

> *"Given the number of vaccine immunogens and expression/delivery approaches under development and the possibility of combined vaccines,* ***there could be a considerable number of potentially efficacious vaccine candidates available for testing in clinical trials****."*[358] *(emphasis added)*

[356] Though the probability functions underlying the vaccine R&D process in 'Strong Medicine' and the APC literature are modelled as it being *less risky,* even though the evidence on HIV *drug* research shows that this is not the way firms treat it.
[357] The notion that "a large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more." (Kremer Appendix 1 p9).
[358] Gilbert. P.B., and Esparza. J., "HIV-1 Vaccine Testing, Trial Design, and Ethics" p615 in Chapter 40 of "AIDS in Africa" 2002, ibid.

The only realistic way to fill out the research space is through a greatly expanded Global HIV Vaccine Enterprise. Incidentally, this would reduce the value of any pre-agreed early-stage APC that had been based on the narrower set of research leads currently being followed; the logic in the model is that if a wider field of research activity is instigated, this will reduce the value of the APC to others since it will reduce the chance of any private firm already working on a particular vaccine from being the one to get the APC. So, the expansion of research activity will simply increase the risk to those private players who have sunk resources already. This serves to show, yet again, the difficulty of optimally setting APCs in an area of highly variable science and where there is also a highly variable level of public- and foundation-financed activity.

4.4. An Alternative: A High-Quality Collaborative Mechanism

> "*I also see an enormous opportunity for pushing forward the initiative to create a worldwide infrastructure – or platform – for sharing and coordinating research in AIDS, and then for encouraging the development of viable drugs. But it is generally recognised that the sums of money required involve at least a doubling of research money for AIDS*", Gordon Brown, Council on Foreign Relations, New York, December 17, 2004.
>
> "*People working together in interpersonal relationships that are dedicated to a goal can produce incredible, incredible things. And that's what has happened here.*" Alphonso Diaz, Associate Administrator for science at the US space agency NASA, on landing on Titan, January 15, 2005.

Klausner et al. suggest a radical alternative to that of 'Strong Medicine' and 'Making Markets' for HIV, the exact workings of which have yet to be fully articulated. The solution, and the best route for developing a safe, effective, and resistant HIV vaccine in the shortest possible time, is, they argue, "a high-quality collaborative research system that goes well beyond the high-quality but separate research projects that we have today." This mechanism would be based on international coordination along the lines of the Human Genome Project, a mechanism whereby many of the funders agreed on a scientific road map, voluntarily divided the work, and agreed to an evolving set of production standards. The frequent sharing of progress and of problems allowed coordination, cooperation, avoidance of unnecessary duplication, and yet internal competition. IAVI has, for example, urged for the creation of a mechanism that enables the results of small-scale clinical trials to be ranked in head-to-head comparisons, so that resources can be focused as quickly as possible on testing the best candidates in large-scale trials. However, so far the global consensus on laboratory techniques and benchmarks needed for this has proved illusory, but it is a very high priority. Such a collaborative framework does not easily sit in the simplistic distinction between push and pull as "Roughly…the difference between funding inputs and paying for outputs."[359]

[359] 'Making Markets' March 2005 p25.

Continuous, ongoing, competition, and not competition through one point and a committee

The collaborative mechanism puts a lot of emphasis on continuous competition – rather than, supposedly, competition policed through one point in the process and one committee – and on the rewarding of 'results'; it just does not do it with a large 'pot of subsidy' at the end of the vaccine development rainbow.

This is the complete antithesis of the modeling of 'Strong Medicine', with its emphasis on multiple (though probably few in reality[360]) independent research leads that provide no information spillovers whatsoever to each other, and that would involve heavy secrecy and strong patents in any real-world applications, none of the circularity described above, all the risk firmly placed on firms and financial markets, and reward courtesy of the largely discretionary behavior of the IAC. Even if there were useful information across projects, the ever-growing level of sunk capital costs in each individual project before any probability of commercial return[361] will mean that sharing of useful information is simply too costly, since it risks wiping out any pay-back of those costs (indeed, many times over[362]). Sharing may be globally efficient, but it is privately highly inefficient.

Indeed, one notable absence in the review of push and pull mechanisms in 'Strong Medicine' is any review of the pros and cons of open collaborative research methods for advancing knowledge, though Kremer and Glennerster are fairly downbeat about them[363]. This is even more surprising – ironic even – when one discovers the heavy, implicit, reliance of the underlying modeling of Kremer and Glennerster, and 'Making Markets', on 'open-source' logic, especially the lack of patents everywhere except at the end of the process and the complete free flow of information, even though 'closed-source' logic is then put back in real-world applications.

IAVI states that the solution to the many challenges

> *"will require multidisciplinary involvement…and creative mechanisms linking basic research scientists with vaccine designers, in fields as diverse as structural biology, robotic crystallization, glycobiology and large-scale non-human primate testing (and) flexibility to move resources among the elements as emerging priorities warrant; and* ***creative intellectual property agreements to provide incentives for data sharing and cooperative research****."*[364] (emphasis added).

Early-stage APCs of the sort suggested in 'Strong Medicine' and 'Making Markets' have little to offer to this. In the case of HIV at least, the relevant yardstick for comparison with the cost-effectiveness of early stage APCs would

[360] See Farlow, 2004, ibid. Chapters 10 and 11 (and also 12) for the strategic slimming down of competition that would more likely result from such a program.
[361] This is ruled out in the 'Strong Medicine' and 'Making Markets' modeling by the assumption of constant per-period probability of discovery, and the 'bygones are bygones' nature of sunk costs.
[362] i.e. to make the gamble pay off in the ex ante expected sense.
[363] 'Strong Medicine' p65-66.
[364] IAVI ibid. p16-17.

be the Global HIV Vaccine Enterprise that we are told will "serve as a forum for the best vaccine concepts and candidates to be prioritized, regardless of where they originate"[365].

Interestingly, the Bill and Melinda Gates Foundation is *also* spending resources looking into these more open collaborative frameworks, with the announcement, last year, of a Global Vaccine Enterprise[366]. The G8[367] and the Bush Administration[368] have also endorsed the approach, the latter describing it as "analogous to the successful alliance and strategic plan that characterized the approach to the human genome project". We explore the components of such an approach in Part 5.

[365] IAVI ibid. p 5.
[366] Klausner, RD, Fauci AS, et al. ibid. Also see IAVI 2004 ibid.
[367] www.g8usa.gov/d_061004d.htm.
[368] www.whitehouse.gov/news/releases/2004/06/20040610-29.html.

PART 5. A COLLABORATIVE GLOBAL HIV VACCINE ENTERPRISE: FOUR INTERLOCKING COMPONENTS

This section is here largely on the insistence of others, who rightly suggest that it is one thing to critique[369], quite another to create. This is the most tentative and exploratory section in this paper. Others will have better – and more – ways to put the pieces of the puzzle together.

> *"Development of effective HIV-1 vaccines requires global cooperative research in basic science, clinical applied sciences, and large-scale efficacy trials."* Gilbert, P.B., and Eparza, J.[370]

> "*The Enterprise proposes to coordinate efforts at a global level, facilitate use of common tools and technologies, and help ensure access to optimized resources. Furthermore, the Enterprise approach is a way of behaving as a global community of problem-solvers, more openly sharing information…Confronting major roadblocks and harnessing these new opportunities requires an effort of a magnitude, intensity, and design without precedent in biomedical research, with the Human Genome Project as a potentially useful model*" The Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise.[371]

> "*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; instead of patents, we should have open access; instead of making consumers pay for R&D through the purchase price, governments should fund R&D directly; and that instead of lending from private capital markets, governments should exploit their lower cost of capital to fund investments*." Ernst R. Berndt writing on behalf of the Center for Global Development, 17 December 2004.

In its current cloak of strong patents, secrecy, and go-it-alone projects, 'Strong Medicine' sets up an unnecessarily confrontational stand-off with those who argue for more open collaborative approaches, and even encourages some to suggest that the approaches should necessarily compete. Instead, the most

---

[369] Though this author feels that critiques alone are extremely valuable. No mechanism is going to be perfect, so knowing the exact degree of imperfection of each is extremely important. If mechanisms have fundamental flaws, much delay and waste can be avoided by discovering these sooner rather than later. And since one can only know after the fact whether a mechanism will work and it is impossible to conduct 'trial runs', it is much better to spend relatively trivial amounts of time and money at this early stage. The notion of rushing in to do something is extraordinarily inept.

[370] Gilbert, P.B., and Eparza, J., "HIV-1 Vaccine Testing, Trial Design, and Ethics", Chapter 40, p612, in "AIDS in Africa" Second Edition, Kluwer Academic/Plenum Publishers, 2002.

[371] "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan," Plos Medicine, Volume 2 Issue 2 February 2005, http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020025.

powerful setting for a purchase commitment for a complicated vaccine like HIV is likely to be as a fairly late part of a much larger package of measures (or, in a collaborative setting, possibly relating to intermediate stage goals), and therefore comprising a relatively small proportion of the overall package's cost; information revealed by earlier open, collaborative, mechanisms would be used to set the terms of the purchase commitments, the overall size of which would not be set in advance. They would not be multi-billion dollar pre-determined pots of money to supposedly pay for large proportions of the *whole* R&D process (or even very much of it), giving all the IP to one or two large pharmaceutical firms at the end, but would be relatively much smaller, carefully-targeted, pots, with the emphasis of public funding placed on the collaborative aspects of the process and much more public ownership of the eventual IP and know-how. The real issue is how the one mechanism feeds into the other, and *not* how they might compete.

Since the underlying approach of 'Strong Medicine' rules out collaborative issues of any sort, it should not surprise us that we encounter some awkward problems making this collaborative framework work for something as complicated as a HIV vaccine. A combination of challenges leads us towards a solution with at least four *interlocking* components. Each is necessary. To have one without the others is, in most cases, worse than not having it at all. Readers' views on the following are especially welcome (this is, after all, a largely exploratory section):

5.1. Fresh Approaches to Vaccine IP

One of the reasons cooperation is currently lacking in HIV vaccine development is precisely because we do not have creative intellectual property agreements that enable open communication and vaccine development paths that combine access to reagents, platforms, and technologies of potential commercial interest owned by different entities. This calls for some fresh approaches to IP, but this *must* be in *advance* of any permanently fixed contracts.

As a few simple examples, this might involve[372]:

i) Pooling of complimentary patents[373] common to all potential vaccine developers and the freedom for all potential developers to use them;

ii) More use of, and development of, open-source type licensing agreements;

iii) More use of liability rules, such that the use of small scale improvements could be made for vaccine purposes without needing agreement beforehand, and a mechanism (even just involving credits) to later repay if the IP proved useful;

iv) New ways in which the IP can be designed to more easily allow firms to acquire technology that might 'undermine' those firms experiencing, and creating, replacement effects (i.e. the effect when pharmaceutical firms are less able to work on products, such as HIV vaccines, because they run the risk of replacing markets for other products, such as AIDS treatments[374] or when firms hold back from

[372] The reader is encouraged to add more to the list.
[373] Not substitutable patents.
[374] For more details, see Farlow, ibid. 2004 various places.

investigating multiple leads since each new lead imposes a negative externality on every current lead);

v) IP to foster competition, especially at the manufacturing stage;

vi) Less IP attached to the final vaccine and to the know-how of the final vaccine. We have found many reasons to doubt that the post development vaccine price could contain large portions of the cost of R&D without it continuing to cause a range of problems – from dynamic consistency to problems with eligible and non-eligible countries. Neither is it clear that developers themselves would want to bear the reputational risk of 'winning' the results of a highly collaborative global effort, and face a legacy of pricing controversies in non-eligible countries, who had all paid heavily towards that global effort. It must surely be possible to design the IP and other features of the mechanism such that developers are rewarded for their efforts, and participants in the Global HIV Vaccine Enterprise rewarded for theirs too. The paradox might be that long-term IP rights to HIV vaccines are quite the opposite of what developers operating under such a mechanism would want.

Incidentally, many of these approaches to IP are designed to reduce risk, and hence capital costs, in a collaborative setting. One of the few 'benefits' of the currently very low (compared to what is needed) levels of funding for HIV and malaria research is the opportunity to think through changes in vaccine IP regimes. It is easier to make changes now rather than later when any APC is in place and litigation and a raft of other issues would become much more intense. Pushing for large early-stage APCs risks closing the door on this opportunity.

5.2. Novel Financial Tools: with the Type of IP, Finance and Collaborative Process Inter-Related

In the HIV science described above, collaboration does not just end when vaccine research leads are released to pharmaceutical firm trials. Collaboration extends to the very end of the process, and, indeed, back to those working on earlier parts of the process elsewhere, with information provided late in the pursuit of one potential vaccine lead being fed to those working on earlier parts of the development of other potential vaccine leads elsewhere, to help them adapt and improve. There is, however, a fundamental problem in using equity-based finance and allowing the built up of large sunk costs in order to fund such collaborative, highly cumulative, backwards-and-forwards iterative activity[375].

Part of the deal for those drawn into late-stage collaborative vaccine trials would involve sharing confidential information – well before a product is even near to being ready – for translational studies aimed at optimizing, combining, and comparing candidate vaccines with process development studies to concentrate on

[375] To avoid being misinterpreted (again) see Farlow 2004, ibid. Chapter 12 for the reasons why large pharmaceutical firms are largely motivated via equity finance. The section here draws attention to the fact that there is a potential conflict between equity finance and collaboration (something that should be pretty obvious) that needs to be fully worked through for both equity finance and collaboration to work together.

making sure that the leading candidates are developed. But this could mean that the successful vaccine will not be the one being worked on by a firm or will be a combination vaccine not including the firm's vaccine in its formulation, precisely because of some information the firm revealed during this collaborative process. Indeed, the incentive not to truthfully share both good and bad information in ways that risk undermining one's own research will rise as the sunk capital costs rise, i.e. approaching ever-later stages of the process. Late stage trials are already very risky; they are even more so if individual firms are expected to 'give away' information in this way.

The sunk cost – information conflict

We face a conflict, with forces pulling in varying directions. For the sorts of activity connected to 'openness' and 'sharing', we would like finance to be such that risk is passed on to the sponsor and away from the company or whoever is carrying out the research. We may wish to 'insure' firms – in the shape of access to debt-like instruments and up-front sources of finance – when they engage in such acts. Indeed, we might quite like them *not* to use 100% equity finance – and hence to not fully be paid via an APC based totally on equity finance. However, insuring large pharmaceutical firms against risks will conflict with the fact that equity finance is central to the incentive structure of large pharmaceutical firms[376].

For those parts of activities that are of a less collaborative nature and where incentives to put in 'high effort' are important – for example achieving a certain 'quality' of trials and in reaching certain other benchmarks – we would like finance to be more equity-like, placing risk on the firm or whoever is carrying out the R&D. If, for example, collaboration becomes less important very close to the end of the development process, finance would, ceteris paribus, also become more equity like, and more like that being presumed from the start in 'Strong Medicine'. However, these tradeoffs are also affected by the level of built-up sunk costs and capital costs, suggesting there should be more 'insurance' even late in the process when sharing and collaboration is important. It should be recognized that there is this fundamental, and difficult to calculate, tradeoff for HIV vaccine research right to the very end of vaccine development. One consequence is that both 'push' and 'pull' are likely going to be present to the very end of the process, and no pure pull mechanism of the sort presented so far (on the notion that pull 'takes over') is likely to be calculate-able in advance.

Much of the self-fulfilling 'quality' crowding-out described above is driven by stock markets denying resources to those trying to work on higher-quality, or indeed 'different' research leads because, in a completely un-collaborative setting, it is too 'risky' to do so. In the collaborative framework, this guidance over quality ex ante means much more control over large pharmaceutical companies – especially at intermediate stages – than stock market finance would tolerate. Yet, while this guidance imposes risks on individual developers, it reduces collective risk and improves the collective outcome[377], and it should be possible to

[376] Farlow, 2004, ibid. Chapter 12.

[377] See the sections above that describe the way that more transparency of information can be used to guide firms to less 'bunch' their research leads.

coordinate in ways to share this gain. This is ultimately good for equity investors too.

More directly feeding finance to biotechs, not-for-profits, etc.
Another component of the finance mechanism involves more directly feeding finance to small biotechs, not-for-profits, and others so that they can take projects further. These already struggle to attract finance, and the APCs in 'Strong Medicine' are much less likely to improve this situation given their bias towards large pharmaceutical firms. In chapter 12 of Farlow 2004 the importance of venture capital and the way in which many firms and researchers are literally 'strapped for cash' is explained in much more detail. These firms are not helped at all by a mechanism that forces them to rely on a long track-record of free cash-flow and 'deep pockets' finance. It is not clear whether curious layers of venture capital could not somehow be created from some of the front-loaded funds, and a mechanism created for *all* potential developers to compete for these 'pots' of front-loaded funds on the basis of a track-record of vaccine performance and reputation for cooperation developed over time inside the vaccine enterprise framework, with the record for this generated by the collaborative part of the process, with rewards linked to performance on pre-agreed criterion, including on trials. This could involve a rôle for financial options, allowing these non-big pharmaceutical researchers and developers to trade part of the expected future rewards. As part of this, it is also not clear to what extent 'success' in a collaborative setting should *only* be judged on the basis of the end vaccine, since this is the very reason for the heavy dependence on free cash-flow and equity finance in the first place – and the build up of levels of sunk capital costs.

Curiously perhaps, in collaborative settings, these novel financial instruments are *needed* to support the market-creating purchase contracts at the end of the process. However, it can be seen that the exact proportion of equity finance could *not* be set in advance – which is another way of suggesting that the size of APCs could *not* be set in advance either. 'Strong Medicine' and 'Making Markets' implicitly presume that the proportion of equity finance could be set in advance, but this is not surprising given that the approach presumes away all collaborative features to the underlying science, replacing them with no build up in sunk costs, no information sharing, and all trial leads treated as totally independent drawings from a pool of potential leads. A finance mechanism build around a model that has been radically simplified to fit that mechanism is not that likely to suit real-world vaccine HIV, malaria, and tuberculosis R&D problems.

5.3. An Open Collaborative Information Processing Mechanism Linked to IP and the Financial Mechanism

The underlying principle is to create competition between a set of vaccine 'enterprises' – maybe one per region globally as suggested in the G8 and Whitehouse announcement in 2004 – but legally *enforce* regular updating of information, and use IP and financial instruments to control the process and reward both effort and sharing. This is the part of the mechanism that draws heavily off the experience of the human genome project.

There is a big difference however between developing vaccines and releasing gene sequence data. In the case of vaccine development, there are potentially very large sunk costs both for trials and manufacturing but also in the shape of capital costs, before anything vaguely like a result can be posted. Meanwhile, information is being posted that can undermine the value of that investment. If anything, this makes matters even more challenging, and it also needs the other three components to work too.

The 'open' collaborative part enables strategic decisions about where to expand research leads and also what quality of research leads to pass on to those working at later stages, and how much to 'insure' and how much to incentivize. This helps expand out the focus and reduce the overlap discussed above. Paradoxically, it is precisely the lack of collaborative thinking that is encouraged by 'Strong Medicine', that has held back the creation of a global consensus on laboratory techniques and benchmarks and mechanisms that enable the results of small-scale clinical trials to be ranked in head-to-head comparisons, so that resources can be focused as quickly as possible on testing the best candidates in large-scale trials. We saw many times above that the notion of 'controlling' through expectations of a committee's behavior at a point late in the process, simply does not work.

5.3.1. Expanded highly transparent clinical and preclinical trials

An important part of this iterative, adaptive, research process would be an expanded, integrated, international preclinical and clinical trials system, with considerable transparency of information – of preclinical and trial results – among vaccine developers and regulatory bodies in a large number of regions or countries. Instead of emphasizing just those with free cash flow (regardless of their vaccine expertise) the collaborative enterprise would include full participation of all relevant parties including those in developing countries. Again, this is antithetical to the approach of 'Strong Medicine', with its emphasis on decentralized, uncoordinated clinical trial and laboratory evaluation systems based on the notion that each (generally large pharmaceutical) firm already has internally *all* the information it needs. We nevertheless saw that in real-world applications of APCs there would already supposedly be much of this information being gathered about private firms and that there would also be a great deal of centralization of the public research process anyway, but none of it being shared or used in a collaborative way (in fact this would have to be ruled out from the start).

The need for trust in trials

There is also a range of issues relating to 'trust' in vaccines, and the general suspicion there may be concerning the motives of pharmaceutical companies and the use of inferior products on the poor. Any international trials program will be utterly dependent on the trust of developing countries. Given the ongoing controversies over clinical studies for nevirapine[378] and other controversies, the notion of secrecy of ongoing results (at the core of the model of 'competing HIV vaccines' along the lines of Kremer Appendix 3) would be simply unacceptable in

[378] See, for example, "Under suspicion: the HIV drug that held out hope for millions: Fresh cause for concern over the side-effects of nevirapine" Neville Hodgkinson, The Business, 30/31 January 2005.

the case of HIV vaccine trials and beyond. Nobody has really explored the way the current system of vaccine research (especially for complicated, composite, therapeutic vaccines) undermines itself by it's own secrecy. There are obvious tensions between openness and proprietary information, yet at another level, the sharing of information, if is strictly enforced, can mitigate some of these risks. Pharmaceutical firms, in particular, would gain nothing from taking a reputational and financial hit across their entire portoflio of products from keeping poor vaccines on the market.

Harmonized regulation
Key to many of the practical cases above were high standards of drug and vaccine regulation and quality control in emerging economies. There is a strong need to harmonize the regulatory procedures of all countries so that the same application can be submitted in most if not all countries, for example in Africa. The danger of complicated and different systems is that those applying for registration will choose do so in other 'easier' markets first.

5.3.2. The special challenges of therapeutic vaccines

In the case of HIV, these are aggravated further by the realization that we may not (at least initially, but maybe ever) be looking for a preventative vaccine, but instead a therapeutic vaccine that 'only' delays the onset of AIDS. This may still be valuable. Since the rate of HIV progression is linked to the viral load in a person's blood and secretions, if vaccine-elicited immune protection can be achieved against disease progression, it may also slow the rate of HIV transmission in a population. However, it complicates the process of evaluating the success of a vaccine, since, unlike a 'standard' vaccine, detecting signs of prevention are replaced as markers of success by the much more long-term therapeutic effect (incidentally, how does an APC, or indeed prize, allocate itself over multiple developers in such an environment?). 'Ongoing results' on the health of those who have taken therapeutic vaccines should, and would, be very openly monitored for many years even after vaccines are released, something never experienced in quite the same fashion with previous vaccines. This suggests that ways need to be found to encourage competiton even as information on ongoing results is openly available, and that not *all* competition (and reward) should hang on the end vaccine itself as the APC and other models presume. For example, we discussed above the very real dangers (to developers) of therapeutic vaccines being replaced over time. Common knowledge that all are being transparent might, paradoxically, help some form of compensation linked to information revelation to help ease this particular problem.

Ethical issues
This is also complicated by a range of ethical issues surrounding vaccine trials – thus raising the issue of developing country willingness to take part in trials and to use vaccines – and by the need to mix vaccine with non-vaccine approaches and to continue major preventative and treatment initiatives long after, and indeed in coordination with, vaccine development. This is summarized well by Choi and Letvin, and is worth repeating in full:

"Vaccines to prevent infections by other infectious agents have been evaluated in populations in the developed world and then used worldwide to

eradicate a microbe. The testing of HIV vaccine candidates poses an unprecedented problem in this regard. The population at risk of HIV infection, and therefore the populations in which an HIV vaccine can be most readily assessed for efficacy, are in the developed world. If an HIV vaccine prevents overt disease but does not prevent infection from occurring, a highly sophisticated evaluation of vaccines will be required in any large-scale studies of vaccine efficacy. However, the infrastructure that will be needed to monitor such vaccine efficacy does not exist in these geographic regions. Therefore, the testing of HIV vaccine approaches in at-risk human populations presents a challenge to the medical and scientific community."[379]

The analysis (contained in Kremer Appendix 3, and earlier sub-notes) underlying the modeling of APCs for HIV vaccines, presumes multiple independent competing vaccines, that information can be kept totally private (even though it is derived supposedly in secrecy and used by the IAC to make decisions), that collaboration (and the problems this creates for contracts and ownership) can be ignored, that efficacy results can be ascertained in real time (in order to arrange payments), and that risks caused by lack of monitoring and other infrastructure can be ignored. Therapeutic vaccines as complicated as those for HIV do not fit this model at all well (indeed the Kremer modeling makes no concession to the difficulties of HIV vaccines compared to, say, flu vaccines). It is not at all obvious that an ever-bigger APC, with ever more gyrations to get around the paucity of information it would come to rely upon, with risk shifted heavily to private industry, would automatically crack such a complicated challenge. But this is the basic solution put forward in 'Strong Medicine' and underlying 'Making Markets'.

5.3.3. A more creative use of industry

The emphasis of 'Strong Medicine' is on the power of stock markets to discipline private firms. Yet Klausner et al. claim that the costs of developing new vaccine candidates, especially protein-based immunogens or noninfectious particles, and the scientific risk of failure are so high, that "reliance on industry to carry the major load for discovery and development for HIV vaccines is unrealistic". They call for "creative new public and public-private partnerships…with industry's development expertise a key element that must be marshaled effectively."[380] In particular, the lack of manufacturing capacity and of the uniformity in production facilities needed to produce vaccines to the standards needed for human clinical testing, has repeatedly delayed HIV vaccine clinical trials programs. This calls for the creation of dedicated manufacturing facilities and personnel devoted to the development, scale-up, formulation, stability, safety, toxicology, and production of experimental HIV vaccines. The skills for this are largely, but not exclusively, found in the private sector. The importance of such manufacturing infrastructure is even more important given that the major focus of HIV vaccine development has shifted away from large pharmaceutical firms to small biotechnology companies, or nonprofit or academic organizations, which have little or no vaccine manufacturing capabilities and experience. APCs are not the most

[379] Choi, E.I., and Letvin, N. L., 'The Vaccine Book', p253.

[380] For some reason such statements always seem to be interpreted by proponents of early-stage advance purchase precommitments as automatically meaning support for their approach. The statement is, of course, open-minded.

creative or efficient way to activate this, and we have seen that they tend to concentrate resources into a few reluctant hands rather than broaden the financial base. Why seek to concentrate the manufacturing infrastructure in the hands of those less likely to hold vaccine development projects in the first place, to the determinant of those who do?

The collaborative approach is very strongly in favour of a role for commercial players, but is much more creative about it than 'Strong Medicine', and much more mindful of the need to handle the risks through contracts that allow an element of risk sharing, and of the need to consider access to finance of the different players. Unlike in the models of 'Strong Medicine' where all the risk is placed on the developer for all stages – here the risk is distributed in part (maybe even largely) away from firms.

5.3.4. More competition, but not all via a committee at the end

For all the talk of competition, systems based on early-stage APCs rely on a committee, the IAC, to enforce competition in the R&D process. This is very different from typical competitive tenders. The IAC seeks to achieve competition before it gets to act, but based on the expected rules and/or discretion that it exercises in the end product 'market' (and only in the end product market) when it does act. That it would be a 'competitive system' for HIV is a dubious claim – no more than a caricature.

In contrast, there is plenty of room for competition in a collaborative mechanism as the human genome project proved, with opportunities for competition at multiple stages of the R&D process as well as, possibly even more so, in the end market where technology transfer is central to increasing competition and driving down manufacturing costs. In collaborative systems, competition is able to be in *real time*, at all stages including the competitive manufacturing tenders at the end. This, it is argued, is crucial for the success of cheap vaccines. It is false to dichotomize one mechanism as driven by competition – when it clearly is a very curious sort of competition and open to capture by special interests – while characterizing the other as weak and feeble because of 'lack of competition'.

Leading proponents of APCs for HIV constantly brush over the fact that the IAC, a committee, is *the* source of all competition, but then fail to give a convincing explanation as to how the IAC would perform such a function and/or not be captured. It is generally a bad principle – less robust to institutional, cultural, and practical failure – to concentrate the driving force for competition down to one point, institutionally and temporally, rather than trying to create competition at many layers and from many sources over time. This latter notion is much more capable of being a part of a Global HIV Vaccine Enterprise than of an APC.

Let's stop the caricature

The frequent distinction between push as referring to inputs and pull as referring to outputs is, in many ways, an unhelpful (though deliberate) caricature. The notion that collaborative mechanisms are not based on results or competition is stretching things: "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…" (italics added)[381]. The point about a collaborative approach along the lines of the human genome is that there *is ongoing* competition between many more players, with evaluation and funding chances ongoing, rather than the much more limited competition between a few wealthy players driven by the potential vagaries of the decision of a committee at the very end of the whole process, based on grand set of ex ante heroic assumptions.

5.3.5. How much private industry?

There is insufficient time here to discuss the degree to which the public or private sector might provide the skills needed to get products through the last sections of development; others are much better qualified to say. The general argument given in favour of the private sector 'taking over' the last stages of vaccine development is that the private sector – essentially via the stock market – is more capable of incentivizing good over bad outcomes[382]. But there are other angles to this. One possibility is that equity finance is simply more appropriate for some activities over others, and equity finance is more amenable to private sector provision. Another possibility however is that it is much easier to 'rent seek' in later stages than at is in earlier stages. We also know that the early stage activity is often very risky indeed and, quite likely, private firms cannot internalize sufficient benefit to make this worthwhile.

One problem of feeding all late stage activity through private firms is that the development and regulatory approval of drugs and vaccines for the poor has to compete for the limited pool of skills with the development and regulatory clearance of drugs and vaccines for the rich:

> "*In effect the private sector, being the only source of the skills needed for the last section of the development pipeline, endows powerful (private sector) monopoly in its own right.*"
>
> "*The skills monopoly over the last section of the developmental pipeline therefore puts the private sector in a strong position to demand exclusive rights over any products that are developed. Is this an efficient way of stimulating the necessary R&D? It is an expensive matter to develop and licence a vaccine product, but how expensive exactly? How can it be known whether the monopoly rights granted wildly over-reward the private sector for their contribution, or whether they simply make a viable return on the resources they have invested? Typically, it cannot be known as these costs are treated as confidential but it is now an open question…How much reward is provided for how much input?*"[383]

Given the reluctance of the private sector to take forward candidate vaccines, an alternative sees the missing developmental pipeline skills bought in from organizations other than multinational pharmaceutical firms, or by the creation of a whole new entity such as a 'National Vaccine Authority'. Some have argued

[381] Berndt, E.R. ibid.
[382] See Farlow, 2004, ibid. Chapter 12.
[383] Garrison. C., ibid. p33-34.

that the development of such an authority is long overdue[384]. From the perspective of the discussion here, the key issue is that there would be no point setting up an APC for HIV and then expending yet more resources on setting up such an authority, since it would either just crowd the APC out (by expanding, it harms the prospects of private industry 'winning' the APC, hence private incentives are harmed even for an APC of a given size) or (if the APC was failing) it would have to struggle to avoid the APC harming the vaccine authorities' ability to function. Clearly, deciding for or against a 'National Vaccine Authority' is not something that can be separated from the decision whether or not to go with an APC.

5.4. 'Contingent Purchase Commitment' Contracts, With Much More Emphasis on Production and Distribution

The fourth component of the mechanism draws off recent 'pull-work' and seeks to incorporate this with the three components described above. But there would be a great deal more emphasis on the very real practical problems of ensuring vaccine delivery. It is crucial to realize that the contracts about to be described would be highly inefficient without the other three components. This is pertinent in light of the current GSK Biologicals case, which looks to be generating purchase commitments that break from the 'Strong Medicine' mold, but without any of the supporting components described above.

More like standard procurement contracts

Unlike the APCs in the 'Making Markets' and 'Strong Medicine' literature, the contracts set up to pay for 'results' would look much more like standard competitive procurement contracts, and may not (and probably would not) involve full equity-based finance. Since a lot of the overall R&D costs would not be covered by the contracts anyway, nowhere near as much would be extracted through vaccine prices to pay for R&D, and vaccine prices would be much nearer to average manufacturing costs to start with. It would be impossible to set the terms of these much smaller purchase commitments on the basis of the information available at the very start of the process as suggested in 'Strong Medicine' and 'Making Markets', but they could be set up in advance to be *contingent* on information as and when it is revealed. For lack of better terminology, we may call these '*contingent purchase commitments*'.

Variable equity finance and more control over IP

By being more contingent and variable until the terms are set, and yet much more like standard procurement contracts once the terms are set, these contracts enable the collaborative part of the process to vary the quality and number of vaccine leads being pursued by late-stage manufacturers – yet do it without harming those already working on late-stage leads and without increasing the risk of such developers further. This allows the proportion of activity covered by equity finance to vary. Intuitively, it is impossible to know in advance what proportion is to be insured (collaboration) and what proportion is to be incentivized (by equity), and it all has to be adjusted to adapt to the credit conditions of those involved in the process. Risk, and hence payoff, are related to things researchers and developers have control over – such as *quality* of vaccine work and trials – and

[384] Institutes of Medicine Council on Vaccine Development, 5 November 2001.

hence can be motivated on. In diametric opposition to the 'Strong Medicine' approach, quality would not be controlled entirely through payments at the end of the research process, but *during* the process, via the open collaborative part of the mechanism.

This would solve many of the problems listed above. There would be more guidance on the quality of vaccines, much less of a role for an IAC presetting conditions and the size of pots of funds years in advance based on heroic assumptions (even as it tries to avoid being captured by special interests), fewer APC institutions and pre-determined rules, more control over the eventual intellectual property, products priced pretty close to marginal production costs, and with faster release to mass competitive generic producers to drive manufacturing and delivery costs down.

The problem with large early-stage vaccine APCs is that because so much of the overall R&D is *still* being extracted in the final vaccine prices (we saw above how the logic requires that the payments rewarded to each 'winning' firm be *hugely* disproportionate to its own costs) this starts to drive all kinds of distortions, not just on quality but also on information gathering, sharing, strategic use of patents, capture of the IAC, etc. Obviously as the recovery of R&D expenditure shifts away from the end of the process to earlier stages in the process, this weakens some of the incentive effect of the pull (though we argued it was weak for HIV anyway, and there are plenty of ways that one can make up for this), but the amount brought forward is offset by gains. Again, this suggests a mechanism for locating the optimal point at which to switch from front-loading to end-loading, and certainly *not* that it should all be end-loaded.

The biggest gain is in quality

Probably the biggest gain is in quality of vaccines. With less R&D extracted through end prices, this removes a great deal of the pressures described above and elsewhere[385] to dash for poor quality to get the 'big early prize' and – in a self-reinforcing fashion – *helps* those guiding quality of vaccines in the collaborative part of the process.

Because they are less dependent on their exact terms being fixed at the start of the process, 'contingent purchase commitments' could be designed to adapt to intellectual property regimes that allow for much more sharing of information. The late-stage issues would be of a much lower order anyway, if there were less sunk expenditure to recover through vaccine prices.

Collaborative earlier mechanisms, by reducing the severity of many of these late-stage problems, might actually help the efficiency of 'contingent purchase commitments'. The exact workings of the Global Vaccine Enterprise have yet to be finalized, but could easily incorporate some forms of late-stage, 'contingent', purchase commitments.

Flexible, but less of a problem with credibility than APCs

[385] Farlow, 2004, ibid. Chapter 7.

It might be argued that this lack of pre-determined size makes these contracts less 'credible' that those described in 'Strong Medicine' and 'Making Markets', but we already found that, in reality, this was a major problem with the APCs described in this literature. Any individual developer working under *that* mechanism faces layers of discretionary decision makers, due to the heroic informational assumptions that would have to be made at the start, and they would be exposed to a great deal of uncertainty about what they would get from the mechanism (and this all shows up in the level of capital costs). In the 'Strong Medicine' mechanism, the fixity of the size of the APC at the start comes at a very heavy cost. We argue that this shortcoming is less of a problem anyway if the other components described above are also present.

Another way to think about this, is that if up to $10bn[386] is to be made available for tackling each of the more difficult vaccines, how exactly should that level of funding be split between the purchase commitments and other parts of the process? Since this cannot be known in advance, we either have to plump for a fixed split along the lines of 'Strong Medicine' and adjust afterwards through discretion, or face the reality of our unknowing and have a flexible split from the start, and adapt other parts of the funding framework to this. 'Contingent purchase commitments' just bite this bullet from the start.

It is also central to the efficient working of the 'Strong Medicine' mechanism that the 'pot' of subsidy available for those who win APCs is large and *fixed* at the start (though in the details of the framework it is not fixed for any particular developer, and – indeed – the layers of uncertainty, discretion, and risk mean that the overall *expected* size is not effectively fixed *anyway*). Supposedly, the laws of motion push in the direction of the optimal number of firms working on research leads *given the size of the pot* of subsidy, with the optimum number of firms chosen via choice of the size of the pot (we saw that this would not be the case anyway if there were just a few large pharmaceutical firms, much hidden information, and a general inability to 'know' all HIV science for all time). It follows that it should not be possible under any circumstances for policymakers to alter the size of the pot after the mechanism has started to operate (in practice, this seems to have been interpreted as not lowering it, though it actually also should mean not raising it at a rate higher than the rate of interest), and that firms form their optimal strategies on the basis of their expectations of the strategies of other firms, and never of the holder of the 'pot'.

A mechanism more able to work out optimality

A couple of significant observations follow from this. First, that in a world of a great deal of hidden activity and opaque use of other research support devices, firms operating under the free-for-all 'Strong Medicine' and 'Making Markets' mechanism would struggle anyway to know how *optimal* their own intensity of activity truly was (it is anyway more likely that the mechanism would end up based on a few large pharmaceutical firms, which is decidedly non-optimal). Perfect competition and perfect information (and therefore no need to ever 'share' information) and perfect application of the mechanism always and everywhere, resolve this in 'Strong Medicine' and 'Making Markets', so that there is no risk to

[386] This is just a guess; nobody knows the right figure.

players *from the mechanism itself*. But it is hardly satisfactory to assume the problem away.

In reality, linking payments to the performance of the *whole APC mechanism* imposes a great deal of risk on developers; risk that does little to motivate them and is costly for them to handle (it shows up in the required size of the fund). Basing contracts on achieving a certain 'performance' may be more efficient than basing contracts, *per se*, on the end vaccine and the *relative behaviors of others*. Part of the purpose for making the 'contingent purchase commitments' more like standard procurement contracts is to remove this 'mechanism risk'.

Rather than an elaborate set of assumptions and the perfect application of an idealized – though essentially low-tech vaccine model – to high-tech vaccine problems, collaboration and sharing of information are instead used to achieve the right intensity of activity. But this does not sit well in the 'Making Markets' framework. Paradoxically, we saw that that framework did anyway involve huge amounts of monitoring of 'intensity' and that it would struggle to do this against a background of complete non-collaboration. At least here the monitoring is working *with* the collaboration.

More flexibility to allow expansion and adjustment of collaboration

Second, once we shift attention to the collaborative mechanism, we realize that since we do not really know in advance how the collaborative part of the process will evolve, firms cannot therefore know in the aggregate how much of the overall 'pot' will be used in the non-collaborative part of the process and how much of it they collectively will be picking up in purchase commitments. Therefore, if they face 'Strong Medicine'-styled APCs, they cannot individually know how much R&D they should be doing to try and win an APC (though, at least, the sharing of information helps this problem). In addition, once there is any control by those 'running' the collaborative mechanism over the research leads being followed, then the value of contracts for research leads is dependent on the other contracts so far given out or expected to be given out. When accepting a contract, a firm is aware that the contract-giver can 'harm' the value of the contract they have been given through giving out more contracts. But this creates a fundamental problem if there is a flexible need to increase or decrease the number of contracts or to re-target activity. One cannot re-target or ramp up activity without harming those already engaged in activity. The assumption of perfect competition amongst large numbers of vaccine players removes this risk in 'Strong Medicine', but this is totally at variance with the reality.

A practical example

As a very practical example, if an APC is set up on the basis of the current narrow focus of research leads for an HIV vaccine, how should it be set? How do private firms react if the collaborative mechanism expands (as it may well do if it ever has the appropriate level of resources) into the areas of 'neglected' leads, including even funding some of the trials itself? This risks destroying the value of the currently-set APC based on the currently-active non-neglected leads. Firms could have one of two responses. Engage in research and sue whenever the value of that research is undermined. Or, expecting this anyway and not wanting the bad press, don't engage in research in the first place.

Or would the APC be set up on the basis of the expected future expansion of the focus of the Global HIV Vaccine Enterprise into these areas of neglected leads? If so, it ends up being set at a level that is totally wrong for the current limited focus.

The upshot to all this is that it proves impossible to set payoffs for the APC part of the overall collaborative mechanism that would not in some sense have to be *absolute* through contracts that are much more like standard procurement contracts. Bluntly, it is impossible to handle, in the ex ante terms of an APC, the sort of scientific uncertainty generated by conditions such as HIV/AIDS (or malaria or tuberculosis) or uncertainty about where the collaborative mechanism will evolve over time to tackle it.

The cost of HIV vaccine distribution is likely to be high: The need for "Advance Distribution" commitments

The total cost of all six EPI antigens is $1, but the delivery costs in Africa are $12[387]: "Thus financing vaccine distribution may be as important as, or more important than, financing vaccine purchases."[388] Yet 'Making Markets' spends no time worrying about the distribution issues. These are likely to bite much more than normal for HIV vaccines. HIV vaccines will not at first be delivered to infants and children, the target of most current vaccination programs. It will not therefore be possible to use the existing vaccine distribution infrastructure. The initial targets will be high-risk groups – commercial sex workers, truck drivers, adolescents – for which there are currently few such distribution and monitoring mechanisms in place. To this we might add that the greatest current need is in countries that have the lowest levels of infrastructure and the highest opportunity costs already (the opportunity cost is high where, for example, there are very few nurses per head and many other healthcare demands already). This lack of pre-existing infrastructure and the fact that may high-risk categories of potential recipients of a vaccine are much less likely to be amenable to tracking and multiple dose treatments, is yet another reason why multiple doses for an HIV vaccine may be less useful than a single dose vaccine, and is another reason why vaccine developers are put off from investing for such markets. Rather than putting all the emphasis on large payments to pay for a long process of R&D, precommitted payments should go into an "AdvanceDistribution" mechanism, something that will benefit all investors into vaccine R&D – public and foundation as well as private.

As a reminder, these contracts become inefficient without the other three interlocking components.

5.5. The Real Challenge

There is a tendency in the current debate on this issue to visualize the solution as one pure system. In truth *all* mechanisms are highly imperfect. The best policy in such circumstances is to try to exploit various tools for different parts of the process up to the point at which each tool has a marginal impact on the problem

[387] Berkley, S., 2002. ibid. p590 and reference therein.
[388] Berkley, S., 2002. ibid. p590.

equal to every other tool. The real challenge is to work out how each part of this larger mechanism creates and handles information and risk, and how different parts fit together to reduce overall risks and costs (including, and even especially, capital costs), to speed up discovery, and to generate high-quality vaccines. This would include working out the exact point at which a 'contingent purchase commitment' might optimally cut in. We can only hope that these much more innovative possibilities are not simply drowned in a sea of large, yet ineffectual, early-stage APCs, or indeed a pond of inadequately-sized and ineffectual APCs that give just enough water for politicians to sale their boats, but such that the distraction stops them from doing the really important funding initiatives.

PART 6. MALARIA VACCINES IN THE CONTEXT OF A GLOBAL VACCINE ENTERPRISE

6.1. The Problems of Malaria Vaccines

We know that "*the parasites that cause malaria are much more complex than the viruses and bacteria that heretofore have been controlled by vaccination*[389]". This is picked up in the multistage lifecycle of the parasite. This generates a number of challenges for malaria vaccine research:

i) Frequently, the proteins expressed by each of these stages of lifecycle are antigenically distinct. For example, if a vaccine manages to achieve high levels of antisporozoit antibodies (to defend against the sporozoits inoculated into humans by the Anopheles mosquito), these antibodies generally do not recognize the asexual erthrocytic 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 epitopes;

iii) This is further complicated by extensive within-strain antigenic variation.

In summary:

> *"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 unfavourable to the host, and greatly complicate the challenge for vaccine developers."*[390]

This is all compounded too by the complexity of the human immune response. Unlike HIV for which "*natural immunity does not appear to have a strong impact on the final outcome of HIV infection"*[391] this 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 sever 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*

[389] Hoffman, S.L., and Richie, T.L., 'The Vaccine Book', p294.
[390] Hoffman, S.L., and Richie, T.L., ibid., p295.
[391] Lee, T-H. and Novitsky ibid. p596.

parasite…Much progress has been made, but no vaccine delivery system has been shown to be optimal or adequate."[392]

This suggest that the optimal vaccine will vary over time as the rate of transmission changes (for example 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 and precise disbursement of any APC funds across vaccines over time, even as the rules governing this disbursement must be credibly fixed in advance based on knowledge of the future science and vaccine needs.

6.2. The GSK Biologicals Case

"*It could easily take a decade to develop malaria, tuberculosis, or HIV vaccines"* Michael Kremer and Rachel Glennerster[393]

"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[394]

"*Who has been briefing Mr Brown…?"*
Michel Pletschette, European Commission Directorate General for Research, 25 November *2004*[395]

There was a recent announcement that some sort of advance purchase agreement was being struck to help GSK Biologicals take forward a promising malaria vaccine lead[396]. The recent UK Treasury line[397] is that this purchase agreement would be open to *all* malaria vaccine developers and not just GSK Biologicals, and that the press had wrongly misinterpreted it as somehow attached to GSK Biologicals. However the exact nature of the commitment was expressed very unclearly – in what seemed to be an addition to a speech – at the time of the original GSK Biologicals vaccine 'breakthrough' in a way that seemed to indicate that the commitment related to *these vaccines* in particular. The full text is:

"*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*

[392] Hoffman, S.L., and Richie, T.L., ibid., p298.
[393] 'Strong Medicine' p74.
[394] www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_105_2004.cfm.
[395] Pletschette, M. WHO Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 25 November 2004.
[396] http://news.bbc.co.uk/1/hi/health/3742876.stm
and http://news.bbc.co.uk/1/hi/uk_politics/4038377.stm.
[397] Private communications with HM Treasury officials.

> *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.*" (emphasis added)
>
> Speech by the Gordon Brown at the BBC World Service Trust conference 24 November 2004[398]

As *any* malaria vaccine expert could have told Gordon 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 three counts. Similarly, Brown wrote in an op-ed in the British newspaper 'The Observer' in early June 2005:

> *"But the long-term search for an anti-malaria preventive vaccine has been boosted by recent medical trials in Mozambique arising from a partnership between GlaxoSmithKline and the Gates-led Malaria Vaccine Initiative…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…"*[399]

Given that GSK was putting all the investments in place to bring this research on, 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 is also not a correct interpretation of the underlying vaccine development problem[400]. Indeed, the above quote seems to indicate that the purchases would lock in for "the vaccine" only "when developed", which is outside of the 'Making Markets' usage of APCs to cover the costs of R&D and "the vaccine" development in the first place, and it suggests that the heavy costs of vaccine development would be paid for from alternatives to those of an APC. If so, the figures of $3bn or $4bn, and the 'Making Markets' analysis are largely irrelevant to this case. At the moment, however, it is all rather unclear.

Given the scientific understanding above, and the clear dangers that in incentivizing one activity, it may be that all kinds of other activity are disincentivized, one of the main dangers to be avoided is to use APCs (and indeed funding into preferentially selected PPPs) that reduce the problem to one large pot of subsidy with all the required rules and structures required to drive good incentives simply missing.

---

[398] http://www.hm-treasury.gov.uk./newsroom_and_speeches/press/2004/press_94_04.cfm.
[399] The Observer 5 June 2005 http://politics.guardian.co.uk/development/comment/0,15709,1499651,00.html.
[400] 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.

From what can be made out from the information released so far into the public domain (that is, practically none), the apparent GSK Biologicals 'deal' (if there is one in writing yet, which is not clear in itself[401]) is *not* along the lines of the recent 'Making Markets' proposal (that itself is a fairly vague proposal on many of the issues)[402]. 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 private vaccine developers, rules about efficacy limiting players' room for maneuver, plenty of monitoring to help set later rewards, modification to account for push payments not strictly motivated by the APC, and – so as to enforce credibility – no discretion by sponsors to engage in procurement behavior after product development that bids the total value of the winning developer down to a level nearer to that firm's expected actual costs of development, and – because of the scientific difficulty and ex ante problems in judging costs and epidemiology – lots of discretion. There would be a huge disjoint between what a developer would get from the APC and what they had actually spent on R&D, but they would still *not* get the whole pot of subsidy[403].

Instead, from what can be made out so far, the GSK Biologicals 'advance purchase commitment' seems to be much more like a standard procurement purchase commitment, as described above (though it is not at all clear what the nature of the contract is). If we know that there is a high likelihood of slipping into this kind of purchase commitment anyway, then some of the other parts of the collaborative mechanism described above start to sound slightly more sensible too perhaps? We noted above, however, that initiating only one of a package of measures that needed to be initiated together is not only less strong but that it was even damaging, potentially harming the efforts of other developers to find a 'globally' superior set of malaria vaccines.

Incidentally, from the 'Making Markets' analysis, it is *required* that the exact nature of the contract be placed – and indeed be policed – in the public domain so that *other* developers will know exactly how to respond optimally. There could be no secrecy in the terms set for, or handling of, GSK.

6.3. The PPP Setting

> **"***Public-private partnership leads to scientific breakthrough in malaria vaccine development*" Headline, GSK Biologicals website[404]

---

[401] Nowhere on the GSK Biologicals or GSK websites is there the slightest hint to any APC, something one might think highly unusual if GSK Biologicals or GSK were to regard the announcement as a financial breakthrough worth signalling to their investors and useful for positive PR purposes. In addition, the most recent G7 Finance Ministers statement is slightly more toned down than previous announcements about such commitments, talking only of "exploring" the use of advance purchase commitments. Maybe policy makers have seen through some of the hyperbole and come to realise just how difficult it is to make such instruments work in practical reality?
www.hm-treasury.gov.uk./otherhmtsites/g7/news/g7_statement_conclusions050205.cfm.

[402] It is not clear publicly exactly what it is yet, so this section will probably have to change over time. It would help if the details were placed in the public domain.

[403] 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'.

[404] GSK Biologicals website:

"*This project demonstrates the power of collaboration between the public and private sectors*" Jean Stéphenne, president and general manager of GSK Biologicals[405]

"*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[406]

"*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 TB 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[407]

The RTS,S/ASO2A trial was conducted by the Centro de Investigação em Saude da Manhiça (CISM). GSK Biologicals and PATH's Malaria Vaccine Initiative (MVI) co-sponsored the trial, which was approved by Mozambique's Ministry of Health.

"*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[408].

Dr. Alonso, the principal investigator of the study, heads the Center for International Health of the Hospital Clinic at the University of Barcelona. Mozambique's Minister of Health, Dr. Francisco Songane, said his nation was proud of its part:

"*We did this not only for the people of Mozambique, but for the people all over Africa whose health and development suffer greatly from this terrible disease*."[409]

---

www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10392, 15 October 2004.

[405] GSK, ibid. London, Friday 15 October 2004.

[406] "GSK in collaboration with European Union." http://www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379.

[407] http://science.gsk.com/about/disease.htm.

[408] *Pedro L Alonso* et al, "Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial", The Lancet, Volume 364, Number 9443 16 October 2004 www.thelancet.com/journal/vol364/iss9443/full/llan.364.9443.primary_research.30985.1

[409] www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=360 (and elsewhere).

To key advocates of APCs, however, PPPs for malaria are between only a quarter and a third of the effectiveness of an APC[410], and the latter is to be preferred anyway.

This all hints at one of the other big problems with this case, when looked at in a much greater context. The RTS,S/ASO2A vaccine was and is being developed within a PPP framework, with strong support from the European Union and the European and Developing Countries Clinical Trials Partnership[411]. Strictly speaking, if GSK Biologicals were drawing from a 'Making Markets' APC fund (with the drawing related to the vaccine's 'quality'), the *proportion* of GSK's overall research carried out before the commitment was announced would have to be cut from any eventual APC payments (observe the disincentive to keep down the costs of later stages of development), as would any proportion of total funding accounted for by non-private funding in its development from now on (observe the incentives to distort this too), so that such APC payments would be reward for the *fresh* GSK equity finance brought into the project. Otherwise the APC funding will simply crowd out funding that should have gone on alternative vaccine researchers elsewhere; and other researchers 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. It will be interesting to see how expected subsidy levels, tax allowances, and support from the European Union and others will be treated in the overall calculations of the size of the eventual purchase commitment payments, since it would require that the company be extremely transparent with the necessary information. Or will these issues just be ignored, thus weakening the instrument?

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 the RTS,S/ASO2A project fully equity financed, in pursuit of the APC payments, and the PPP sponsors should be free to find *competing* vaccines to support. 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 to actually face the choice. Indeed, the Gates Foundation are currently negotiating a further major injection into this particular malaria PPP, suggesting that GSK are less convinced of the power and usefulness of the APC route for developing a malaria vaccine.

Barder[412] says that "the proposal is intended to complement…public private partnerships and other approaches,"[413]. Yet nowhere in the APC literature is the interaction of the APC mechanism and the PPP mechanism analyzed (by which one does not mean statements that they are intended to interact, but, instead, hard factual details of *how* they are to interact). For example, the typical PPP contract with private players involves risk-sharing in exchange for some control over the IP, lower vaccine prices and access in developing countries. How does this gel

[410] And between a fifth and a quarter of the cost-effectiveness for HIV. See Kremer, M., No 10 Policy Unit Summary p2 and tables on p4.
[411] http://www.edctp.org.
[412] Barder, O. ibid.,19 November 2004.
[413] Barder, O., ibid., 19 November 2004.

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? Or is the public/foundation allowed some IP ownership too? But how does that conflict with the need to attract more *additional* global private funding and the fact that giving IP to non-private players implies giving part of any APC pot away? 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 No. 10 Policy Unit Appendix 7 calculations is that the APC achieves additionality by being the only incentive device present. Are PPPs phased out? 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 might have actually meant something in practical reality. This rather contradicts the notion that this mechanism is not being promoted *regardless* of other approaches, rather than in collaboration with other approaches[414].

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 *other* vaccine players and the overall vaccine enterprise and the expected quality of any vaccines generated (but the public will never notice, so the policy makers have less incentive to spell this out, never mind act upon it).

To complicate matters, Tarcisio Hardman Reis[415] argues that since such finance by a government to advantage its own domestic private companies is a form of subsidy, such contracts "might be considered as subversions for the purposes of the EU and possibly represents unfair competition for WTO." Furthermore Ries 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. The way this particular contract (or is there a contract yet?) seems to have been set up so far does seem to 'unfairly' advantage one domestic producer over many other European, global, and smaller companies. Just the risk of this being acted upon by competition authorities and others at some future point in time is a risk to the firm itself. Maybe this is why the firm is not so apparently keen on the idea in the cold light of day, and it gets no mention on the firm's website?

Or perhaps GSK plan to use the PPP approach, and any purchase commitment is to scale up production if ever a vaccine is developed, therefore having nothing to do with the 'Making Markets' notion of a malaria APC?

6.4. The Problems of Setting Minimal Conditions, Controlling Quality, and Crowding Out

Would this case have got a 'Making Markets' advance purchase commitment?

This case shows the difficulties of setting minimal contract conditions in advance. It is not clear how the GSK Biologicals case would have faired had a pre-existent

[414] Berndt, E.R. ibid.
[415] Tarcisio Hardman Reis CIPIH Forum 16 Nov 2004.

APC of the type discussed in 'Strong Medicine' 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% of permanent protection against attacks in children bestowed by one malaria vaccine shot in a low resource setting (the results so far are '30% protection for six months based on three shots in a highly-resourced setting')[416], and had other vaccine developers sunk resources working towards *that* goal, the GSK vaccine would have had to be denied any promise of APC funding or, if the firms was offered a contract breaking the original contract, all other firms would have had to be compensated (perhaps after litigation). It is highly unlikely that the British government would encourage the latter, since it would put developers off from trusting such contracts ever again, and these costs would weigh heavily against the possible gains from breaching the terms of the original contract. 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. Even the ex ante knowledge that GSK might be given APC funding 'against the rules' would damage the value of the investments of other developers.

It may be that the only reason this particular potential vaccine might now be able to attract a large purchase commitment of a procurement variety (again, it is not clear what the exact state of play is on this) is precisely because there was no early-stage APC of the 'Strong Medicine' variety in place in the first place.

Difficult to use purchase commitment quality rules

The case also indicates the difficulties in using the rules of purchase commitments to control quality ex post. It would be very difficult to put off funding for the current GSK vaccine in preference for a, supposed, vaccine effective against 80% to 90% of attacks that is somehow 'out there', when policymakers now have a 'bird-in-the-hand' 30%+ possible effectiveness, even if the rules dictated this 30% effective vaccine should be abandoned.

The case also raises the issue of how to control vaccine characteristics over time through APCs[417]. On the first point, let us imagine for a moment that there is, somewhere in the pool of potential vaccine leads 'out there', 'a' malaria vaccine lead that will one day cut 90% (or, dare we hope, 100%) of malaria attacks in children in one shot, and that the level of APC to find and bring it to market is,

[416] The vaccine, known as RTS,S/ASO2A, has shown potential against Plasmodium falciparum malaria, the most severe form of the disease. It acts at the 'pre-erythrocytic' stage, before the red blood cells are infected. A recombinant protein that fuses a part of the *P. falciparum* circumsporozoite (CS) protein with the hepatitis B surface antigen molecule, RTS,S, has been under development by GSK Biologicals for more than 15 years In the phase-II double-blind, controlled trial, involving 2,022 children in southern Mozambique, half were given the vaccine and half a placebo. Malaria attacks were cut by 30%, new infections by 45%, and severe disease causing death by 58%. In contrast to the previous trials of this vaccine in adults, which suggested that vaccine efficacy was short-lived, protection in these children lasted at least six months. See *Pedro L Alonso* et al, ibid, and "Vaccine efficacy: winning a battle (not war) against malaria," Van de Perre, P., Dedet, J-P., The Lancet, Volume 364, Number 9443, 16 October 2004 (The title of the latter article is rather telling).

[417] For studies into the bacterial and viral resistance to existing malaria and tuberculosis medicines see: Zumla, A, Grange M, "Multidrug resistant tuberculosis – can the tide be turned?" Lancet Infectious Diseases, Vol 1, 2001; Ridley, R, "Medical need, scientific opportunity and the drive for antimalarial drugs". Nature, Vol 415, 7 February 2002.

say, $10bn. This includes an allowance for all the faults of APCs listed above. This is an expensive approach though we do not know just how expensive (or, indeed, whether, given the use of APCs, the $10bn is still too low). Currently, on the basis of a narrow pool of research leads (based on globally really very small levels of malaria vaccine research) an 'early' research lead shows promise to 'cut 30% of attacks'. Though this is a good vaccine lead when you have few or no similar leads, nevertheless the 'low' quality of *this* lead is itself partly the result of the very poor levels of funding in the past and also partly the result of the lack of past collaborative effort to generate high-quality vaccine leads. Let there be only $3bn made available for a purchase fund to cover the risk-adjusted development costs of *this* vaccine (should it, indeed, be successfully developed and should an APC be used to fund 'development'). This is the figure that GSK has apparently been offered according to the Center for Global Development, and much lower than many of the original figures that the Center for Global Development was presenting.

Let us presume that negotiation does not put in place the $10bn fund. Maybe for reasons of political expediency, quality (especially over time) is not deemed an important consideration and some much lower target is set, something just enough to feed one big player perhaps and still hope to come out looking good. Two cases come to mind:

i) The first is where there is no absolute market promised for this vaccine, but a set of rules to allow this 'early' vaccine to be easily replaced if a higher-quality vaccine is developed, with GSK barred from supplying any vaccine in this case or getting any of its R&D costs back. If there is a later big R&D push, with much higher levels of research funding and even a collaborative mechanism put in place to explore a wider range of new leads to try to find the 90% lead, this will destroy the value of the work being done by GSK Biologicals on the 30% lead. They (and policy-makers) will need to work out *in advance* what the chances are that the funders will encourage this greater body of research and the chances that it will destroy the value of what GSK is doing. GSK might indeed be interested in ways to 'insure' against this.

ii) If, instead, an absolute level of market *is* guaranteed for this developer regardless of what is happening on other vaccines, and should the vaccine be developed, then the required fund to find and develop the 90% lead is now *higher*. Not only is it $10bn plus the expected $3bn of this vaccine (depending on whether it is likely to be claimed), but, since the company is being promised an absolute level of market, those working (or potentially working) on the wider range of leads will perceive the chance of a large initial market now reduced and the average expected cost of developing the 90% vaccine now even higher[418].

[418] Logically they should expect the first vaccine to be replaced and for them to get the *whole* market, but that would require paying for the first vaccine and never using it.

> If a better vaccine is developed than this one, how will GSK be treated? Would 200-300 million of their vaccine treatments be purchased and never used? Would some countries have to take these vaccines, if capacity in the non-GSK vaccine is not built up fast enough? Does the first year or two of distribution of the GSK vaccine cost $3bn, but then the next developer or developers gets another $10bn? Or less? What if the follow-on vaccines are much better vaccines and need the $10 billion to get developed? Ex ante what does GSK perceive to be its likely treatment? Will its $3bn promise be lobbied down by policy makers to be nearer its actual costs of development to look more 'reasonable' ex post even if this is totally inadequate in the 'ex ante' sense with all risk factored in? Will GSK be disincentivized even as other developers are also disincentivized because they worry that the extra cash will not be made available and the 'easy' portions of the market will have gone?

The conclusion is that the terms of the $3bn deal, and the mechanism in which it is embedded, have to be set along with a commitment (backed up by resources) to find 'the 90% (100%) vaccine'[419] spelled out to GSK from the start. Indeed this effort should be initiated *now*, so as *not* to make it less likely to happen, and should be part of the thinking about *this* case.

The political danger is that the early efficacious lead is much more salient than the lost 90% lead that is never seen or felt (even as GSK has to face, and pay in its capital costs, the risk that the greater lead will be followed some time, and so even GSK holds back on its intensity of effort). We never know about what we do not get. Politicians (and policy makers) with limited horizons, like to take credit for the self-fulfilling things they bring about by their own shortsightedness, especially if nobody notices. But this should not be encouraged by those who should know better.

Stymieing the criteria

The case also illustrates the very real dangers that changes in criteria will stymie those who are working on superior vaccines. Before the GSK Biologicals case came along, most of the APC literature discussed efficacy rates of 90%, down to 80% as 'bad' cases[420], and emphasized the importance of minimizing the number of doses, on the basis that in very poor resource settings there is little point in having three or more booster shots given the high distribution costs of the last shots, the low level of health service personal and record keeping, and the likelihood that many would not come back for the required booster shots. Then, the CGD set the base case for a malaria vaccine at 60% effective protection for

[419] This is proxy language for a 'set of vaccines'.

[420] See, for example, www.pm.gov.uk/files/pdf/Appendix%207.pdf, p10. "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' 'Strong Medicine' p78. Kremer Appendix 4 p20 also discusses 80%.

five years from a three-dose course[421]. This became: "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,"[422] before, in the final report's contract term sheets, becoming 50% efficacy for 24 months from up to four doses, with flexibility to lower even further.

It is pretty obvious why the criteria might be repeatedly lowered like this (along with the sums of money being proposed). But, this does not look like a particularly good set of criteria in a poor-resource setting: If there are four immunizations in a treatment and if even 70% of those receiving treatment return for each boost (in some resource-poor settings this would be considered good), then only just over a third get the full treatment. If the vaccine is 'only' 50% efficacious, this will prevent 'only' about a sixth of cases. The fixed costs of distribution are just as high as for a 100% effective vaccines, and the opportunity costs of distribution are higher the more immunizations that are required (this bites heavily in settings with already very low levels of health professionals), and the high opportunity cost of continuing drug treatments remain nearly as high as before. Is this a good deal for all the PPP funding absorbed? For the countries relying on this vaccine?

Incidentally, who pays for the distribution and health-system costs of the four-dose vaccine treatment and the continuing high levels of drug treatment 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 'pot' has gone on this vaccine?

An example of dynamic inconsistency

This is another form of dynamic inconsistency. It is probably fair to say that these vaccine criteria would not have been even considered, let alone vocalised, before the recent GSK case. This does not auger well. The ability to tone down criteria 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 lead 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 object to the 'tougher conditions' when the earlier vaccine lead of GSK has been set only 50% or so (and may yet be allowed at something lower)? Why should the 40% or 50% lead get *anything*?

Incidentally, had a malaria APC been set 10 years ago, is some of the recent commentary from key players suggesting that the terms of *that* commitment would have turned out to be very wrong, and way to high? Have these ex post

[421] "Advanced Markets for a Malaria Vaccine: Estimating Costs and Effectiveness," Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., and Williams, H. 5 January 2005.
[422] Barder, O., CIPIH Forum, 27 November 2004.

rationalizations for lower requirements demonstrated some of the difficulties of setting the terms efficiently far in advance?

Bidding the price down?

When the original 'Making Markets' draft 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 later the cost had dropped to $4bn then $3bn (in the space of the same meeting). 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*[423]*, providing an incentive to pharmaceutical companies to produce drugs*[424]*. For Malaria, the market size needed to deliver the malaria vaccine*[425] *is $3 billion (CGD, 2004)."*[426]

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 purchase commitment 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 issues. What does all this say about the veracity of the original figures? Of the current figures? Of *any* figures? If a good-quality vaccine or flow of vaccines was calculated to need a $6.25bn fund just a few months ago, and policymakers (and lobbyists) are happy to sacrifice quality, just to sell an idea and get 'influence', what does this say to investors and developers thinking of investing in 'better' vaccines? If those promoting the approach don't trust the approach, why should developers? If the whole exercise is a game in political opportunism, why should investors treat it any other way?

Crowding out other private developers, and quality made worse

As a very practical example of 'crowding out' and of the research distortions that may be caused (and pertinent given the recent GSK case), imagine offering an APC to a range of malaria vaccine developers some at or near scratch in their R&D and some who have vaccines much closer to market (helped there by a great deal of previous push funding perhaps, properly calculated to *include* funding of all failed leads and capital costs). If the size of the purchase commitment is set on the basis of all developers being at or near scratch, and if the near-to-market group do not have purchase payments removed commensurate with their position

---

[423] As we have shown, this is not the case and drastically simplifies a highly difficult set of issues. Such agreements supposedly guarantee an *additional* size of market – the whole point of such instruments. This statement is therefore a hypothesis and *not* a fact.

[424] 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.

[425] Where did the notion come from that there was such a thing as "*the* malaria vaccine"? We saw above that even the most cursory view of the literature reveals the need for an evolving stream of vaccines.

[426] http://commissionforafrica.org/english/report/thereport/cfafullreport_copy.pdf page 409, Chapter 6 Footnote 92.

and previous help, then they will be massively over-advantaged (in the expected sense they are taking up too big a *proportion* of the 'pot' since they are more likely to 'win' it) and over-paid (they get paid too much for what they have done with their own private funds) compared to the near-scratch developers.

And it aggravates the 'quality' problem. Probabilistically, quality is made worse. 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 would 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 mechanism towards current whatever-quality vaccines, that 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!

However one looks at it, near-scratch and near-market developers need the overall size and distribution of the purchase commitment to be modified commensurate with their current position (though think of the accounting and monitory issues involved in doing this). In real applications of 'Framework Agreement'-type tenders, the likelihood is that these ex-post funding adjustments would not take place[427]. Other finance mechanisms are much more capable of being adaptable to the current condition of each potential user of them.

GSK Biologicals should be funded, but…

The GSK Biological purchase commitment is based on the currently best available lead, a lead that should be funded (though the level and method of funding is completely another issue) even though many would argue that the cost is greater than alternatives, were we to be operating on a much more level playing field to start with. The funding in this instance should not obscure the fact that there need to be many more leads explored in the first place to guarantee the highest chances of a 90% or 100% effective vaccine, and that the terms of the current GSK 'deal' should not be set carelessly in ways that jeopardize this greater future vaccine.

If anything, that we are considering £3bn to incentivize just one vaccine lead that has achieved, so far, 'only' 30% effectiveness against attacks in the first six months (and even this is hotly debated by some vaccine experts), does rather suggest the potential expensiveness of *not* using more collaborative approaches to achieve the 90%+ effective vaccines we ultimately seek. $3bn is *half a century's* worth of the entire public and private spending on malaria vaccine research at current rates of expenditure, and over *three and a half century's worth of* what MMV has been spending – that for all its smallness, produced 21 drugs and is currently supporting 20 vaccine candidates at various stages of pre- and clinical

[427] As confirmed by Berndt, E.R., ibid.

development[428]. In this topsy-turvey world it is still possible to go from discussing umpteen-billion dollar proposals, most of which will go on capital costs anyway, 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.*"[429]

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 it rather suggests perverse priorities. The GSK case, rather than pointing us in the direction of a 'Strong Medicine' mechanism, it turns out, challenges us to set our sights on much bolder approaches[430].

Interestingly, with the GSK case already seemingly fitting more into the 'standard procurement' contracts described above in the collaborative vaccine model, it does rather suggest exploring ways to use them in a collaborative setting, and to set terms accordingly. But this should be discussed and pushed for now, not in five or six or more years' time.

6.5. Various Malaria Vaccine Approaches and the Impact of the Malaria Genome

> "*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*." [431]

> "*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*." [432]

---

[428] www.malariavaccine.org.
[429] "Malaria Vaccine R&D: The Case for Greater Resources" at: www.malariavaccine.org/files/Two-page-funding.pdf.
[430] Incidentally, the author's understanding of what is going on at GSK and GSK Biologicals (from various internal and external sources) is that the more commercial wing at first regarded the contract as a 'success', but the wing dealing with MMV and actually having to *do* malaria vaccine research, regarded it as not so good, especially from a PR perspective, and a big negative factor in their multiple efforts to advance relationships with non-pharmaceutical researchers and others in malaria vaccine research. They would have preferred something else. Maybe that is why it gets no mention on the GSK Biologicals website and why all the more recent emphasis has been on PPP funding to actually 'develop' a vaccine?
[431] Hoffman and Richie, "The Vaccine Book' ibid, p298.
[432] Hoffman and Richie "The Vaccine Book', ibid. p295.

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. A great deal more needs to be done on this third approach.

That there are three competing approaches, with the third 'coming up on the outside' as it were, does raise interesting and complex issues that, again, point away from a 'Strong Medicine' approach and towards more standard procurement approaches.

Serious problems for private investors

How should a firm working on the first or second approaches respond if they are suddenly challenged to invest, in the expected value sense, billions of their own funds in developing a vaccine based on that approach? 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 the third approach works better, the government may actually hope never to use any (or very little) of the vaccine based on the first approach? What if a firm invests heavily in response to the offer, only to see the government massively scaling up efforts on the third approach? Conversely, what if the government 'blows everything' on the first 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 the third approach? How does the government work out *in advance* how to optimally redistribute the overall payment and how much should they pay up-front for vaccines based on the first or second approaches, so as to leave the 'optimal' portion over to be spent on vaccines based on the third approach? Or is there a bottomless pit? Is the whole notion of a 'Making Markets' fixed pot of APC subsidy and the 'Making Markets' mechanism described above simply a mirage anyway? The attitude at the moment seems to be to concentrate on the immediately salient approach and let other approaches worry about financing themselves later (or expect that the government, or the IFF, or whoever else will offer even more contracts later, or that these better vaccines can just be dispensed with anyway).

Of course, none of these problems really arise in the APC literature. We discussed above, and elsewhere[433], 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

[433] Farlow, 2004 ibid. Chapters 5 and 6.

of new scientific paths to spoil the simple 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?

6.6. Other Non-Vaccine Malaria Needs

> "*This tragedy need not happen. It is almost entirely preventable using technologies that are already available. Widespread use of insecticide treated mosquito nets and a new class of malaria drugs known as artemisinin combination therapy (ACT) can radically reduce disease and death…*
>
> *…We estimate that for £300 million we could have enough nets to cover virtually all pregnant women and children under five who need them in Africa. I can announce today that the UK is ready to meet more than its share of the total cost through a contribution of at least £45 million - to cut deaths from malaria in Africa. I will be pressing the G8 to make a commitment to meet the rest of this bill.*" Prime Minister Tony Blair, World Economic Forum, Davos, Switzerland, 2005.

The recent Millennium Project[434] identifies 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 antimalaria 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 50%[435].

New drugs are needed and are much more easily possible

Until about 20 years ago, the drug chloroquine was the standard malaria drug. It was cheap (about 10 cents per treatment) and worked well. However, chloroquine-resistant strains are now rife. But 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, that had been used for centuries in traditional Chinese medicine. These are now the standard malaria treatment in Asia, where they are described as the "best ever anti-malarial drugs"[436]. These are

---

[434] http://unmp.forumone.com.

[435] http://allafrica.com/stories/200501260806.html.

[436] Arrow, K., 'No time to waste in the fight against malaria', Financial Times, January 6, 2005. Kenneth Arrow chaired the IOM committee on malaria that produced the report 'Saving Lives, Buying Time'. See also the findings of the International Artemisinin Study Group: "Artesunate combinations for treatment of malaria: meta-analysis", The Lancet, Vol. 363, 3 January 2004, pp. 9-17. Tuberculosis also can be treated with DOTS therapy, which cures up to 95 per cent of cases,

not 10 cents but about $1 per child treated. But that is still cheap. Africa does not get them, and millions suffer and die as a result, for the sake of $500m or so per year. That is about 3 to 4 days of current levels of military spending in Iraq.

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)[437] - 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 drug combination therapies – ACTs – will also be extremely cost effective, even in the most resource-poor countries.

Kenneth Arrow argues that:

> *"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 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*"[438].

Some hard-hitting truths

When the GSK Biologicals announcement was first made, it triggered a flurry of commentary from vaccine 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 to see the more positive remarks too[439]):

> "*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".*

---

even in the poorest countries. And, of course, HIV can be treated, but often isn't – but that is a whole other story.

[437] And a need to discourage the distribution of any solo drug that might encourage resistance.

[438] See Arrow. K. ibid.

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

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)[440].

…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…

We have interventions now that are more effective and much less expensive than the weak vaccine reported in The Lancet…Less than US$20 would guarantee a poor African child access to life-saving interventions. The cost of a malaria vaccine will be in excess of US$60 per full immunization.

The sad truth is that, despite having now developed these 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 such as the World Health Organization, Roll Back Malaria, and the Global Fund against HIV, TB, and malaria — also supported generously by the UK government — have missed opportunities to go to scale with comparatively cheap, life-saving interventions.

Weak strategic leadership, donor-driven agendas making poor people pay for bednets, inadequate planning for drug needs and policies, and lack of sufficient funds have all resulted in less than five per cent of children sleeping under an insecticide treated bednet, and a handful of African countries struggling to implement new effective drug policies.

Communities in Africa under the constant threat of malaria and maintained in a constant state of poverty cannot afford to spend US$20 per child to save them from malaria; rural households have to make difficult choices of putting food on the table or sending their children to school.

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

[440] Bob Snow and Nick White are already out of date. The latest policy briefings of the Centre for Global Development give a figure of $3bn, about half the figures quoted by Snow and White based on the previous policy briefings of the Centre for Global Development and the UK Chancellor. See also Commission for Africa 2005 (who *were* up-to-date with the latest sales pitch it seems).

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 killing 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."

Tough words. But someone has to say them.

6.7. Jumping Linguistic Hoops

Challenged on the worries that the UK's response to the GSK case might distort incentives and disincentivise 'better' vaccines by failing to even remotely live up to the idealized 'Making Markets' approach, Owen Barder said[441]: "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 startling 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 not to falsely misinterpet the proposal, including, for example[442]:

"*James Love expressed scepticism about a 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***

[441] Barder, O., CIPIH Forum, 27 Nov 2004.
[442] Barder, O., CIPIH Forum, 19 December 2004.

> ***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)*** *AdvancedMarkets* ***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)

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." [443]

Then, and *in spite of agreeing* with the list of 'valid criticisms' discribed 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 "can't speak for the UK government" who are supposedly acting on their advice but they can tell you what the latest model says.

How did this all come about?

Maybe this situation came about because most of these 'design issues' were not in the 400+pages of material put on the No 10 Policy Unit website, nor in 'Strong Medicine', nor, clearly, in any advice given to the British government. These design issues were raised in Farlow April 2004[444] *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*. The truth, it seems, is that in response to 'valid criticisms' the paper model is simply changed a bit here and there to make it *sound* more palatable and to make the task of those who made the criticisms in the first place that bit harder, but, in all concrete respects, there is no genuine desire to achieve a better design in practice. The paper model and supporting policy pronouncements are just the PR-wrapping for something much more basic. The GSK case is QED proof of this.

If the 'Making Markets' mechanism is as good as its keenest proponents suggest, 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

[443] www.cid.harvard.edu/books/kremer04_strongmedicine.html.

[444] Farlow, 2004, ibid. Copies were given to key people on the Center for Global Development project.

are not bothered to make sure that *the first users* take the criticisms into account in *their* design. The very things that the advisors criticise others for criticising, the advisors then go and do anyway. Grave worries about being misinterpreted. No worries about getting things right.

PART 7. CONCLUSIONS AND A G8 STRATEGY

Those working on pull mechanisms are to be praised for exploring fresh angles to this problem and for developing a key part of an overall treatment, and, best of all, for applying the proposal to some real-world late-stage and underused vaccines that will shortly, it must be hoped, start to make an impact on unnecessary pain and suffering. However, success on currently existing late-stage vaccines would say little or nothing about the ability to solve the problems of developing high quality, but extraordinarily complex, early-stage vaccines, such as those for HIV, malaria and tuberculosis, and then getting the vaccines manufactured at prices low enough to be of practical use. Claims of effectiveness on these latter problems have been very heavily exaggerated, and are entirely unproven. The whole Center for Global Development endeavor on the late-stage and underused vaccines has been increasingly been used to press a completely unproven experiment for early-stage vaccines just for the sake of getting a 'policy success', whatever the long-term consequences for vaccine discovery and development.

7.1. Ten Steps (and more) to Selling an APC to Politicians

It is never a good idea when lobbying takes over from rigorous and critical self-analysis. When it comes to an HIV vaccine, the real issues should be the level of resources needed for getting the job done, *and getting the job done*, and not defending one model over another and playing games to achieve 'policy successes'. This author welcomes critical feedback on every one of the ideas expressed in this paper, given that this is the only way for ideas to be improved. 'Strong Medicine' and 'Making Markets' (and similar literature) are an object lesson in how to sell a proposal without having to *prove* it works. Here are the main techniques:

1) Whatever method is chosen to stimulate vaccine R&D for vaccines such as HIV, malaria, and TB, the ultimate payment for that R&D will be developed economy tax-payers and philanthropic foundations, and the emphasis should therefore be on *relative cost-effectiveness, and hence speed of discovery and quality of vaccine outcome*. To deflect attention from the need to prove ccost-effectiveness, the first technique is to repeatedly suggest that low levels of current funding for R&D for vaccines *itself* inevitably leads to using an APC. So, for example: "In the absence of an incentive of this sort, there is unlikely to be sufficient research and development into vaccines and medicines"[445], or better still, not using this approach is "*waiting for a vaccine to be developed* without an advance contract" (italics added)[446], and *not* adopting *this* approach is equivalent to doing nothing, 'living with the status quo', and condemning millions to death[447]. Promoters of no *other* mechanism for tackling vaccine R&D has ever made the case for the effectiveness of *their* approach, over all other

[445] 'Making Markets' March 2005, 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 "Strong Medicine" Chapter 9, especially pages 93-95, and p87, "At present, funds are not sufficient to pursue enough of the possible avenues of research."
[446] 'Making Markets' March 2005, p60.
[447] 'Strong Medicine' p125-6.

approaches, on the basis of the truly appalling 'status quo' and of doing nothing.

2) Again, to avoid having to back-up claims about the effectiveness of the mechanism itself, we are told about the effectiveness of vaccines *themselves*. Indeed, the two are constantly conflated[448]. It seems to work[449]. Worse still, the probable success of purchase commitments and procurement arrangements for a range of late-stage vaccines are constantly conflated with APCs for complicated early-stage vaccines for which the power of APCs is very low and unproven.

   The extreme cost-effectiveness of vaccines is well known. Indeed, it might be entirely fair to say that "vaccination… has been and continues to be one of the most important public health interventions *in history*" (italics added)[450]. Most of the APC literature rightly points out the scope for dramatic improvements in health and life expectancy achieved in developing countries consequent on relatively cheap medical advances, yet the highly non-complete coverage of such treatments. The cost-effectiveness of vaccines stands out. But this is a general feature and applicable to *all* mechanisms for encouraging vaccine R&D. One of the dangers of such arguments is that even low quality vaccines can be ex post rationalized; we see some of this logic in the cost effectiveness evidence that argues that even low quality vaccines are cost effective given the very high cost effectiveness threshold of vaccines (though this evidence usually ignores the level of push funding that went in to R&D and the costs of delivery and distribution which are all likely to be very high for a HIV APC and way outstrip a $3bn APC).

---

[448] See 'Making Markets' March 2005 pages 9, 10 (point 8), 16, 24, 36, 37 (especially), 51, 58, 59, 60, 61, p 87 ("a commitment of this size would create a market comparable to a developed country pharmaceutical, while providing a very cost-effective investment for donors"), and p94 ("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"). We showed above that an HIV APC would do practically nothing for innovation today (and maybe even nothing) and put no emphasis on access, and yet: "It is thus clear that purchases under a vaccine commitment would save more lives that almost any alternative use of funds," 'Strong Medicine' p93. "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." 'Strong Medicine' p94. The Princeton University Press promotional material for 'Strong Medicine' boldly states: "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." www.pupress.princeton.edu/titles/7830.html. (Who wrote that?). Incidentally with the HIV vaccine APC now down at just $3bn, and given the sums discussed above, it is clear that most of the effort to get a HIV vaccine will lie elsewhere, however much a 'winning' firm (or the proponents of HIV APCs) might wish to take all the credit along with all the IP rights.

[449] "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" www.cid.harvard.edu/books/kremer04_strongmedicine.html.

[450] Birmingham, M., and Stein, C., 'The Vaccine Book', p3.

No *other* mechanism for tackling vaccine R&D problems has ever made (or would be allowed to get away with making[451]) the case for its *own* effectiveness based on the effectiveness of vaccines *themselves* rather than any evidence of the cost effectiveness of the mechanism itself.

Indeed *no* product or service is sold according to this logic. No Transatlantic airline flight is priced to just pip the cost (including the value of time and hassle-avoided) of taking a transatlantic liner, nor mobile phone call charged according to the alternative of a foot messenger. If air-traffic controllers were to shut down or nurses go on strike for a week we would soon enough work out the 'economic surplus' of their services. But we do not use this principle in working out what to pay them (or anyone else). No computer company has yet managed to get away with selling computers at ten times cost price because of the value of the Internet and the welfare losses of a society without computers – perhaps with advertising copy along the lines of "Computer prices remain cost-effective under a wide range of assumptions about Internet connection, level and speed of Internet adoption, and the amount of money spent on computers in the population"[452]. And they would not even try to argue that poor quality is fine since the cost effectiveness threshold is so very high compared to a world without computers. Instead we expect high quality at the lowest possible prices.

Most other innovations in resource-poor settings could be talked about in similar 'cost effectiveness' language. Following the recent Asian tsunami, the cost effectiveness of bottles of clean water was extreme, but one suspects that the international aid agencies seeking to distribute them would have tried to do so in the cheapest and most efficient fashion, if only to maximize the range of other projects they could fund.

Some have even argued that; "The constant assertion that vaccines are extremely cost-effective and that they could easily win in any competition with other interventions, has always been attractive as a rhetorical claim, but has never been matched by a real desire to put that assertion to the test."[453] Certainly in very resource poor settings where there are many competing sources of morbidity and suffering, setting up vaccine programs may absorb large shares of the medical and other human capital, and a case needs to be argued that they are more cost effective than any other alternative.

3) Sadly, a large proportion of the early strategy to popularize APC for HIV, malaria, and tuberculosis amongst policy makers has been to 'rubbish'[454]

[451] Indeed, Kremer and Glennerster, and others, make strenuous attempts on this score when it comes to *other* mechanisms. See Farlow Chapter 8 on how they do it.
[452] Based on Kremer 'Strong Medicine', p93.
[453] Muraskin, W., (2004) "The Global Alliance for Vaccines and Immunization (GAVI): Is it a New Model for Effective Public Private Cooperation in International Public Health?" Queen's College, City University of New York, JLI Working Paper 1-2, March 2004.
[454] It was not easy to leave this word in. Sadly it is a word (and there were worse) the author has repeatedly heard from those working on alternative incentive approaches and from vaccine scientists.

just about every other approach, while modeling *this* approach as having no problems and never failing. See the discussion in chapter 8 of Farlow 2004 of how this was achieved in the analysis presented to the UK government. Recent analysis similarly ignores nearly all of the practical difficulties of making such instruments work. A debate took place through the auspices of the CIPIH but all this seems to have done is enable the idea to be spun better. None of the tricky questions were faced.

4) Policy makers are told that they do not need to pay till much later and that there are also "no opportunity cost to making the commitment. Because no cash expenditure from public funds is needed until and unless a vaccine is developed."[455] But the value of there being "no opportunity cost" only bites for two equally efficient approaches to solving vaccine problems. If using deferred payment requires the use of a greatly inferior approach, the argument collapses. That policy advisors can't see this simple truth is startling, and that they are prepared to apply the logic to complicated vaccines yet would never dream of applying it to other scientific endeavors (such as sending explorers to Mars) is an indictment. Besides, it isn't even true; someone pays and bears the risks (e.g. pension-fund holders through their holdings of pharmaceutical shares). Repeating such mantras (and they are just mantras) eventually seems to work: "By committing to pay for results, these proposals ensure that if no vaccines are developed, no payments would be made."[456]

   In truth, all that matters should be which approach is likely to achieve the most rapid development of a vaccine or vaccines at the lowest possible cost (or, and exactly the same logic, for a given cost the most rapid development and use of vaccines). Instead, as the policy pronouncements have proceeded, comparative 'cost effectiveness' evidence has been ever more conspicuous by its growing absence. This is even more important in the context of paying for the mechanism via some facility such as the IFF, when part of the penalty of a failing and expensive R&D and procurement mechanism is the instability and cost it imposes on the IFF. As always, there is no such thing as a free lunch. Though, it helps if it is someone else's lunch.

5) The opposite of the truth is said often enough in the hope that the truth becomes opposite. An early-stage APC is described as 'non-interventionist' even though it would be highly interventionist. Nobody 'directs investment'[457] when in fact a committee *would*, but in manner that is very uncertain for many of those investing. It is 'making a market' when only sometimes this holds (when genuine competitive tenders are used) but at other times it is 'regulating' or ad-hoc decision-making via a committee or, worse, a politician. It is 'low on monitoring' when it is high

[455] 'Making Markets' March 2005, p38 ('Making Markets' March 2005, p67, has the same statement but adds "and used").'Making Markets' March 2005 p33 states it "does not require outlays of public spending until the vaccine is available for use."
[456] "UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria" www.cid.harvard.edu/books/kremer04_strongmedicine.html.
[457] Barder, O., CIPIH Forum, 19 November 2004.

on monitoring, and 'competitive' when the competitive element is the weakest link and one of the biggest worries is that there will be too little competition at both the R&D and manufacturing stages. It 'enhances other interventions' when it struggles to do so and is *not once* modeled as doing so, and not the slightest effort is made to tackle the difficult problems of doing so. It is "based on market principles" [458] when it isn't, 'simple'[459] when it is anything but, 'practical'[460] when proper implementation would be a nightmare and potentially very litigious.

The biggest hidden truth of all is that the mechanism is principally a way to create a large pot of funds for just one or two dominant players, and *not* the many as might happen under a global vaccine enterprise along the lines discussed above. This and a previous paper (Farlow 2004) argue that all the talk of competition is something of a smokescreen to dress this underlying reality for public consumption. It would be politically unacceptable for these large players, or probably more precisely those who think that they are helping them[461], to reveal this as their true intent, especially if they are not the most obvious recipients. The APC literature for early-stage vaccines and all its gyrations is simply the politically acceptable cloak in which to hide this underlying intent[462]. As one leading vaccine expert expressed it to the author, why not just say that this is the intention and we can then at least have an open debate about whether this is the right way to proceed, and whether we should just give GSK, or whoever, the money to get the task done? Instead we pretend it is a much more open mechanism. The recent ever-lower pitching of the level of APCs even though this ultimately pitches the whole mechanism to only one or two large firms, simply makes this intent ever more clear.

6) It is argued that surely "the diseases of the poor deserve the same overall package of incentives for research as the diseases of the rich?"[463], even if the truth is that if HIV and AIDS were ravaging rich countires and escalating, it is completely out of the question that politicians would rely on (or get away with relying on) an untried, low-powered mechanism, with no rigorous analysis or critique of its foundations tolerated, no decent empirical evidence provided to support it before locking it in 'for ever' (30 years is 'for ever' for our purposes), with payment pushed off many years into the future – instead of a fully-funded much more collaborative effort to find a high-quality solution. Our interest in APCs for driving R&D into vaccines for the poor only comes about becaue we do not feel that the poor deserve the same treatment as the rich.

---

[458] Barder, O., CIPIH Forum,19 November 2004.

[459] Barder, O., CIPIH Forum, 19 November 2004: "A proposal which is simple, easy to understand, and practical to implement." If you have read this far, statements like this should finally be the real give away of the overall shallowness of the anaylsis.

[460] Barder, O., ibid. 19 November 2004.

[461] Since it is not at all clear that a 'large pharma' executive when presented with the actual workings of the mechanism for an early stage vaccine such as HIV would prefer the mechanism to other approaches. The profit incentive is also a self-preservation incentive.

[462] The fact that these gyrations came way after the original intent was made clear in early versions, does rather suggest that the interest was never the gyrations themselves.

[463] Berndt, E.R., ibid.

7) Blame large pharmaceutical firms when they don't like the proposal. In many places in this paper it becomes apparent that large pharmaceutical firms (or smaller firms, when the details are properly spelled out to them), given the choice, would not necessarily prefer the 'Strong Medicine' and 'Making Market' approach over PPP and the more collaborative approach sketched above for diseases such as HIV, malaria and TB. The APC route faces them with many risks – in particular a great deal of reputational risk once a vaccine is developed – that it is simply not worth it for the size of reward being offered. Perhaps this is why many large pharmaceutical firms are often so lukewarm. But their attitude is often dispelled with "they would be, wouldn't they?" logic – the notion that pharmaceutical firms would always prefer not to be rewarded 'by results' and would rather take subsidies instead. It is much more likely that, though they would be very willing to be part of an effort to hunt down an HIV vaccine, they really *cannot* handle the risks of the 'Strong Medicine' route.

8) Proposals are discussed that are different from the one being promoted. So, for example, all of the language of late-stage purchase success is used even when discussing the merits of early-stage APCs.

9) When critiques are generated, the observations made are used to manipulate and improve the presentation of the proposal on paper, to make it more difficult to critique the proposal in the first place. It is made to sound as if the proposal has cracked the problem suggested in the critique, though only paying lip service to it. But then…

10) The proposal is not adopted anyway. Policy makers should not be alerted to just how problematic would be a proper application of the proposal by making them actually carry it out. That way, policy-markers are not diverted to competing proposals.

A plague of non-evidence for this…

The 'Strong' of 'Strong Medicine' refers to the alleged superior strength, dollar for dollar, of this approach compared to others. It was once claimed that, in the case of a HIV vaccine, a mechanism based on APCs would be four and a half times 'stronger' than current publicly-funded applied research and joint ventures with private companies[464]. Such staggering claimed difference in effectiveness cries out for justification. It is so central to the 'Making Markets' case for a large rôle for an APC for HIV, malaria, and tuberculosis, that we would hope to find plenty of evidence to support it. We do not get it. Instead, these once heavily-used cost-effectiveness figures are generated on the basis of largely non-comparable data, extremely dubious assumptions including many layers of, simply asserted, extreme, failure of all other approaches[465], and never *this* approach which is

[464] See www.number-10.gov.uk/su/health/default.htm Summary p4. This is, of course, a small sub-class of all publicly-funded research.
http://www.pm.gov.uk/files/pdf/Appendix%204.pdf, "A Vaccine Purchase Commitment: Preliminary Cost-Effectiveness Estimates and Pricing", Kremer and Glennerster.

[465] See Farlow, 2004, ibid, Chapter 8. None of these assumptions were ever backed up by empirical evidence. This did not deter a barrage of, highly visible, tables, diagrams, and

deemed to be perfectly applied every time. This is in spite of the myriad of problems detailed above (that are simply ruled out) and the reality of unfolding applications.

Recently, these meaningless figures have not been presented as part of the argument; neither in 'Strong Medicine' nor in 'Making Markets'. It finally seems to have been recognised that this 'evidence' is not good enough and that its original production said more about its weight in lobbying than in any economic veracity. We found above that once we tried to explore the power of such instruments to motivate early-stage vaccine R&D, far from being "the incentive that has been so desperately lacking for biotechnology and pharmaceutical companies to focus attention on these (HIV/AIDS and malaria) vaccines"[466], this is far from the case.

But, the memory of such 'evidence' lingers, spuriously hinting at some sort of empirical validity. The "G8 Finance Ministers' Conclusions on Development" of June 10-11, 2005, even contained the following line: "We recognise also that advance purchase commitments (APCs) are potentially a powerful mechanism to incentivize research, development and the production of vaccines for HIV, malaria and other diseases,"[467] even though *no* shred of reliable comparative cost effectiveness evidence has *ever* been provided for APCs for HIV, malaria or other diseases, a fundamentally basic piece of evidence given their irreversibility. Increasing positive spin about 'strength' has been in inverse proportion to the decline in the veracity of the originally purported evidence of their 'strength'. This is a truly appalling and irresponsible way to behave on the part of those advocating APCs for HIV, malaria and other diseases.

A plague of problems with everything else it seems…

The *only* piece of evidence we are given for the "plague"[468] of failure of *other* approaches, including PPPs, and of *their* "politicization and corruption" is the retelling of the USAID Malaria Vaccine Program debacle of the early 1980s (wasting a couple of ten thousandths of one percent of the total NIH budget of the past 25 years). Fulsome details of this have appeared in just about every treatment of APCs[469]. This is sad. And ungenerous to the many who, often at great personal

---

statements, based on them. Try, for example, http://www.dfid.gov.uk/research/newresearchbgprivate.pdf p9 Table 4, and footnote 30, p13.

[466] From http://www.cid.harvard.edu/books/kremer04_strongmedicine.html "UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria".

[467] www.g8.utoronto.ca/finance/fm050611_dev.htm.

[468] Kremer, M., "Pharmaceuticals and the Developing World," *Journal of Economic Perspectives* 16(4), Fall 2002. p82.

[469] The No 10 Policy Unit website, NBER "Innovation Policy and the Economy", a range of Kremer papers such as "A Better Way to Spur Medical Research and Development: The purchase precommitment as a supplement to patents and government-funded research", Regulation Volume 23, No.2. 2000, and more recently 'Strong Medicine'. When this author was asked to review 'Strong Medicine' for the Lancet, the first person he spoke to who had seen it, quipped that the USAIDS case was yet again getting an airing ('A Cautionary Tale: The USAID Malaria Vaccine Program", 'Strong Medicine' pp 47-49). It should go without saying that criticisms of the repeated use of such cases casting aspersions on others (in place of a greater body of evidence) does not condone the cases themselves. Intent, and words, can easily be inserted that were not originally there.

sacrifice, give their lives to research into these difficult areas[470]. It would be a bit like repeatedly tying the reputation of all those currently working in 'big pharma' to the behavior of the industry in the 1950s when it cornered the tetracycline market, described by the Senate Subcommittee on Antitrust and Monopoly (1959-1962) as "profiteering and anticompetitive behavior with the help of the patent system…the public was ill-served by such practices" [471] Except that *that* behavior killed lives: "One can only speculate about how many peoples' lives might have been saved if prices had been allowed to fall earlier"[472].

After so many years, and given the gravity of proposing a highly *irreversible* mechanism to consume maybe several tens of billions of dollars of taxpayer and philanthropic foundation resources, we should expect a much more comprehensive, and readily available, body of *evidence* to support a core part of the argument. The fact that we do not get it, betrays both a lack of such evidence, and a lack of interest in such evidence.

The incentive to exaggerate, and a big worrying truth

One of the main criticisms of the current system made by Kremer and Glennerster is that if researchers do not have to prove the worth of what they are doing by results, they will "have incentives to exaggerate the prospects that their approach will succeed"[473]. 'Strong Medicine' and 'Making Markets" are an excellent demonstration of this principle in action. Not only is the underlying empirical support distorted but we will never truly know if early-stage APCs will work for HIV, malaria, and tuberculosis until *after* they have been tried; they are an experiment. It is not great reassurance to be told that if the experiment fails and we get no viable vaccines that it "would cost nothing"[474], or that:

> "*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.*" [475]

Not only is this an object lesson in understatement, but it is a staggering way to even consider evaluating a mechanism. It is hard to imagine that any *other* mechanism would absolve itself quite so crudely of the responsibility to prove its worth.

As this line startlingly indicates, policymakers *really would have to wait at least 30 years* because of the legally binding nature of such contracts. The very knowledge that the sponsors might bail-out if things don't seem to be going

---

[470] Referring to the criticism of the way those working on vaccine research are repeatedly tied with the same brush as those who have behaved corruptly: "He is also wrong to say that it [where 'it' refers to the proposal of an advance purchase precommitment, and *not* the criticsm] is uncharitable to the many people who devote their lives to scientific research – on the contrary, it takes the position that these efforts should be rewarded by society as much as the efforts of those who research into other diseases." Berndt, E.R., ibid.

[471] Dutfield, G. Intellectual Property Rights and the Life Science Industries, Ashgate, 2003 p120.

[472] Dutfield, G. ibid. p120.

[473] 'Strong Medicine', p49.

[474] 'Strong Medicine' dust jacket and p63, and 'Making Markets' March 2005 p7, and numerous other places.

[475] 'Strong Medicine' p84 and 'Making Markets' March 2005 p46.

according to plan would itself make failure happen in a self-reinforcing manner (with litigation flooding in from any firm that had based its behavior on the contracts, or even just claimed to have done so). Therefore, the ability to bail-out should be ruled out legally at the start, just as one might deliberately 'tie one's hands behind one's back' to defend an exchange rate mechanism even if it is becoming ever more absurd to do so. This is all aggravated if there are other purchase commitments in place that might be working and would be badly damaged by a breach in commitment elsewhere.

Incidentally, the 30-year quote *really is* in *both* 'Making Markets' and Strong Medicine'. Does the fact that such startling lines can find themselves into both the book and the Center for Global Development paper, and that not one reviewer alerted the authors to remove it, rather indicate how few hands were at work in both? It is hard to believe that a truly collaborative effort would have left such a line in. Should we really be stuck with a failing APC for *thirty* years (perhaps because it was not rigorously stress-tested at the start)? Given Keynes's dictum that "in the long run we are all dead", 30 years is effectively 'for ever'. Perhaps we should be told?

Given the enormous sums involved and the huge bias in the redirection of resources, such woefully-created figures and dramatic – and damaging – assertions are simply not good enough.

That it would cost nothing is not even economically correct:

i) Taxpayers *will* pay via their holdings of pension funds and other savings in the pharmaceutical industry. There is no such thing as a 'free lunch'[476];
ii) It is not clear that if the mechanism fails, those who have sunk investments would not be due some recompense if failure was caused by failure of the mechanism itself, rather than their own behavior;
iii) If this *is* the approach adopted, *not* working is simply *not* an option.

Litigation?

The fact that failure of the framework (not of firms failing to perform under the framework) can trigger an "early out"[477], when billions of dollars of private resources may have already been sunk, is both a risk (of a self-fulfilling nature too) and also a source of potential litigation. Is 'failure' the fault of poor performance by firms, or because of the framework? If the latter, why should those who have invested in expectation of the framework functioning, as had been previously claimed, not have some sort of legal redress and compensation from those who operated or set up the mechanism? The mechanism designers had a duty of care after all. What if the mechanism was set up in ways that risked failure (for example, by deliberately failing to take on board publicly available critiques)? Such "early out" decisions also require that monitoring has been performed correctly, which is another legal minefield when abandoning the approach. Bluntly, the more likely result is that those running the mechanism

[476] 'There's No Such Thing As a Free Lunch' by Milton Friedman *(1975)*
[477] 'Making Markets' March 2005 p 90.

would stick it out with a poorly-designed contract. None of this has been explored.

Simple ideas are politically easy and very persuasive

It is testament to the persuasiveness of drastically simplified proposals, the lack of the desire to think through tough issues, and the political appeal of programs the payment for which can be pushed way off into the future, that the mechanism described in 'Strong Medicine' and 'Making Markets' has "growing political support"[478]. The danger is that the "political support" is built on the basis of relatively simple purchase commitments – with many of the end-stage benefits listed above – and not on the sort of mechanism described in 'Strong Medicine'. Unfortunately, "political support" can say very little about the quality of a proposal, and much more about the quality of lobbying. Contrary to repeated assertions by the authors of 'Strong Medicine', the workings of an APC for real-world early-stage vaccines are not "simple", but the *apparent* simplicity of the mechanism has been a powerful recruiting device. Incidentally, Klausner et al.[479] *also* describe the – very different – global vaccine enterprise approach as having "substantial support from medical and political communities". Both approaches need to rely on critical, thoughtful analysis to win support.

Collaboration and dangers

Resolving how to deal with the presence of both more open collaborative mechanisms and APCs together is one of the next major steps[480]. At the very least, if one approach is to be favoured over the other, the exact empirical basis for this should be presented, and the likely impact of each in real-world – rather than idealized settings – be ascertained. If, on the other hand, they *are* to work together, then the *exact way* in which they would work together should be resolved *before* enacting any irredeemably fixed, legally binding 'for ever' commitments[481]. In particular, the necessary reform of the IP regime underlying the collaborative part of the process would need to be resolved in a way that is also captured in the workings of the commitment[482].

Trying to collaborate around a badly-set purchase commitment

The worse-case scenario would be if many years, and much political capital as well as financial resources, were spent on setting up an early-stage APC, only then to find that it has limited impact on the speed of development, yet still has to remain legally in place, if for no other reason than *some* investment took place under it – or those who have invested would get *fully* compensated and the mechanism abandoned, which is even more wasteful.

---

[478] 'Strong Medicine', p ix.

[479] Klausner et al ibid, p2.

[480] Maybe the reason they have so far not been analysed together is partly to avoid having to analyse comparative capital costs and relative effectiveness generally?

[481] This completely contradicts the assertion that APCs somehow magically (however badly they are set) "enhance the complementary interventions," 'Making Markets', March 2005, p38.

[482] For example, if the IP regime were to be framed in a way that makes certain kinds of technology more open and shared, this would need to be reflected in the contractual terms. The terms of the latter should not clash with the former, or work in a way that leads to greater costs overall (for example, terms may need to be lowered to the extent that those operating under them benefit from the openness).

In the simplistic models deposited at the No 10 Policy Unit website, the science is modeled such that a larger APC does indeed encourage more firms to enter and invest. But the model does not even begin to describe the investments problems faced by typical pharmaceutical firms in 2005 given the current state of HIV vaccine research, some of which were highlighted above. At the current levels of science, firms are supposedly being asked to invest in vaccine research on something they cannot guarantee to internalize the benefits of for themselves, with an investment horizon that is effectively 15-20 years, with levels of uncertainty and capital costs for current research that are *astronomic*, with huge potential difficulties and costs even after a vaccine is developed on account of it being 'only' therapeutic rather than preventative, and probable vaccine production costs that risk eating up most of the fund anyway (with no mechanisms in place to prevent this).

It is perfectly possible to find, many years late, that we have to explore and then adopt a much more collaborative mechanism containing a pro-active forward-funded trial system, against the backdrop of a still existent APC that creates tendencies for behavior that undermines collaboration. If the APC were not abandoned by then, this collaborative mechanism would have to set up a side-mechanism to prevent those pushed through such a forward-funded system from having access to the end-funded APC program, so as to avoid damaging the end-funded program and inciting litigation by those operating under it, while at the same time it would have to prevent those operating under the 'old' APC from wastefully exploiting the collaborative mechanism. Going for a large APC *now* presumes a strong degree of belief that forward funded trials are highly unlikely to be optimal.

Private pharmaceutical firms will be an important part of any mechanism to tackle these complicated vaccines. But a mechanism based on large APCs of the type described in 'Strong Medicine' and 'Making Markets' and a non-collaborative approach would *not* be a very cost-effective way for getting large numbers of them involved, and would lead to slower average speed of vaccine development and lower average quality of vaccines than a highly collaborative mechanism would achieve.

Why perpetuate, and fight, the current problem anyway?

'Strong Medicine' perpetuates the main problem in the current system – that the cost of large amounts of the R&D has to be extracted through the price of the vaccines that have potentially low manufacturing cost. If one of the problems generating low vaccine R&D is price pressure on vaccines once developed, this approach fights these pressures in part only by creating a series of further difficulties related to the high end prices, including large tendencies to push towards lower quality, and more expensive vaccines. The collaborative section above indicates that it *is* possible to create many of the incentive effects – and more – without trying to inefficiently replicate large 'additional' blockbuster (or even mega-blockbuster) markets from the start, and – with the help of 'contingent purchase commitments' – to handle late-stage issues, and still generate products at close to manufacturing cost, with strong competitive pressures to drive those manufacturing costs down.

After a seven year campaign to get this policy proposal to the top of the heap, it is disconcerting to find so little of the underlying mechanism laid bare for early–stage vaccines, and so little empirical evidence to support the assertion that the mechanism is 'strong' for such vaccines. Repeatedly we find that major problems have been ruled out at the start, only then for it to be claimed that the mechanism solves such problems.

The irony of copying public sector failures

Given their assertion that public sector failure is at the heart of the failure of many competing mechanisms, it would be ironic indeed if public sector failure might happen at the level of choosing the mechanism itself as a major part of the approach to developing early-stage vaccines, encouraged by those who paint an idealized picture of it, and who exploit the fact that while we have information on the failures of other mechanisms, we will not have information on the failure of *this* mechanism until it is too late (and even then we may not know how far we actually fell short). To avoid this danger, those supporting early-stage APCs should refuse to tolerate political support that comes without awkward questions or demands for solid empirical evidence.

'Strong Medicine' represents part of a growing movement – of many different persuasions – drawing attention to these issues. All sides in this debate exaggerate to get noticed; it is always nice to think that one's proposals are those chosen by policymakers. Disagreement is part of the discovery process. The author has come across many of those working on pull proposals who are much more sanguine than the chief authors of 'Making Markets' about early-stage APCs. However, the momentum in the proposal, the constant reference to its 'simplicity' and, by implication, that somehow raising doubts about the workings indicates that one has missed the obvious, and the embarrassment in speaking against the herd (the "widespread enthusiasm"[483]) or even in admitting that one had previously accepted a proposal without asking too many questions, has made it ever more difficult to achieve a rational debate about the pros and cons of early-stage APCs. When, at the end of Hans Christian Andersen's tale, a little child squeals that the Emperor has in fact got no clothes on, and the people start to repeat this, the Emperor realizes the situation, and yet carries on the procession to its bitter end, while his chamberlains continue to hold up the train of his cloak, knowing that it is not there. Let us hope that, after reflection, this does not happen in this case.

7.2. The Dangers of a Collapse in Funding for HIV Vaccine Research

Matters are worse. A series of recent articles have made it clear that there are strong pressures for the trimming of current levels of funding for HIV vaccine research due to the size of government budget deficits[484]. This is revealed too in the 2005 Economic Report of the President[485] and in the proposed U.S. budget,

[483] 'Making Markets' p118.

[484] Of particular note see: www.redherring.com/Article.aspx?a=11318&hed=AIDS+and+money&hed=AIDS+and+money§or=Capital&subsector=PrivateMarkets, and www.aidsmatters.org (in particular the announcements of 23 and 25 February 2005) www.aidsmatters.org/uploads/Ch7.pdf.

[485] www.gpoaccess.gov/eop/index.html.

that includes only a 0.5 percent increase in overall funding for the NIH, substantially less than the rate of inflation during the past few years and way below the rates of funding increase of the past decade. In a recent CNN article[486] discussing the way that the US administration has tightened its NIH budget "as it seeks to curb budget deficits that have soared on its watch," Dr. Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, NIAID, is quoted as saying:

> *"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."*

Fauci is quoted as arguing that this tightening may well hit HIV vaccine research especially hard.

This situation is being repeated elsewhere with recent alarmist headlines about the deteriorating state of public finances in the UK as well as all over the OECD. As Harvey Bale put it in a posting to the CIPIH Forum:

> *"Unfortunately, as public budget deficits prevail across OECD countries, there seems little prospect of major new public initiatives on a scale to make a significant difference. So it is best to build on the partnership models that are succeeding (such as the Medicines for Malaria Venture and WHO/TDR), and explore new approaches (e.g., advance purchase agreements) that will have a better chance of success within limited public resource constraints."* CIPIH Forum, 7 Mar 2005.

Several observation are in order:

The US carries more than its fair share. Others should pay more

First, the US has been carrying a disproportionate share of the funding burden for HIV vaccine research. Worldwide funding for AIDS vaccine research has grown from just over $100 million in 1993 to $600 million in 2003, with $520 million being spent by the NIH, perhaps $60 million by the U.S. Department of Defense, and groups like IAVI making up almost all the rest. The rest of the world has not been pulling its weight in funding. If the world is to meet the level of sustained funding – £1.2bn per year[487] – that the Global HIV Vaccine Enterprise suggests is needed to achieve a HIV vaccine or set of vaccines, clearly this is not going to happen without a great deal more of a *global* effort on funding. Instead of giving in to the logic of budget deficits at this year's G8 Summit, the UK should be encouraging other countries to pay their fair share.

It is effectiveness and not the timing of payment that should ultimately matter

Second, what should matter is *not* what "*will have a better chance of success within limited public resource constraints*" if that means suboptimally switching from front-loaded funding to end-loading funding just to fit within a resource constraint, but rather what *"will have a better chance of success"*. As Farlow

[486] www.cnn.com/2005/ALLPOLITICS/02/22/health.funding.reut.
[487] Admittedly, it is not clear what the basis of this figure is.

2004 Chapter 3 argues, ultimately what matters is relative effectiveness of approaches. The exact *timing* of funding flows should be a completely independent issue. If APCs are more effective, then so be it that research activity switches towards using them. But if APCs are less effective, the temptation to avoid early funding flows should not lead to APCs replacing other more effective approaches. If end-loading of funding is most efficient, then 'end-loading' it should be – but it is a means and not an end in itself. Budgetary failings might make far-off payments more appealing for policymakers, but this should not be what dictates how research is financed.

Funding cut-backs are good news for APC advocates

Third, this is good news to leading advocates for an APC for HIV. They have long argued that APCs are a hugely superior mechanism to anything else, and should be the driving force for HIV vaccine R&D. The supporting cost-effectiveness data (though it is no longer used to support anything) argues this very strongly indeed by modeling every other approach as, comparatively speaking, hopeless[488]. Key advocates should be nothing if not happy that that analysis and previous lobbying for the cut in other approaches to make way for APCs is starting to have affect. Indeed, one of the reasons that the model underlying APCs (Kremer, Appendix 3) has no role whatsoever for any other funding mechanism, is because of the vision of APCs as *the* funding mechanism. One of the logical conclusions of the problems of achieving additionality for APCs is to not require them to be 'additional' to much of anything else anyway.

We should rigorously test APCs before risking funding cuts

Fourth, if the emphasis of funding mechanisms is to shift towards APCs, should not policy makers naturally first seek high-quality, independent, analysis of the power of APCs for HIV? Surely we should know *for sure* that such instruments are going to work before cutting other forms of HIV vaccine research to make way for them? When, a year ago, this author discussed the use of APCs for HIV vaccine research with a range of those currently involved in promoting the idea, not one was convinced that they would be used for HIV (as opposed, for example, to pneumococcus and rotavirus). What happened in the intervening year to change the underlying logic? Observe how the figures for the levels of HIV research indicate that very little *privately funded* HIV vaccine research is going on – a tiny fraction of what would be needed in response to an APC. Should not these extremely low levels alert of current privately-funded HIV research not alert us to the dangers of cutting what we have got for what is no more than speculation.

We did some simple maths earlier to show that if a HIV vaccine might take 15 years to develop and need $1.2bn per year of out of pocket trial costs, replacing this flow with a pot of funds at the end of the process, would (if we presume no crowding out at all) require a pot of about %65bn to $165bn. The most likely private response to an HIV APC in the face of such figures is to hardly respond at all. Throw in the problems in setting terms, creating a fully credible adjudicating committee and the huge reputational risks even large pharmaceutical firms would open themselves up to, and the chances of reaction are even lower. The most likely response overall, if the over-hyped power of HIV APCs is believed by

[488] See Farlow, 2004, Chapter 8 for the ways this was done.

policy makers, will be to reassure them that they can cut back funding, and a collapse in HIV research ensues.

One of the dangers of an ideologically-driven approach is that everything is so self-evidently true that the need for proof can be dispensed with. If APCs for HIV will be very weak instruments for the next ten or so years, as this author argues, should we worry (or not) about the impending collapse of funding for HIV vaccine research consequent on such opportunistic behavior?

Why provide reassurance to those thinking of cutting HIV vaccine research?
Fifth, why is such a highly-respected research think-tank – normally working on resolving the problems of developing countries – providing the intellectual succor and reassurance to those thinking of cutting back HIV vaccine research in the face of tightening budgetary pressures, when the replacement mechanism is not even known to be capable of generating *any* of the lost vaccine R&D, especially over the next 5-10 years? Why adopt a PR-based approach rather than a fact-driven approach to doing it? Why encourage such cuts without any concern for the shaky empirical foundations once provided – but no longer trusted upon – as justification for the APC replacement? Why sacrifice intellectual rigor for manipulation of policy-makers and blind opportunism regardless of the eventual consequences? Why be ring-leader for turkeys voting for Christmas?

Should the excesses of the 1990s, and the consequent tightening of budgets, be visited on the poor of the 2000s?[489] Surely, the interests of the destitute should be protected most of all in times of budgetary tightening? Should we be quite so actively complicit?

7.3. Should we Experiment?

It might be thought that we should just let the experiment happen[490]. After all, within a few years or so we should have strong clues as to whether it will succeed or fail. Even just the *possibility* of profitable and efficient new arrangements should cause financial markets to react[491]. Indeed, given the tiny amounts of current private funding for HIV vaccine research and the supposed huge impact on levels of private funding to be expected in response to APCs, just a small absolute reaction should cause a large *percentage* reaction in private investment. No doubt, given the supposed overwhelming strength of such instruments, we should already be seeing such a reaction in the data (maybe advocates are already collecting the data to reveal this reaction to us?). A suitable policy announcement this year – something permanently fixed perhaps, the more permanently fixed the better for generating investment response – should strengthen this reaction dramatically and provide the data we need (though the 'Making Markets' paper

[489] Leaving others to argue the merits and demerits of the Iraq case, one might also observe that since front-loading the war in Iraq has added several hundreds of billions of dollars to deficits, why should this be allowed to oust the funding for HIV vaccine research?
[490] And people like the current author should shut up (something he would quite happily do).
[491] It is early days, but there must even be evidence by now of private firms increasing their finance into malaria vaccine research for the open-to-all malaria precommitment now heavily run in the media. Even by midsummer 2005 the Centre for Global Development should be able to add a table to their reports showing the rises in private malaria vaccine funding across a range of firms.

does not discuss the information gathering mechanism currently being put in place to test this response in the next few years[492]). We would not need to wait 30 years (as the literature suggests) to test it. A few years should do. Perhaps though, with the APC for HIV being so ineffectual (even more ineffectual according to current announcements), maybe those like the current author who think the approach utterly harebrain for early-stage vaccines such as HIV, should simply sit back and wait a few years for the evidence to come in?

The only problem, unfortunately, is that if the experiment fails and, meantime, other HIV vaccine research collapses (or simply fails to expand) because policy-makers have been fed the quick fix they need to avoid tough decisions, the experiment will put us back even further, with long-term consequences for the epidemic in Russia, India and China that do not bare thinking about. Because it takes 2-6 years to do a Phase III trial, it is not as if doubling up funding at some future time will make up the lost ground; it will broaden the search, but will not be able to 'buy back' the time. And we are still stuck with the APC and all the concomitant institutional structure for 30+ years (a five year experiment could not have abandonment of the approach after less than 30 years written into it), and the dangers that though it does nothing to stimulate HIV vaccine R&D, it deters smaller and less powerful developers by creating a convenient market stymieing device in the 'end-game' in the shape of IP ownership rights to the whole R&D endeavor for the one big firm that, after much research by others, has the most resources (and influence) to take the IP.

The sensible approach in the light of the inherently experimental, speculative, nature of knowing if such instruments will ever work, the dangers of losing time, the dangers of losing IP rights, and given that we have never *tried* such instruments on *anything*, even on the most trivial of cases, is to cross-examine – 'stress test' – every aspect of the proposal, and to appeal to independent empirical evidence. But this is not currently on the agenda of the leading advocates. Maybe we really will have to experiment after all?

7.4. Some Thoughts on a G8 Strategy

It is pretty clear from all of the above that – in spite of claims to the contrary – a $6bn HIV APC would do very little to stimulate an HIV vaccine (and the current $3bn pitch, even less). The sums are pretty simple. Because of all the many risks (especially of the science but also of the workings of the mechanism itself), finance costs would gobble up 80% at least of this. 'Crowding out' and many other failures would take care of a good chunk of the rest. Result? Maybe 6 months' worth of what the Global HIV Vaccine Enterprise is currently requesting. If the vaccines cannot be manufactured cheaply enough it will be even worse: 250 million HIV vaccines at a highly conservative $10 a shot costs $2.5bn. Where will that come from? HIV vaccine science might be close to 'rocket science' at the moment, but the economics of it is not.

[492] It is being put in place, isn't it?

It would be silly to fix terms now

Even if policy-makers wanted to fix terms now, expecting little activity in the near-term (though this is hardly the language of the promoters of APCs at the moment) but intending that the APC 'be in place for later when it matters', it would be impossible to do so 'correctly' and cost-efficiently without resolving the relative rôle of other parts of the mechanism first. Even then, fixing now when there is no urgency to do so is not a remotely sensible proposal given that policy-makers would lose the flexibility to learn from, evaluate, and scale up the much more collaborative approaches that are more likely going to be needed to generate HIV vaccines (and this in itself would help to more efficiently set a later-stage HIV purchase commitment as and when a vaccine is looking much more likely). Besides, we have no experience of using APCs. Surely, given the huge importance of credibility and of keeping the capital costs of developers down, the last thing investors want to see is a mechanism in place that then needs constant rounds of reformulation as it is realised just how unworkable it is? Hardly confidence inspiring. And wasteful if there was no real need for terms to have been set yet.

The big gambles

The discussion above suggests many big gambles would be taken in fixing an HIV APC. A few stand out:

1) The " Framework Agreement as tender" that places a potentially huge amount of 'mechanism risk' on developers, especially those we wish to encourage, and may simply prove non-credible and have to be abandoned mid-stream. The alternative is to be stuck with it even if it is not working and is extremely costly, so as not to 'undermine confidence' or trigger litigation. Credibility is a delicate subject. It is not always helped by something being fixed. If the thing that is fixed proves to be badly fixed and needs radical reform later, this harms credibility, and it would have been better to have waited before making a fix;
2) The payment structure supposedly for incentivizing a range of quality and vaccine resistance issues but that puts heavy risks onto developers (especially the 'higher quality' developers) and would never work anyway. There is no evidence that there is the slightest intent to carry out such a payment structure in practice anyway;
3) The lack of competition in tender structures at the end of the process that undermines the drive to cheaper production costs and ultimately weakens access;
4) The bias in the mechanism towards the current few large firms, even if they are not that keen to react to the mechanism, with the device simply giving a large, influential, firm the ability to 'take all the IP' at the end of a mostly publicly- and foundation-financed endeavor, and the highly uncertain impact on the structure of the industry, with the very real danger that fewer and not more vaccine players are active;
5) The implications of the reputational risks to large players not fully understood;
6) A whole range of IP problems;
7) The dangers of aggravating a potentially better, more collaborative mechanism;

8) In the case of the UK, the huge political capital wrapped up in the IFF. A few early expensive white elephants would be the best way to sink the IFF[493].

Incidentally, purchases of currently existing vaccines and even late-stage purchase commitments may only hint at these problems, and may even give quite the opposite signal.

We can learn a lot first

Given the leagues of extra complexity for HIV and malaria, it is brave to suggest that *nothing* can be learned from early applications. While 'Making Markets' argues that "The analysis in this report shows that such contracts can be developed *and implemented successfully*" (italics added)[494], a more balanced response of one vaccine expert to the *'Making Markets'* report was:

> "*It has a continuous optimistic tone indicating that all problems can be solved while in fact many of the problems have never been solved before and may represent insuperable barriers.*"[495]

Maybe the Center for Global Development should adhere to its own previous wise counsel:

> "*These market-based mechanisms are not panaceas - like all experiments, they should be treated as pilots that are carefully evaluated at each stage.*"[496]

> "*A purchase commitment or price guarantees approach would need time and experimentation to evolve into an optimum design. The first step in developing these commitments as a tool for encouraging R&D would be to try in a few cases where current R&D incentives are inadequate and where the pull approach seems well suited to fill the gap.*"[497]

Instead, is it right to play God with an untried mechanism on HIV, and suppress the slightest hint of lack of faith in the mechanism? Why encourage a 'debate', but rush ahead anyway without bothering to evaluate any of the most critical feedback? Why not learn to walk first, rather than try to run, fall badly, and be permanently paralyzed? Worse, force this on others.

A permanent fix is a permanent fix

Contrary to the views some are starting to articulate, no permanently fixed APC could be fixed *now* with all the troubling details left to be dealt with later. First, the 'commitment' *is* a legally binding contract, even before it gets any 'takers', since firms work towards it on the basis of publicly-declared terms. These terms *cannot*, and should not, be changed. If terms are set very suboptimally from the

[493] Though it looks increasingly unlikely that much, if any, vaccine development will be funded by an IFF.
[494] 'Making Markets' p93.
[495] Mahoney, R.T. CIPIH Forum 21 December 2004.
[496] "Give the poor a choice", Easterly, W. and Whittle, D. Financial Times, August 26, 2002.
[497] Kremer, M. 'Strong Medicine' p114.

start, not only will this jeopardize its own survival but it will also risk damaging other parts of a more general approach. As an example from another area of economics, no country would ever consider entering a permanently fixed exchange rate mechanism without full consideration of the optimal parity. If the rate is set too low it runs the risk of excessive inflation. If it is set too high it runs the risk of deflationary pressures and unemployment. *Both threaten the credibility of the mechanism and its continued existence.* Once in the mechanism, any doubt about parity or even slight hint that the mechanism might be replaced even if it isn't working, is itself damaging and will impose heavy costs, even if some major change in circumstances may have cast doubt on the original parity. Like badly-set exchange rate systems, outside of the crisis situation when replacement of the system is forced, policy-makers are stuck with a badly-set APC.

The notion that the APC could be set very large to overcome these potential problems is damaging in its own right. If there is no rush to join, the more sensible measure would have been to spend some time first learning about what the behavior of the mechanism was first.

Private investors put off by an overemphasis on APCs and a lack of critical analysis

Besides, obsessing about an early HIV APC right up to the G8 summit, to the exclusion of obsessing about the other, perhaps more difficult and collaborative, parts of the R&D framework, will put private investors off *even more* since they will come to understand (and price in to their investment decisions) that the risks of ever getting an HIV vaccine are so high, and the expected time to delivery so very far off, that all the figures discussed above have to be multiplied so many fold that there is even less incentive to engage in early HIV vaccine research. Those lobbying hard for an 'early' APC for HIV to the exclusion of lobbying for the more collaborative parts and 'front-loaded' parts of the approach to developing a high-quality HIV vaccine, need to reassess whether it is the wisest use of their influence and not, in fact, counterproductive.

Private investors are also put off when they discover that investment proposals being put to them have not been fully thought through. How likely is it that private investors will believe that the APC mechanism will work for them, when they discover that the last thing those promoting it had shown any interest in doing was critically and rigorously cross-examining the validity of the mechanism rather than just lobbying for more supporters of it? Given the utter centrality of credibility for the 30+ years of the life of the mechanism, the rational approach, it would seem, is not to show the slightest interest in having yet another supporter, but loads of interest in finding out just why the critics are critics at all. It really is quite incomprehensible, and contradictory to the inherent logic of the mechanism, that transparent and critical analysis is not more openly encouraged. And it is not a good sign for investors either.

Private investors are also put off when the strategic and reputational risks to them are not fully spelled out. In many of the sections of this (and the earlier) paper we have come across potential strategic manipulations of the commitment mechanism, many with negative consequences for the mechanism even if positive benefits to those doing the manipulation. How should we interpret this? On one

level it might suggest that the mechanism should be designed better to avoid these outcomes. On another level, and probably the more likely outcome, firms (especially large pharmaceutical firms) are likely to want to avoid mechanisms that put them in such unenviable strategic situations. Given a choice between a PPP with equal present discounted value compared with an APC, most large pharmaceutical firms would prefer the PPP, since it avoids placing all kinds of risk, but especially reputational risk, onto their shoulders. Yet again, we find that though the APC tends to pitch itself more towards the large pharmaceutical players, not even they are likely to want it over what is to them a less risky alternative.

7.5. A Set of G8 priorities and a Big Opportunity Being Wasted

The advice here (for what it is worth) is that those pushing heavily for an HIV APC should concentrate their efforts instead on the following order of priorities:

1) Fully funding the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies:

> *"This would be a more tangible proof of sponsor commitment (as it is by The Gates Foundation) and could usefully 'lock–in' donors to the eventual, hopefully successful, outcomes…e.g for Malaria a major injection of cash over the next 5 plus years into MVI and into EMVI (and perhaps others)."* [498]

> *"The development of new medicines, however, must be viewed in the context of the wider health issues facing low income countries. 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."*[499]

2) Asking sponsors (who would be those that eventually pay for the vaccines) to bite the bullet and ramp up the pathetically low levels of resources going into some of the existing global/regional consortia/PPP's[500] and emerging Vaccine Enterprises, rather than issuing huge way-off financial promises. The Global HIV Vaccine Enterprise has recently started to price what is, conservatively, needed for HIV at twice what is currently being spent, or $1.2bn per year. Most of the current levels of funding come form the US. There is no reason why the US should be expected to keep carrying the majority of the burden. The UK should urge members of the G8 summit, especially the non-US members, to put in place at least this level of funding for the next ten to fifteen years (should it take that long), with suitable opportunities for review. That is $12-$18billion over ten to

[498] Jones, T., CIPIH Forum 29 November 2004.
[499] International Policy Network "Incentivising research and development for the diseases of poverty" 2005 p17.
[500] Just for current activities, PPPs are estimated to need an *additional* $1–2 billion over the next two to three years. [500] Sander, A. and Widdus, R. "The emerging landscape of public-private partnerships for product development", IPPH, 2004.

fiteen years for HIV. Those working on malaria and TB make similarly strong cases.

3) A combination of more targeted funding and, where applicable, purchase commitments for all the late-stage products in which they are likely to have at least some strength, including hepatitis B vaccine, haemophilus influenzae vaccine, rotavirus vaccine, HPV vaccine (when that product soon enters the market), 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, and a pneumococcal vaccine against the important strains in developing countries. In these cases, the scientific risk is relatively low (not in all cases, but certainty much lower than for HIV, malaria, and TB), yet the market risk very high, the capital cost proportion of expenditure (relatively) low, and the advantages of purchase commitments in creating more certainty very high. The emphasis in many of these cases 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.

Later, the experience gained from this can be used to work out how purchase commitments might ever be made to work for greatly more complicated vaccines such as HIV (for example, the highly likely problems making the mechanism work for rotavirus will almost certainly require a major rethink on how to make the mechanism work for HIV). Even then, it is highly unlikely that purchase commitments for HIV or malaria should put much of their weight on the R&D of such vaccines, and should instead concentrate on the, nevertheless hugely important and difficult, task of production and distribution.

4) Putting in place an 'Advanced Distribution Commitment' commiting to fully funding the delivery mechanisms for HIV, malaria, and TB vaccines once developed. This would cut in *after* competitive tenders have driven the production costs of such vaccines as low as possible. This is quite the opposite of the current lobbying effort. It puts next to no emphasis on extracting R&D costs through the vaccine prices[501]. There is not even any talk within the 'Making Markets' proposal of ways to address the need for funds to distribute the vaccines, i.e. an 'Advanced Distribution' scheme. Why not? Why the topsy-turvey priorities? This distribution commitment is not just a financial commitment. It includes a commitment 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 a commitment to tackle institutional failure and corruption that holds back provision of healthcare and access to medicines.

5) Meanwhile, totally downplay APCs for HIV, and instead push home to policy-makers that they need to bite the bullet about paying for up-front HIV vaccine work through a much more collaborative system than we now have, and by fully backing the Global HIV Vaccine Enterprise and other vaccine enterprises. The

[501] Refer to the discussion of the collaborative mechanism above for why this can be made not to harm those performing the R&D.

HIV vaccine enterprise should have complete control over whether or not it chooses to set competitive-tender style purchase commitments and should not have a large separate APC imposed upon it from outside in advance, given that this (especially the IP implications) risks aggravating its problems.

The hugely positive signal of success on the purchase commitments for the diseases listed above, the credible knowledge that they can be modified to make them effective and will be used again, coupled with the bullet-bitten approach of policy-makers to doing something of real power to drive HIV vaccine research forward and the front-loaded funding needed to do so, will make eventual HIV purchase commitments – if ever they are used for HIV vaccines – more powerful, cheaper, and easier to set.

Don't waste this year's and next year's big opportunity

This year's G8 could present a big opportunity to do something radical about achieving HIV, malaria, and TB and other vaccines, and this should be played much more strategically than it is. Tealeaves-in-teacups aside, one cannot rule out the possibility that many of the objectives that the UK is pushing for the G8 will fall well short, even fall completely flat. The IFF will stumble without US support and the dangers the other members perceive in going it alone. And the French have a very different proposal for increasing finance for development based on a Tobin tax, so there is genuine tension over a key UK objective both within Europe and the US. On top of this, the environment package has been heavily watered down already. The debt right-off package is doing relatively better but is also struggling. The global HIV vaccine enterprise (and vaccine enterprises generally), coming up on the outside as it were, has much going for it.

First, the US has already expressed commitment to it with President Bush's announcement at the G8 Summit last year, and he and the US administration can be challenged to make good on their high-sounding promises. There is a tendency for the holders of G8 Summits to want to do something 'different' from previous holders, which they can label as their 'own' bold new initiative. This is not the time for such games.

Second, the next G8 holder, Russia, has *more than any other country to gain from a global HIV vaccine enterprise*[502] and could be a great deal more willing to take the baton than currently seems the case (and *can*, and should, be persuaded to do so). Russia's HIV/AIDS epidemic is already a nationwide phenomenon. Under worst-case scenarios, the rate of infection in less than ten years' time will be similar to sub-Saharan Africa today (11%). On conservative assumptions, by 2025, cumulative new infections are estimated between 4 and 19 million in Russia, 32 and 100 million in China, and 30 and 140 million in India with the cumulative death toll estimated between 3 and 12 million, 19 and 58 million, and 21 and 85 million respectively. Russia will suffer worst economically however. Even a mild epidemic, it is predicted, would cause the Russian economy to be completely stagnant to 2025[503]. In all three cases, in spite of the huge economic

[502] See section "A Long-Term Threat" in Farlow, A.W.K. "Emerging Market Risks: An assessment of the balances of emerging market risk and the sources of crises." November 2003.

[503] The principle reasons are: i) the demographic structure such that the loss of economically active cohorts is relatively more damaging in Russia than the other countries; ii) the rapidly revolving

impact, the figures are swathed in secrecy, and political leadership is in denial. So, passing an emerging Global HIV Vaccine Enterprise onto the Russian G8 agenda would have a double impact by helping Russia and others to face up to their impending crises too[504]. From Russia's perspective, an HIV APC is the least desirable outcome, since by being a non-eligible market it would face much higher prices than for vaccines generated under a global HIV vaccine enterprise.

Third, a powerful case can be made for a global HIV vaccine enterprise.

At a very crass level (but that is what strategy is all about sometimes) the UK could yet find itself looking for a 'success' from this year's G8 summit, and the global HIV vaccine enterprise could be dramatic and fitting enough to fit the bill, and the UK could play a useful, and well-respected, pivotal role in getting it fully off the ground, taking it from the US and passing it forward to following holders of the G8 reigns including Russia. Given the increasing budgetary pressures both in the US, the UK, and elsewhere, now is a better time than later to do something to push the initiative forward. This would be no mean achievement, whatever else comes out of this year's G8 summit. Instead of wasting energy and political capital trying to set, permanently, a large, currently ineffectual, HIV APC of the sort being proposed in the literature (that would nevertheless be a source of instability to any emergent IFF), this strategic opportunity should not be squandered.

The truth is…

Large portions of this paper was written before discovering that the APC for HIV being proposed by the Center for Global Development had, yet again, been trimmed – to $3bn this time. Given that pitching ever-lower is dangerous and also weakens the incentive, why keep pitching ever-lower? We showed above that $3bn was an essentially random figure unrelated (contrary to what it should be) to the underlying science and costs of developing a HIV vaccine[505]. If the $6bn commitment was going to do nothing positive soon, what would a $3bn commitment achieve? At current rates of scientific risk, capital costs, horizons, and crowding out, a $3bn level of payment for a HIV vaccine could not, in the near future, possibly stimulate more than a few months of the current levels of effort that the Global HIV Vaccine Enterprise says is needed. So what *would* the $3bn do? With the payment coming at the end of a huge public and foundation funded effort, it is hard to imagine that most of the 'additionality' of the $3bn would not be crowded out, leaving the fund to essentially go to the one big private pharmaceutical firm that positioned itself best in the 'end-game'. And that is about it. The line that "a large incentive might bring in a single major pharmaceutical firm" [506] comes back to haunt us. Incidentally, it is not as if large pharmaceutical firms would ex ante want this, even though they may be pressured

---

prison population and the brutalizing military service, both of which act as a giant petri-dish for all kinds of disease; iii) the very high rates of, and widespread nature of, needle usage (there are a quarter of a million needle injectors in Moscow alone); iv) the dislocation caused by the rapid move to 'capitalism' and the rise of commercial (and largely unprotected) sex; v) the fact that HIV is already much more widespread at such a relatively early stage in the its epidemiology.

[504] The author's contacts in Russia suggest that there is a chance of making HIV a top priority on the Russia G8 agenda. Increasing further those chances should be a high priority.

[505] See section 2.2. above for the details.

[506] Kremer, M., No 10 Policy Unit, Appendix 1 p9.

to behave this way ex post. It is just another example of the reputation risk they are expected to face by taking part in an APC.

The truth is that $3bn is not the figure generated by a serious discussion of the level of funding needed to create incentives to develop an HIV vaccine. It is the cost of political favour, of getting policy makers to say 'yes', and of allowing the chief APC advocates to declare "success". The figure is pure opportunism, and is not based on any scientific or economic logic. It does not even suit large pharmaceutical firms ultimately, given the huge reputational risks they would have to take on to try to win a 'highly lucrative' APC for HIV. For HIV and other early-stage vaccines they would be better served by decently-funded PPPs. The only thing it could achieve for them is the stymieing of emerging market vaccine developers undermining their dominant positions. Ultimately the mechanism for early-stage vaccines does not really suit anyone except those lobbying for it.

Similarly, the Center for Global Development was set the task of critically and rigorously evaluating how and *if* APCs might ever work for a range of diseases, including HIV, but the intent, it now seems, always was to simply use it as a rubber stamp for a lobbying effort the result of which had been set a long time ago. If this had not been the case – and in light of the permanence of the mechanism – then the most skeptical and troubling analysis would have been at the heart of everything, rather than analysis largely based on the faith of believers[507]. But by this stage in the game, the notion is not to set in place a workable and fair 'mechanism' with an emphasis on very broadly-defined 'quality' (so all the stuff above about rules for distributing the APC to ensure quality and market enhancement and all the rest, were just a waste of breath) but simply to get a PR[508] and 'policy success', for which workable and fair mechanisms and troubling analysis are just a distraction.

With just such opportunistic maneuverings, the way things are going, the G8 summit in July will come and pass with politicians patting themselves on the back that they have $5billion-$10billion of pretty ineffective, ill-structured, dim-and-distant APCs in place, but none of the really difficult and powerful parts of the mechanism for driving HIV, malaria, TB, and other vaccine development and distribution. For years politicians have managed to get away with putting

[507] The believers did not include many industrial economists, financial economists, or those involved in the practical aspects of vaccine manufacture and distribution – the most obvious sorts of people required to check the idea – but towards the end the believers did seem to include a lot of lawyers, who are good at contracts once an idea has already been decided upon.

[508] This author experienced this PR-based approach to policy-making first hand. Having discussed in person a large file (Farlow 2004) willingly contributed to the Centre for Global Development's effort, he was at first told that the idea would not be applied to HIV. Then he discovers that the approach borrows from that critique to come up with the "Making Markets" angle and is applied to HIV and other early-stage vaccines. Then he is told that that file had only been cursorily looked at and dismissed (remember, this is an irreversible policy with plenty of risks and dangers to it, so dismissing even what those receiving it described as something containing plenty of valid points, is foolish). Then, ideas from that file are quoted back at him in correspondence in the Lancet (ideas that were no longer in the public domain – the file had since changed, and there were no public copies available, so this correspondence was based on an original copy). So, in summary, an approach that is willing to take parts of a critique that could be used to make the PR more polished, but having no interest at all in the underlying critique. This has been the story of the 'consultation process'.

extremely low emphasis on vaccine R&D and the distribution and healthcare systems for making full use of the results. Challenged at long last to put proper emphasis on vaccine development and use, and with all the impending dangers of collapsing research funding, especially for HIV, is our best response to feed them quite such an easy cop-out?