An Independent Assessment of
Tuberculosis Vaccines:
The Case for Investment

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SUMMARY OF ASSESSMENT

At the request of Aeras Global TB Vaccine Foundation, this is an independent evaluation of "Tuberculosis Vaccines: The Case for Investment"[1] – a report commissioned by BIO Ventures for Global Health (BVGH) with analysis performed by the Boston Consulting Group (BCG) – and a wider analysis of investment case possibilities given the specifics of TB.[2] This assessment was prepared to aid discussions between Aeras Global TB Vaccine Foundation and the Bill and Melinda Gates Foundation during the grant renewal process of Aeras Global TB Vaccine Foundation in the summer of 2007.[3] A presentation based on this assessment was presented in a meeting between Aeras Global TB Vaccine Foundation, the Bill and Melinda Gates Foundation, and other interested parties in Washington in July 2007.

The derivation of the Net Present Value, NPV, of investment into TB vaccines is a far from exact science. Declared NPV is sensitive to the quality of inputs into its calculation, with potentially wide disagreement on assumptions leading to wide possibilities in the NPV figure coming out of the process. Given this, the objectives of this assessment are to check the data provided to the author by BCG, to stress-test the NPV possibilities more than the original BCG report, and to look at some more qualitative context-sensitive issues relating to TB vaccines, and especially TB vaccine product profiles, that may complicate how we view future market and investment possibilities.

Efforts to do this in the preparation of this assessment were often connected to efforts to understand the data and methodology used in the original investment case. Some of these are referred to at the start of this assessment. This is also reflected in the narrative of the assessment as the author went through replacement, booster and prime-boost vaccine cases in turn, finding data and methodological issues mounting. On the one hand, highlighting this can look critical of the original analysis. On the other hand, if this is not recognized before reading the assessment, the assessment will come across as unnecessarily incoherent.[4] Good quality advice requires us to carefully pick apart exactly what is going on in the figures.

These issues also generated problems when performing alternative scenarios. In particular, it is unclear whether to do scenarios based on original data or on newly constructed data. And, since each 'new' scenario is reset to a base case, the reader must be extremely careful each time to read the results with respect to the specific base case.

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[1] "Tuberculosis Vaccines: The Case for Investment. A Report Prepared by BIO Ventures for Global Health, October 2006, http://www.bvgh.org/documents/BVGHTBVaccineReport10-6FINAL.pdf.

[2] As a member of the recently-established Task Force on Economics and Product Profiles of the Stop TB Working Group on New Vaccines, the author is working with others on refining methodology and use of disease-based evidence in TB market and investment case analysis.

[3] The Bill and Melinda Gates Foundation renewed funding of Aeras, with a five-year grant of $200m, http://www.aeras.org/newscenter/news-detail.php?id=712.

[4] Several requests were made for clarification from those who put together the original investment case, in the hope of removing these issues from discussion.

The results are open to revision once some of the issues are resolved; some of the results may even prove redundant.

With these strong caveats the assessment can be read.

At the beginning of the assessment, the simple basis of NPV as an investment appraisal tool is explained. Since NPV involves the balance between discounted expected values of revenues and costs, the assessment gathers scenarios under the two broad headings of revenues and costs. Scenarios are then performed in subgroups under these two headings. On reflection, more could have been done to analyze the issue of appropriate methodology and rates for discounting. As a sobering introductory exercise it is shown how sensitive the NPV figures presented in the original report are to some relatively small rich-world changes in vaccine uptake.

The assessment first heavily stress-tests the value of rich markets – replacement vaccine, then booster vaccine – and then repeats the exercise using some of the extra data provided by Aeras. It was only much later discovered that the figures used for booster vaccines by BCG were simply scaled-up replacement vaccine data, calling into question the notion of this as analysis of 'independent' cases. It is observed that there does not appear to be any catch-up in any of the data. How much catch-up there should be in replacement vaccine in infants is not clear, but one might expect it for booster vaccines in adolescents and adults. That the figures for booster sales appear to be scaled-up replacement sales figures does not help.

Removing rich-world replacement data from the original spreadsheet data provided by BCG, we see a collapse in NPV into heavily negative territory. Various scenarios are then performed on replacement data showing what happens if there is rich-world uptake but not on the scale envisaged in the report. Returning to the base case, the effect of altering rich-world dose price is investigated, first presuming that rich-world sales are unaltered (not unreasonable, given low price sensitivity of quantity demanded), and then looking at cases with lower uptake than envisaged in the report. The role of the competitive event in the case of rich markets is discussed.

The case of rich-world booster vaccines is then analyzed. At the time this was done, it was already clear that there was a problem making the private-market booster figures add up. Given that the overall figure of 601m dose sales in the spreadsheet is the same as in the report, this issue was initially ignored, since consistency of the two figures seemed to suggest the figures were correct. It is also possible to do middle income and rich market changes leaving this issue to be resolved later. This also shows that, according to the data (and ignoring this issue), removing rich market sales pushes NPV into heavily negative territory. A further partial rich market uptake is analyzed and the follow-up data provided by BCG is reviewed.

Sticking to the base case figures again, the rich-world figures given to the author by Aeras from Sanyour are inserted into the spreadsheets (ignoring Sanyour's more pessimistic poor-world scenarios, so as to concentrate on the rich world only). Various

long-run steady states are attempted (given that Sanyour was much more pessimistic about the long-run steady state after an initial catch-up phase). The early catch-up phase is beneficial to NPV, while the lower long-run equilibrium pulls NPV down. The reasons for such different interpretations of long-run sales need exploring.

This is followed by a more qualitative assessment of the incentives of rich nations to adopt vaccines meeting profiles described in the report, given the need for such vaccines to fit into those nations' current prevention and treatment strategies. It is argued that a range of issues have been ignored that would tend to drive rich and poor countries to have different incentives to adopt solutions, that the sourcing of the evidence on willingness to pay in rich markets is very limited, and that the presumed rapid response of organizations to change is overly optimistic.

Starting with the base case (hence returning to a 'default', and therefore 'high', rich-market setting) attempts are then made to analyze what would happen if the value of non-rich markets were to change (poor, middle-income, private sales, China, India, etc.). This is where replacement and booster sales data started to be an issue as various checks were performed (usually involving dividing spreadsheet revenues by the prices given in the report to see what 'implied' sales levels lay behind the revenues, and then comparing to the sales levels in the spreadsheet). For replacement vaccines, private-sector sales data does not match at any dates and private-market sales seem to have been undervalued in the report. China registered the opposite discrepancy, with private market sales overvalued, starting from 2022 (the other markets did match up). Though the discrepancies nearly cancel and leave total figures the same, the problem is that private market sales and sales to China are at very different prices so will have had a big impact on the revenue figures.

Given these unresolved issues, various scenarios are done taking out private replacement data, putting in some India data (a highly speculative exercise) and pulling various markets forward, revealing the power to impact NPV heavily in a positive direction.

Reviewing the booster sales data, we find that again the private-market data is off (and the middle-income data by a tiny bit too) and by a constant amount as well, suggesting some sort of global error. The 'implied' quantities are much lower than the listed quantities. Again, it would appear that the private sales are being undervalued if the private-sale quantities in the spreadsheets are accurate. A new set of NPVs are done presuming the higher quantities (of course, the fault could be the other way – that the revenues are correct, but the quantities are wrong). Using this new set of data, a number of scenarios are done varying the level of rich-world sales. With no high-income sales, NPV never goes negative in this case. NPV is rescued by the high private-market revenue.

Clearly it is important to know what is going on in the private-market figures. In particular, in the revenue figures in the report the power to price discriminate in the case of booster vaccines is not present, while under the adjusted/corrected figures it is.

These new figures (holding rich markets constant in the base case 'setting') are then analyzed according to different rates of private market uptake.

The assessment then turns to the prime-boost data. We only have the combined prime-boost sales and revenue data, requiring us to explore the possible underlying sales patterns of each of the two vaccines in the combined package. After a lengthy exploration of the advantages and disadvantages, it seems that the methodology adopted in the report was to simply add both sets of sales data in the single vaccine cases to get the combined case, with one exception: Replacement sales in rich markets have been excluded. Thus also any problems in the boost data have been carried through to the prime-boost data. Furthermore, a simple manual addition of the original prime and replace vaccine spreadsheet data generates a figure starting in 2022 that is 7 million doses per year lower than that reported in the report. The discrepancies are listed.

To analyze how the data was added up, various checks are done. First, the NPV is checked manually, using revenues per market reported. Given the differences between these revenues and those revenues listed in the report, the discrepancies are listed; they are surprisingly large in places. NPV on these data is generated and is much higher than that quoted in the report. This was very puzzling. How could working with the same raw data regarding quantities and prices, and approximately the same methodology, produce such a dramatically different result? Nevertheless, various scenarios were done of different possible price trajectories across markets.

A series of queries about the data ensue before a number of interesting, even surprising, findings appear. First, the average price in the early period for private prime-boost sales is just over $10 and much lower than the $26 and $29 listed in the pricing table in the report; in the latter period (after 2022) the average price is just over $7, higher than the $4 prime but much lower than the $22 booster, in a period when more than half the sales are booster. Second, instead of moving about as expected, the average price (surprisingly) stays constant, something not possible if relative quantities of prime and boost vaccines change over time, as they might be expected to do if relative quantities are sensitive to relative price (and if there are periods of catch-up with one but not the other). Third, it is then discovered that the booster vaccine figures are simply scaled-up prime figures. In the case of high-income markets, the ratio is a constant 1.82 for all years 2013-2030. For private-market sales it is 2.21 for years 2016-2021, and then 1.39 for years 2022-2030. For middle-income markets it is 4.07 for years 2018-2024, followed by some variance in the closing years (and, incidentally this 4.07 persists through the competitive event). In conclusion, the prime and boost figures have not been derived independently, and it is also unclear how the 'profit maximizing' condition, which is supposed to be working through quantity adjustments as prices change, can be working.

In the Aeras/Gates meeting in Washington in July 2007 to discuss a number of independent TB market assessments including this one, a message was relayed from BCG that there were a number of errors in the report. These pertained to pricing errors in Table 1, and errors in the way quantities were added up across categories in the spreadsheet such that there was not a complete match of the type of sale with the type of

price quoted. Subsequent requests yielded little further insight that would have enabled this section to be removed..

The assessment then returns to the original data, and interests itself with coverage and pattern of build-up of demand for the various vaccines. The use of the "average Hep B adoption curve" to pattern this build-up is explored, given its many nuances and the differences between the cases of Hep B and TB. The state of EPI coverage is also discussed.

Sticking to the original base case (and therefore the rich market base figures), a number of replacement vaccine scenarios are done, again showing the power of pulling forward non-rich market sales.

The assessment questions the assumption of 66% booster coverage given the need to develop sustainable delivery mechanisms and the limitations of diagnostics. Knowing what the fully burdened costs will be is an important unresolved issue.

The assessment then reviews a range of issues pertaining to efficacy and coverage/market penetration, and it observes that it is quite difficult to use the report to guide investments towards target product profiles since it does not much analyze response to product profile. Nothing is said of the discontinuity in the acceptable target product profile in rich markets (well understood by those working on cost effectiveness analysis and TB policy in these countries), and the way this impacts (in the expected sense) NPV.

The assessment then questions a range of issues pertaining to the way the questionnaire protocol was put together, and especially the way efficacy and lives saved were articulated to generate measures of willingness to pay. It pays particular attention to the treatment of booster vaccines, given that the report finds that they contribute heavily to impact (Fig 6 of report) in a way that should have generated a very positive impact on willingness to pay if adequately articulated in the questionnaire protocol.

The revenue section finishes by reviewing a range of issues. First, the impact of probable delay to licensure. Second, the impact of other new interventions, especially new drugs, and the consequences of the continued progression of MDR-TB and XDR-TB; these two issues are big uncertainties that financial markets must be factoring in to their evaluation of NPV. Third, a range of epidemiological issues, such as the consequences of the latent nature of much TB, and the role of immunological memory. It is concluded that the pattern of behavior of the data in the report and supporting material, indicates that the use of this epidemiological analysis was fairly minimal outside of a partial use to derive Figure 6 in the report.

The assessment then turns to cost issues. Higher costs, whether from R&D costs or from cost of goods sold (COGS), will pull down NPV at any given level of revenues. This assessment has very strong reservations about the way the R&D costs have been worked out in the report. One particular concern is the way a 'probability adjusted' R&D cost figure was derived for each of the vaccine cases. It is not clear how results derived *from*

the perspective of one company can be straightforwardly extrapolated to the population level. Nor is it clear how "probability of occurrence" is treated. The figures seem quite rudimentarily calculated. The report observes a 35% chance of *at least one* success and that this has been used to attrition-adjust the figures. It is not made clear if this is "the cost to bringing a single, successful product to market" or the cost of bringing "at least one single, successful product" to market. In both cases there is no notion of 'expectation' of outcome or of any probability distribution around an expected outcome. Some fairly basic notions of uncertainty are missing. Given the consequences of TB, we might rather be interested in the expected costs of generating "95% chance of getting at least one vaccine" to market (controlling for vaccine characteristics). The only way really to analyze this – and it is still a somewhat imperfect approach given all the informational limitations – would be to use portfolio analysis. The consequences of this are reviewed, especially the way in which is raises costs and should lead to several products that then have to be factored into the market equation.

The assessment then reviews attrition rates, finding, first, that there is wide disagreement over them, and second, that we really do not have a good fix on appropriate attrition rates (and trial sizes) in this case. This begs the question of what sensitivity analysis over attrition rates would do to the range of NPV. The assessment does not do this here. But it does do the next best thing, and simply explores what happens if R&D costs are higher. A table is created that can easily be added to any of the scenario figures so far created to show the impact of these higher costs on NPV in each scenario.

It is suggested that it would be extremely useful to break down the 'aggregate' cost figure into the costs needed to get to each stage of development, and hence the 'remaining costs' and expectations to get to product at each point in the chain of product development, and NPV from that moment onwards. Having a better calculation of the cost of 95% of "at least one success" and the average costs of each new product based on this 95% thinking would also help. There also seems some lack of clarity in how sponsor funds are treated in calculations.

A range of scenarios are done changing COGS. It is fairly mundane to suggest that this has little impact on rich markets given the profit margin, but if the quantities are big enough and the sales early enough, it is shown that there is potential for big impact on NPV from sales to poorer market if COGS are much lower. Ensuring good pressure to keep COGS down has very favorable impact on R&D investment incentives.

The report presumes facility capacity sufficient to produce 120m doses, such that as demand rises in response to lower COGS, the number of doses demanded eventually exceeds the threshold to incur the cost of another plant. Thus, NPVs decline with lower COGS. However, if the notion is to have greater developing country sales from the start, one might build a plant size commensurate with this. A bit more exploration of optimal plant size in light of this possibility would be useful. Given this behavior of NPV, and given the importance of COGS, suggestions are made for exploring scenarios/incentives/policies that might be adopted to make technology more affordable.

It is worrying, and perhaps rather telling, that views on COGS changed dramatically (and, thus, so would have NPV) even as the report was being written.

The next section takes the report figures at face value and observes that the three Financial Returns scenarios listed in the report (Table 2, replacement, boost, prime-boost) do not appear to be independent of each other. Negative NPV prime-boost outcomes will weigh heavily on investors, the more likely it is that developers will succeed in producing *both* replacement and booster vaccines, with this rising the closer sponsors target "95% chance of at least one success". Scaling up to hit this 95%, both raises costs and lowers (expected) NPV via this affect. This is shown by simply looking across the data in Table 2 of the report. Then higher cost data is put in. Clearly, all of these issues should be better studied together, and the above is itself a pretty rudimentary way for looking at them.

Before concluding, a range of other issues are raised. These include: discussion of the appropriate discount rates to use, including for different players, for combinations including sponsors, and for different parts of the product development chain; the need for NPV values at different stages of the product development chain (such that even if overall NPV is negative, we might like to know at what point it might become positive, since this avoids us panicking into initiatives too soon when seeing that private sector investors are not responding); some thoughts about how many leads to take to the end of phase II; and the value of specific R&D costs extrapolated back to 2005. It is also observed that positive NPV requires several events simultaneously coming together, and that it would be useful to rank these events by probability of occurrence and some suitable time-frame.

In conclusion, an implicit assumption in the reasoning underlying the report is that industry has not spotted a big investment opportunity, and that if only industry had better information it would invest heavily. This logic, incidentally, is also a comment on the failure of equity investors (in the case of 'big pharma') and more specialist investors (such as biotechnology funds) in the case of biotechs, either because they are not being 'rational' investors, or because, though rational investors, they suffer from a free rider problem in analyzing information such that there is underinvestment since nobody has the incentive to gather the information to know that the investment opportunity exists. One would usually be skeptical of such arguments. First, industry, and especially the financial industry, puts a lot of resources in to trying to work out the value of markets. Second, it is hard to believe that stock market investors regularly fail to spot such profitable opportunities. If investors are not investing, this tells us something about their information that reports, and analysis like that above, are somehow not quite capturing.

It is crucial not to get too obsessed about these figures. Whatever use the report and the above analysis have, it is not to justify spending regardless of more important issues like getting the science right. Hopefully this assessment has indicated that the level of NPV measured is not a precise science, and one must be mindful of, and debate and explore, the range of possibilities, and, in sponsor funding decisions, to treat it as secondary to getting the science right.

1. INTRODUCTION

At the request of Aeras Global TB Vaccine Foundation, this is an independent evaluation of "Tuberculosis Vaccines: The Case for Investment"[5] – a report commissioned by BIO Ventures for Global Health (BVGH), with analysis performed by the Boston Consulting Group (BCG) – and a wider analysis of investment case possibilities given the specifics of TB.

The mission of BVGH is "to break down barriers that hinder industry involvement in global health product development and to catalyze industry investment through new market-based solutions." It is therefore understandably a high imperative for BVGH to know what true market already exists for new and improved TB vaccines, how to strengthen currently weak markets, and how to build markets where they do not currently exist.

The spirit of this assessment is therefore to get a better grasp of the 'true' value of TB vaccine investment, or at least to come up with ranges that reflect possible value. It will benefit nobody if this assessment tries to exaggerate in either direction. An overly optimistic view only leads to disappointed investors and slow private sector response when alternative, targeted, sponsor support might have speeded progress. An overly pessimistic view will fail to exploit private sector resources. In each case, contracts underlying the investments of sponsors (such as BMGF funding into Aeras) will turn out to be wrong, possibly needing renegotiation with all its attendant uncertainties and delays.

The intent when this assessment was initiated was that BCG would be heavily consulted from the start, to help clarify problems with the data and analysis as they arose, and to achieve fairness. As a first step, BCG, via BVGH, were therefore asked to perform a series of changes to assumptions to see what happened to the NPV and IRR calculated via their model. The desire was to see more of a stress-test than had been performed in the original report. A limited number of new scenarios were done. However, in spite of genuine efforts to the contrary, in the end this assessment was created largely independent of BCG involvement. This is mentioned not by way of complaint, but because it has limited the ability to do this assessment in ways that if not recognized may reflect adversely on it.

Plenty of new scenarios for NPV have proved possible with little more than the basic BCG data. The problem has not been in the ability to model new NPVs, but rather in the lack of clarity of some of the data given to work with.

A number of assumptions underlying this assessment that have not been verified are:[6]

1) It is presumed that all figures in the 2013 cost column are *end of that year* cost figures. If this is not so, all the figures will need to be adjusted;

[5] Tuberculosis Vaccines: The Case for Investment, A Report Prepared by BIO Ventures for Global Health October 2006.

[6] A range of these were put to BVGH to be put to BCG. But response did not prove forthcoming.

2) In particular, facility infrastructure cost cash flows incurred "over the previous year are projected forward at 15% cost of capital and *capitalized in vaccine launch year*". This meant that "R&D cost cash flows incurred over a period of 14 years were projected forward at 15% cost of capital and capitalized *in vaccine launch year*" (Source: BVGH/BCG analysis, note attached to Fig 5). It is presumed here that the figure shown in both the spreadsheet and the report is the value capitalised to end of 2013, and thus requiring a further full year of discounting to get back to 2005 NPV. This is the way the NPV function in EXCEL works (it presumes all figures are end of year figures);
3) It is presumed that when a figure for R&D costs is calculated and slotted into the BCG spreadsheet for year 2013[7] this is a year-end figure;
4) The data in the BCG spreadsheets on private markets and China (revenues and sales) for replacement vaccine do not seem to match up (see comments below);
5) The data on booster vaccine from private market sales do not seem to match up (see below);
6) The Prime-Boost figures seem inconsistent too. In particular, rich-world high-risk groups purchase of replacement vaccines seem to have been excluded from the demand quantities underlying the prime-boost calculations;
7) Similarly, during the reworking of some of the data it became clear that something was wrong with the prices or the sales data that were used in the revenue calculations for the private markets in calculating prime-boost revenues. Since none of the tables in the spreadsheets provided by BCG show linking equations, that would reveal the proprietary models used, it is not possible to know which of the figures are the 'correct' ones to work with;
8) There are a range of unresolved issues about appropriate rates of return to use in calculations. This assessment probably over-relies on the original BCG framework so as to produce results comparable with the BCG report. A more thorough redoing of the report would spend a great deal of time exploring appropriate rates of return. Here, we just use the three values the report uses to achieve this comparability.

This assessment has tried to link the limited original data that was provided back to the data given in the report and to the background work of BCG to create as much of a pool of overall data as possible, to overcome some of the paucity of data. Within limitations (as explained below), it is possible to rework some of the figures underlying the report under a variety of different assumptions. However imperfect, this assessment has a go, and feedback (and, indeed, correction) is very welcome. Readers must debate assumptions and decide on what the more likely outcomes are, since even this reworking presumes rather too much about the validity of the exercise and the methodologies used. Any measure of NPV or IRR is only ever as good as the quality of information that goes into its derivation. And if asked to perform a market assessment, it is much easier and quicker to come up with NPV and IRR figures than it is to analyze a range of tougher,

[7] The specific note about this, p16, is: "Note: Facility infrastructure cost cash flows incurred over the previous year are projected forward at 15% cost of capital and capitalized *in vaccine launch year*; the value of R&D cost cash flows incurred over a period of 14 years, projected forward at 15% cost of capital and capitalized *in vaccine launch year*. Source: BVGH/BCG analysis", italics added).

practical, context- and country-sensitive questions about delivery and uptake for the product at hand in order to work out likely market sizes. Precise-sounding figures can create a false sense of security, and may detract from a more thorough and qualitative understanding of the problem. This assessment therefore offers some qualitative assessment of the evidence too.

1.1. NPV

This assessment will concentrate on scenarios for NPV.

Net present value (NPV) is a standard financial methodology for appraising long-term investment projects. It measures the excess or shortfall of cash flows, in present value terms (i.e. all figures adjusted to be based in one year at the 'start') after financing charges are met. NPV = Present value of *net* cash flows.

To derive NPV, each cash inflow/outflow is discounted back to its Present Value, then the values are summed. Where there is no uncertainty over values:[8]

$$NPV = \sum_{t=1}^{n} \frac{C_t}{(1+r)^t} - C_0$$

Where
t = the time of the cash flow
n = the total time of the project
r = the discount rate
C_t = the net cash flow (the amount of cash) at time t.
C_0 = the capital outlay at the beginning of the investment time ($t = 0$)

So long as NPV is positive, risk neutral investors[9] should invest.

The above is a little too simplistic. If there is any potential variability of input values, uncertainty, even disagreement, the NPV derived will vary – potentially very considerably. There is no such thing as *the NPV* of an investment; there are only hypothesized values of NPV based on more, or less, reasonable assumptions. To the extent there is disagreement over inputs to the NPV calculation, there is disagreement over NPV, however much those disagreements may have been assumed away to get a 'clean' result. In many ways, the issue is not whether or not information feeding into TB vaccine NPV is perfect or not (it won't be); it is whether or not there are systematic biases in the data fed into the calculations or the way the data is used, and whether or not all possible ranges of value have been explored, and whether or not the assumptions used make sense. Open debate over differences of opinion on these issues is healthy. Such debate will help get us closer to the 'truth' about NPV and the value of investing in TB vaccine R&D.

[8] This is the methodology used for the base case by BCG.
[9] Perhaps because they can diversify such as to be in effect risk-neutral on this investment.

Another measure for appraising the value of a long-term investment project is IRR, internal rate of return, of a project. IRR is the annualized effective compounded return rate which can be earned on invested capital. It is the 'yield' on the investment. If IRR is greater that the rate of return that could be earned on alternative investments, also taking account of a 'suitable' risk premium, then the investment should be done. Alternatively, IRR is the discount rate that would result in the NPV of a series of cash flows being zero. If IRR is greater than the cost of capital into the project, the project will add value.

Since there are unresolved issues about some of the data, this assessment only presents NPV values for now. When discussing current potential sponsor funding, this might help, since it gives a dollar measure of the investment problem faced which is calculated roughly contemporaneously with the sponsor decision being made.[10]

1.2. SENSITIVITY OF NPV

It should be immediately apparent to anyone viewing the data underlying the case of TB vaccine development that NPV is a balancing act between several very large flows of resources, over very long periods of time. These flows are also highly non-contemporaneous. If NPV comes out a small positive value, this suggests sensitivity to even small changes in underlying assumptions on either the cost or revenue side.

How much does it take for a change in assumptions to yield a big change in the NPV figure? How much does it take to turn a positive NPV into a small – or, indeed, large – negative value? A hint can be found in the revised figures submitted to Aeras by BCG on 16 April 2007 in the table below ("BCG Replacement Vaccine: TB Model Results"). These show relatively small changes in the assumptions regarding "adoption by High Income Markets for their High-risk Populations". This is a huge enterprise over perhaps twenty to thirty years (R&D and significant sales), and yet the replacement vaccine optimistic NPV nearly *doubles* when prisoner coverage in high-income markets is modeled as going up by just 15%, from 70% to 85%, and homeless coverage down by just 10%, from 70% to 60%. Had the homeless percentages stayed the same, this suggests that an extra 15% coverage of prisoner population alone could well have *doubled* NPV. The base case NPV nearly trebles when homeless coverage goes down 10% and prisoner coverage goes up from 50% to 72% (all else the same).

What if the percent went down by more than 15% (something we will consider below as not at all out of the question)? What if expected efficacy and immunological memory had been lower than the base cases in these calculations, causing significant drop in sales or price per dose in the rich markets, perhaps even seeing the collapse of sales in such markets? These risks have to be worked in to calculations.

NPV is also sensitive to timing and discount issues. A very different measure of NPV can be generated from the same outlay of real resources by shifting the timing of that

[10] At the time this independent assessment was being created, the Bill and Melinda Gates Foundation and Aeras Global TB Vaccine Foundation were in discussions over a $200 grant extension. This sponsor timing is thus roughly contemporaneous with the timing of the figures in the report and this assessment.

outlay or by making assumptions about that timing that are not strictly accurate. Because of the power of discounting too, one has to watch for perverse results, especially at inappropriate discount rates. For example, when costs are discounted over long periods of time (BCG amortize costs forward to 2013 and then heavily discount backwards) an overly high discount factor can massively reduce the NPV of one set of costs modeled as falling just a few years after another set of costs.

BCG Replacement Vaccine: TB Model Results

	Original			*Revised*			
Assumptions	**Baseline**	**Pessimistic**	**Optimistic**	**Base**	**Pessimistic 1**	**Pessimistic 2**	**Optimistic**
Adoption curve	Patterned on average Hepatitis B adoption curve (Source: WHO tracking 2005)			Patterned on average Hepatitis B adoption curve (Source: WHO tracking 2005)			
Pricing	Model calculates profit maximizing price balancing adoption price thresholds with revenue potential within user-defined upper bounds			Model calculates profit maximizing price balancing adoption price thresholds with revenue potential within user-defined upper bounds			
Adoption % High Income Markets (High Risk Pops)							
Healthcare workers	75%	60%	90%	75%	38%	60%	90%
LTC residents	75%	60%	90%	75%	38%	60%	90%
Homeless	50%	30%	70%	40%	20%	25%	60%
Correctional officers	75%	60%	90%	75%	38%	60%	90%
Prisoners	50%	30%	70%	72%	36%	30%	85%
Immigrants	0%	0%	0%	0%	0%	0%	0%
High-income markets	High-risk populations only			US + non-EURO: high-risk populations only; EURO: High-income countries using BCG now(1) would adopt BCG replacement vaccine for its birth cohort + high-risk populations			
Results							
IRR	25%	20%	30%	34%	23%	29%	39%
NPV ($M)	$34.7	$2.2	$67.2	$96.1	$20.4	$61.1	$127.6

(1) Includes Finland, France, Greece, Ireland, Portugal, and Slovenia
Source: BVGH-BCG TB model

TB model results 16Apr07.ppt THE BOSTON CONSULTING GROUP 1

The base case scenario is described as "BVGH's best estimate of the potential market for a TB vaccine."(p15).

1.3. DATA AVAILABLE FOR THIS ASSESSMENT

The following data were made available for this independent assessment:

- Original spreadsheets for BCG analysis, giving the breakdown of the data underlying key figures in the report, and especially:
  - Fig 3, Global market demand by segment;
  - Fig 5, Cash Flow by Year and market for three Vaccine Scenarios, a replacement vaccine, a booster vaccine, and a prime-boost combination.
- BCG provided the results of some extra scenarios for replacement, booster, and prime-boost.[11] These essentially modeled different penetration rates for high-income country high-risk groups.

[11] Contained in the file 'Scenarios Aeras Gates 5 4 07 v3.doc Appendix'.

- A PowerPoint presentation showing alternative scenarios for high income market, provided by Mark Sanyour.[12] These had not yet been used to work out alternative NPV figures. It was possible in this assessment to extract the data and use it as an alternative possibility in the original BCG worksheets. This is just for illustrative purposes, since it was not possible to do this perfectly.

In this author's opinion, many of the new scenarios provided by BCG are dependent on a base case that itself could be stress-tested much more thoroughly. This report will therefore try some more radical scenarios regarding this base case (alongside some simple scenarios too). In particular, BCG performed no scenarios involving changes in key inputs such as expected R&D costs, which, as we will see, would have heavily impacted NPV. Since there was strong disagreement over these costs (and the underlying science) reported to BCG, this should especially have been stress-tested. We also find below that issues like COGS (cost of goods sold) do matter in some scenarios.

It has been possible to do a range of additional NPV scenarios based on the original BCG data. The issue is the degree to which these alternative NPV scenarios seem sensible or are supported by those in the field. This reworking also revealed the limitations of some of the underlying data. This requires a frank debate.

The results of some of these scenarios are reported as provisional until the queries noted above (and in various points throughout this report) have been settled. NPVs reported here should certainly not therefore be reported as final and authoritative.

[12] TB patients 5-4-07.ppt.

2. REVENUE IMPACT ON NPV

At a very basic level, NPV is the balance between discounted expected *revenue* and discounted expected *costs* from all possible sources of cost. This report thus divides its attention between revenue and cost issues under a range of prime, boost, and prime-boost vaccine scenarios.

In the BCG report, reference is made to the "BVGH market-demand model". In previous BCG reports, the BCG 'market-demand model' used has been a framework based on 'leakages'. In this reviewer's opinion, this latter framework is not very satisfactory. Neither framework is spelled out in any detail in the report.

The markets covered can be roughly divided into:

1) Markets for high-risk individuals in high-income countries;
2) Public-sector markets in low- and middle-income countries;
3) Private-sector markets in low- and middle-income countries.

Different scenarios have been done for this assessment cross-cutting these market sectors. We now turn to each in turn, starting with the rich markets.

2.1. VALUE OF RICH MARKETS

2.1.1. Rich market scenarios: Replacement vaccine

Because of low prices in the very poorest of markets, much of the NPV of TB vaccine development in the BCG report comes from richer markets, and, indeed, from high-risk groups in these markets, especially in the richest market of all, the US. We are therefore especially obligated to check these rich market figures and the logic of relying on them.

It is also worth observing that because of high rates of discount, sales more than about six or seven years after licensure contribute little to investor returns (this is why, for example, a prescheduled[13] 'competitive event' hardly impacts IRR.

The following table shows some additional NPV calculations performed by BCG allowing for some changes in rich market high-risk groups:

[13] It has to be somehow prescheduled and 'committed' since at the 2022 date when the event is modeled as taking place, the value *then* of avoiding the competitive event might still be high even though the calculations performed *now* show little value *now* in avoiding the 'competitive' event. At the time of that future event, investors are doing what we are doing now with a 6-7 year horizon, and it will be worth them resisting the competitive event.

Assumptions	Base 1	Base 2	Pessimistic 1	Pessimistic 2	Optimistic	Aeras Vaccine
Adoption curve	Patterned on average Hepatitis B adoption curve (Source: WHO tracking 2005)					
Pricing	Model calculates profit maximizing price balancing adoption price thresholds with revenue potential within user-defined upper bounds					
Efficacy	Efficacy in newborns and adults					Limited to newborns w/o evidence of efficacy in adults
General Population Coverage	US + non-EURO: high-risk populations only (1); EURO: High-income countries using BCG now (2) would adopt BCG replacement vaccine for their birth cohort + high-risk populations					EURO: if using BCG now, adopt for birth cohort
High-Income Market High-Risk Population Coverage	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide; lower penetration than base 1	Use in targeted populations limited to high-burden areas (e.g. NYC, TX, FL, CA)	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide	N/A
High Income Market Adoption % (High-risk Pops)						
Healthcare workers	75%	60%	38%	38%	90%	N/A
LTC residents	75%	60%	38%	38%	90%	N/A
Homeless	40%	25%	20%	20%	60%	N/A
Correctional officers	75%	60%	38%	38%	90%	N/A
Prisoners	72%	60%	36%	36%	85%	N/A
Immigrants	0%	0%	0%	0%	0%	N/A
Results						
IRR	**34%**	**29%**	**15%**	**22%**	**39%**	**11%**
NPV ($M) @20%	**$90**	**$59**	**$(31)**	**$15**	**$122**	**$(61)**
Peak Ann. Rev.	**$532M**	**$487M**	**$354M**	**$422M**	**$579M**	**$308M**

Observe that all these figures are based on one measurement of expected cost of R&D and expected COGS. It turns out that consideration of these costs is important, but we leave that till later.

2.1.2. Further scenarios based on BCG Figures

Given the importance of the rich market, many extra scenarios were done on the original BCG rich market figures. These, and the corresponding new measures of NPV, are reported below. There is a very important caveat to bear in mind when reading these figures: All of these calculations are done on the assumption of no alteration in the cost assumptions underlying the NPV figures of BCG. Further scenarios involving different cost assumptions are presented in the cost section further down.

Catch-up?

Carefully reviewing the original BCG replacement figures, it seems that there is no catch-up phase. Rich market demand starts at about 0.5m doses in the first year of licensure, rising to close to 3m by about year 6 or 7, stabilizing at about 3m thereafter. The alternative figures of Sanyou are much more optimistic about early sales because of a large catch-up motive, but are much more pessimistic about long-run steady state sales in these rich markets (as well as being very negative about poor markets). Some discussion would be welcome as to why BCG do not seem to presume a pattern of sales commensurate with a catch-up phase (including some thoughts as to what it does to manufacturing and cost issues).

As an extreme case, let us remove the rich market high-risk sales from the original BCG base case figures (requiring also removal of revenues and COGS), but keeping the BCG assumptions about other costs (R&D and manufacturing) and probabilities of success.

SCENARIO:
No high income market

NPV at end 2012 at 20%	($493.77)
Discounted to 2005 at 20%	($103.55)
NPV at end 2012 at 10%	($352.49)
Discounted to 2005 at 10%	($168.60)
NPV at end 2012 at 15%	($446.72)
Discounted to 2005 at 15%	($143.21)

All NPV are heavily negative. If costs of development are higher than BCG presume (see below) these NPVs become even more pointedly negative. The impact of these higher costs can be roughly calculated from the 'ready reckoner' below. For example, if R&D costs are $400m higher (value capitalized to end of 2013, so based on much lower nominal figure), the following discounted (to 2005) NPV figures are derived:

At 20% (170.66)
At 15% (252.21)
At 10% (381.18)[14]

Similarly, if COGs are $1 or $2 for those markets that are still being served, this too can be done, and some cases are done below.

Clearly, sales in these rich market high-risk markets are key to the BCG finding of positive NPV in the case of replacement vaccines.

To assess the harm of presuming lower – though still positive – high income markets than BCG presume, two scenarios were done (with appropriate adjustment to COGS in light of change in quantities):

SCENARIO:
50% less high income market compared to report,[15] based on original BCG figures

NPV at end 2012 at 20%	($172.26)
Discounted to 2005 at 20%	($36.13)
NPV at end 2012 at 15%	($39.19)
Discounted to 2005 at 15%	($12.56)
NPV at end 2012 at 10%	$180.68
Discounted to 2005 at 10%	$86.42

In this case, for discount rates of 15% and 20%, NPV is negative.

[14] Observe how the figures rise at lower discount rates. This is partly because of the way the BCG figures are worked out. Amortization is at 15%, even if discounting is at 10%. This is clearly a limitation of the way the figures are worked out.
[15] Throughout, the comparison, unless otherwise specified, is with respect to the report, which itself is not 100%. We drop this henceforth from scenario descriptors.

SCENARIO:
20% less high income market, based on original BCG figures

NPV at end 2012 at 20%	$20.64
Discounted to 2005 at 20%	$4.33
NPV at end 2012 at 15%	$205.32
Discounted to 2005 at 15%	$65.82
NPV at end 2012 at 10%	$500.59
Discounted to 2005 at 10%	$239.43

In all cases NPV remains positive; at discount rates of 20% only marginally positive. However this is based on the presumed BCG costs, and we see later that these NPVs are vulnerable to higher costs.

2.1.3. Rich-world per dose price

The BCG replacement vaccine figures are based on $75 per dose in rich markets through to end 2021. In 2022, price falls to $20 even in rich markets, since the envisaged competitive event affects all countries including rich countries.

The $75 quoted willingness to pay seems to have been sourced in a very limited way, from New York health officials. Some more exploration of the relationship of this price to efficacy (giving us a handle on the value of efficacy too) would be helpful. Eventually, while performing a long series of scenarios across all types of vaccines, it became less clear how these prices are justified.

A number of scenarios were done (again, based on the same R&D costs and success probabilities as BCG), with some positive level of rich market uptake but at lower levels and at lower prices than BCG envisaged (again, in all cases COGS is adjusted).

SCENARIO:
High income pays $50 and not $75 till competitive event in 2022, based on BCG original figures. High income sales level stays same[16]

NPV at end 2012 at 20%	($52.96)
Discounted to 2005 at 20%	($11.11)
NPV at end 2012 at 15%	$119.08
Discounted to 2005 at 15%	$38.17
NPV at end 2012 at 10%	$400.63
Discounted to 2005 at 10%	$191.62

[16] One might expect sales to rise in response to lower price, but sales are much less price sensitive in rich markets than in poor markets, and as a first approximation we imagine – in what appears to be the spirit of the report – that sales stay the same in rich markets.

SCENARIO:
50% less high income market, original BCG figures. Now, only get $50 in high income market till competitive event

NPV at end 2012 at 20%	($273.37)
Discounted to 2005 at 20%	($57.33)
NPV at end 2012 at 15%	($163.82)
Discounted to 2005 at 15%	($52.52)
NPV at end 2012 at 10%	$24.07
Discounted to 2005 at 10%	$11.51

In this scenario, NPV was negative at discount rates of 15% and 20%, and only marginally positive at 10%. This figure is extremely sensitive to higher R&D costs.

SCENARIO:
20% less high income market, $50 dose price till competitive event and then $20

NPV at end 2012 at 20%	($141.15)
Discounted to 2005 at 20%	($29.60)
NPV at end 2012 at 15%	$5.88
Discounted to 2005 at 15%	$1.89
NPV at end 2012 at 10%	$249.96
Discounted to 2005 at 10%	$119.56

In this case, NPV was only marginally positive at discount rate of 15%, and negative at 20%.

The competitive event

It is not clear how and why the competitive event benefits all. What if the event was handled in such a way as to allow higher rich-world prices to persist for longer even as prices in poorer markets fell? In contrast to drugs markets, the supply chain situation for a replacement vaccine allows for much easier use of differential pricing (conditional on making the right capacity decision in advance). Why not exploit this for the benefit of the poor by allowing prices to persist for longer at higher levels in richer markets? What if licensing and other agreements can stipulate higher prices post-2022 in these richer markets?

If funders are interested, one could model the result if a high income market price of $75 was sustained after the competitive event.

This competitive event seems not to match any major quantity changes in the data (if one looks at the BCG market sales figures, there is no apparent impact on volumes), which one might expect if price and quantities tend to adjust to 'profit maximizing' levels. It would be worth exploring the reasons for this.

The 'competitive event' is modeled as heavily cutting the price of vaccine to rich markets in 2022. The present discounted value, PDV, of this cut is currently very low. Nearer the time the PDV will be higher. Will there be no resistance to this? Can this competitive event somehow be pre-committed? What if it is not?

2.1.4. Rich market scenarios: Booster vaccine

On inspection, the spreadsheet of data provided by BCG comes from their base case scenario for booster vaccines; the total doses of 601m over period 2013-2030 calculated from the data on the "Boost Demand" page of the BCG spreadsheet matched that in table 2 of the BCG report.

However, there were problems making the private market booster figures add up, and so one can only really reliably make changes to the middle income and rich markets with the data provided. Later, when doing some new prime-boost scenarios, the prime-boost figures were 'corrected'. This added a large positive component to NPV. On reflection, maybe this 'correction' could have been done in this section too. However, given time constraints and lack of clarity as to where the problems lay, this was not done. All new NPV figures in this section are therefore conditional on the private market figures that seem to have been used in the report, and subject to any 'corrections' made to those figures.

In all cases, COGS were adjusted to reflect lower or higher quantities of sales, but no adjustments were made to R&D costs, maintenance and other costs, something that may not be a reasonable assumption to hold if quantities are greatly different. Booster NPV scenarios alone were performed on the original raw booster page provided by BCG.

SCENARIO:
No high income market for booster vaccine at all, based on original BCG figures

NPV at end 2012 at 20%	($644)
Discounted to 2005 at 20%	($135)
NPV at end 2012 at 15%	($542)
Discounted to 2005 at 15%	($174)
NPV at end 2012 at 10%	($336)
Discounted to 2005 at 10%	($161)

SCENARIO:
50% high income market, based on original BCG figures

NPV at end 2012 at 20%	($37)
Discounted to 2005 at 20%	($8)
NPV at end 2012 at 15%	$250
Discounted to 2005 at 15%	$80
NPV at end 2012 at 10%	$742
Discounted to 2005 at 10%	$355

The following table explains what happens if COGS is $3.5 given various assumptions about rich high-risk markets:

Assumptions	Base 1	Base 2	Pessimistic 1	Pessimistic 2	Optimistic
Adoption curve	Patterned on average Hepatitis B adoption curve (Source: WHO tracking 2005)				
Pricing	Model calculates profit maximizing price balancing adoption price thresholds with revenue potential within user-defined upper bounds				
Efficacy	Efficacy in children and adults				
General Population Coverage	US + non-EURO: high-risk populations only (1); EURO: High-income countries using BCG now (2) would adopt booster vaccine for children under 14 + high-risk populations				
High-Income Market High-Risk Population Coverage	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide; lower penetration than base 1	Use in targeted populations limited to high-burden areas (e.g. NYC, TX, FL, CA)	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide
High Income Markets Adoption % (High-risk Pops)					
Healthcare workers	75%	60%	15%	38%	90%
LTC residents	75%	60%	15%	38%	90%
Homeless	40%	25%	8%	20%	60%
Correctional officers	75%	60%	15%	38%	90%
Prisoners	72%	30%	14%	36%	85%
Immigrants	25%	0%	0%	0%	40%
High-income markets	US + non-EURO: high-risk populations only; EURO: High-income countries using BCG now(1) would adopt BCG replacement vaccine for its children under 14 + high-risk populations				
COGS*	$3.5	$3.5	$3.5	$3.5	$3.5
RESULTS					
IRR	**33%**	**23%**	**14%**	**18%**	**41%**
NPV ($M)@20%	**$131**	**$25**	**$(64)**	**$(18)**	**$208**
Peak Ann. Rev.	**$755M**	**$600M**	**$462M**	**$530M**	**$870M**

(1) High income countries: 34 countries including US, Australia, Canada, UK, Korea, Singapore and Japan.
(2) Includes Finland, France, Greece, Ireland and Portugal (Note that non-EURO countries that currently administer BCG to infants now and have higher rates of TB, such as Korea and Singapore, are assumed under these scenarios to only adopt for their high-risk populations, not for children.)

2.1.5. Sanyour figures for rich markets

The Sanyour figures took a strongly contrasting view of potential market trajectory in rich markets, and especially the US, compared to the BCG figures.

In particular, the figures are heavily front-loaded on account of a catch-up phase, with many more rich-world sales in the early period compared to the corresponding BCG

figures. After this period, rich-world sales fall back and stabilize at just over 1.4m doses per year, less than half the BCG long-run steady state for rich markets.

A couple of clarifications first:
The Sanyour figures cover the seven richest markets. Within this, a huge proportion of the value of sales (hence profit, and NPV) comes from the US high-risk market. This was the case also with the original BCG figures.

BCG presume that those non-EURO countries that currently administer BCG[17] to infants and have higher rates of TB, such as Korea and Singapore, only adopt for their high-risk populations, and not for children. Below, we will catch up on the situation in France where a recent policy change has seen a switch to use only in high-risk infants. No figures were available for this and it is not clear how this appears in the data.

Thus, probably, the NPV calculations performed here using the Sanyour figures will undervalue rich-world high-risk markets to the extent that sales in such markets are not picked up in these 7 lead markets. Sanyour (and others) would probably argue that the effect is marginal on NPV because of the low number of sales in rich markets outside of these 7, and especially outside of the US.

For now, and given the paucity of data this reviewer has to work on, we presume that the Sanyour data can simply be inserted for all rich sales in the BCG tables to see what happens to NPV.

SCENARIO:
Sanyour rich market figures put into rich market section of BCG figures (but note that this excludes Finland, Greece, Ireland and Portugal purchasers of current BCG vaccine). Ignore Sanyour pessimistic poor market case.
This scenario just concerns itself with high catch-up in high-income rich markets, poorer long-term steady state in rich markets, and presumes that all non-rich market sales in the sales data are subsidized.

NPV at end 2012 at 20%	($160.83)
Discounted to 2005 at 20%	($33.73)
NPV at end 2012 at 15%	($135.42)
Discounted to 2005 at 15%	($43.41)
NPV at end 2012 at 10%	($101.77)
Discounted to 2005 at 10%	($48.68)

Some slightly more complicated scenarios were done. These are reported here in ‘long form’.

[17] It is a bit unfortunate that the abbreviation BCG covers both meanings. This assessment has tried to make it 100% clear each time this abbreviation is used what it is actually referring to.

SCENARIO:

Replace only rich market with Sanyour figures
COGS figures adjusted downwards to reflect lower rich market level from 2016 onwards
2013
2104 same
2015 same
2016 all adjusted to new steady state volumes
No competitive event affecting US market, but does affect rest of the world.

NPV at end 2012 at 20%	$89.34
Discounted to 2005 at 20%	$18.74
NPV at end 2012 at 10%	$530.18
Discounted to 2005 at 10%	$253.59
NPV at end 2012 at 15%	$255.11
Discounted to 2005 at 15%	$81.78

SCENARIO:

Replaced only rich-world market with Sanyour figures
COGS figures adjusted downwards to reflect lower rich market level from 2016 onwards
2013
2104 same
2015 same
2016 all adjusted to new steady state volumes
Allow competitive event to affect US market as well as rest of the world in 2022 (i.e. all US prices down to $20 per dose)

NPV at end 2012 at 20%	$48.28
Discounted to 2005 at 20%	$10.13
NPV at end 2012 at 10%	$401.82
Discounted to 2005 at 10%	$192.19
NPV at end 2012 at 15%	$183.83
Discounted to 2005 at 15%	$58.93

Thus, the Sanyour catch-up period was beneficial to NPV since early sales are less heavily discounting in calculating NPV. In contrast, the lower long-run equilibrium value of sales pulls NPV down compared to the BCG figures. The reasons for such different interpretations of long-run sales should be explored.

These figures however have to be seen in the context of R&D costs, as will be discussed below. At discount rates of 15% or more, the NPV are positive, but would not be sufficient to offset significantly higher R&D costs.

Both BCG and Sanyour have adopted a generous notion of what the price of vaccine of 70% efficacy will be in rich markets. Indeed, in effect, we are discussing the value of 40% *more* efficacy for a BCG replacement vaccine, since rich markets have the current

BCG option available to them, but only France among major OECD countries uses current BCG vaccine at birth, and – we shortly see – this has been much curtailed just recently. In the BCG replacement vaccine scenarios, the extra efficacy is described as 40%. It would be valuable to see the full reasoning behind the expectation of $75-$100 per dose price at this level of improvement in efficacy.

2.2. LIMITATIONS OF RICH MARKET UPTAKE

It is clear in all above cases that rich markets sales are key to positive NPV. However, one's interpretation of rich market uptake of TB vaccines in part depends on how one feels about how a new TB vaccine potentially fits into current prevention and treatment strategies according to efficacy of that vaccine in such high-income high-risk settings and any potential problems it might cause to those strategies.

What are the incentives to replace current prevention and treatment strategies in rich countries?

The report observes that "Epidemics of similar impact [to poor countries, and especially those being ravaged by HIV][18] have been avoided in the developed world only by constant monitoring for infection and prompt, vigorous treatment of exposed individuals, including those with latent disease. Without an effective vaccine, populations worldwide remain unprotected from infection." This potentially conflates two very different situations.

A single patient with active infection can spread TB to 10 to 15 people per year. The control of choice to prevent TB in richer countries has been identification and rapid treatment to prevent active infection. The only major OECD country to have adopted current BCG vaccine as standard is France. The case of France is also something of a historical fluke. Albert Calmette, a French bacteriologist, and his assistant and later colleague, Camille Guérin, a veterinarian, were working at the Pasteur Institute in Lille when they developed their, BCG, vaccine. The French government felt natural motivation (even obligation) to introduce the vaccine into general vaccination regimes.

Recently, France tightend up on even this by suspending routine use of BCG in infants and moving to recommending only in high-risk infants.[19]

To motivate an argument that there would be incentives to adopt a new TB vaccine (replacement or boost, since it turns out that both are treated the same in terms of price in the report), the report refers to cost of treatment ("For example, in New York City, the cost to diagnose and treat an outpatient with TB is $2,500. However, in 75 percent of the cases, diagnosis is made only after the patient is hospitalized at a cost of $17,500 to $22,500 per patient. New York City public health officials suggested that vaccines priced at $75 per regimen would be cost effective."). This is the only evidence given to

[18] Comment not in original.

[19] http://www.lefigaro.fr/sciences/20070711.FIG000000023_bcg_vers_une_suspension_de_la_vaccination_obligatoire.html

back the $75 price for both replacement and boost vaccines, and it says little about the cost effectiveness analysis that would be needed to back a country-wide decision to replace or complement the current monitoring and vigorous treatment with a vaccine meeting the product profiles described in the report.

i) The vaccine may not have high enough efficacy (one can imagine a much weaker impact of use compared to a highly endemic region where monitoring and control are much weaker);

ii) Each case that slips through the current monitoring and control approach indeed costs a great deal to deal with. However, if TB is under control via other approaches, how much does widespread use of a less than fully efficacious vaccine of not particularly long (and uncertain) immunological memory actually 'save' in treatment and monitoring in such settings? For example, the current BCG vaccine, though safe and inexpensive, is not used in the United States and large parts of Europe. In these countries, TB is much less prevalent and is controlled mostly via antibiotics. The report does not explore the incentives that have led to this being the solution of choice. The above observation suggests that if the currently existing BCG vaccine was added to this prevention and treatment strategy, it would add very little value (and more costs) while still maintaining all the costs of the current monitoring and treatment strategy. This seems to be one reading of the current solution choice. How much 'better' must the new vaccine-based solution be to change the dynamics of this choice?

In the key US market, on which the report's high-income figures so heavily depend, BCG vaccination is not routinely given to adults because health officials and policy makers have decided that they have a reliable Mantoux test, are able to accurately detect active disease, and rapidly treat it, and that it is more beneficial to society to continue with this approach than vaccinate against a relatively rare condition.

Furthermore, public health officials dealing specifically with TB may reason that the signals on which the current strategy depends will become less clear if there is vaccination of a strata of the population – as envisaged in the report – with that strata then circulating though the general population. What is the impact on current coping strategies of all the false positives? And having a proportion of ex-prisoners and the homeless vaccinated and circulating in the population requires good records on such individuals, if reliable testing and rapid treatment strategies at the population level are to be relied upon.

In other words, a potential 'vaccine' solution has already been driven to the fore for poorer countries but not so obviously for richer countries. How much better does the quality of the solution for the poor have to change till it becomes the option of choice (or part of a broad spectrum) for richer nations too? The report does not really grapple with the degree to which rich and poor countries might have different incentives to adopt solutions. In fact it contains no analysis of the differences epidemiologically and economically that might drive different solutions in the two settings, and hence how 'good' a vaccine has to be to serve both settings.

Unfortunately, this also calls into question the analysis done of willingness to pay given all these competing treatment and prevention options in the face of a not completely efficacious vaccine. The report relies on interviews and 'voices' in the health sector of New York (individuals no doubt very familiar with the costs when a TB case is hospitalized in New York). But, what do these voices know about the greater cost-benefit analysis that would have to underpin any change in policy at the population and nation level? One can well imagine scenarios where a vaccine would be very welcome in a low income country with poor treatment and control, but less so in a low prevalence country with good control. The report does not explore this.

In this reviewer's opinion, the methodology used in the report takes an overly optimistic view too of the response of organizations to change their practice quickly. Certainly, given the required size of the rich market and the requirement that it be activated soon after licensure in order to make the NPV analysis favorable (because of the high rates of discount to investors), it would be extremely valuable to have some more in-depth analysis of the mechanisms for achieving quick uptake in such markets for a 70% replacement efficacious replacement product. In putting this assessment together a wide range of opinions were sought. This revealed that an understanding of the US penal system, with its separate jurisdictions and decision-making processes, suggested that achieving wide, high, and rapid uptake in that system of a product of the profile described in the report was not at all a given. Similarly for booster vaccine; though one would expect there to be a negative knock-on to booster sales if replacement vaccination has not been a success or, conversely, a positive knock-on to replacement vaccine sales if the booster helps to make replacement vaccines more valuable. Again, a range of issue here have gone unexplored.

Incidentally, given the importance of achieving uptake in some of these high-risk groups, it is notable that no marketing expenses are tabulated in the cost figures for rich-country high-risk markets provided by BCG (though reference is made to them). These would naturally have pulled down NPV, the more so the more some of these groups are expensive to reach (LTC, homeless). It would be useful to see further analysis of the costs of reaching some of these groups, and systems for approval and regulation in such settings. It would also be useful to see some closer scrutiny of the relationship of potential uptake to efficacy.

2.3. VALUE OF NON-RICH MARKETS

The Sanyour figures were much more pessimistic about the value of poorer markets than the report. For now, this assessment works with the original report figures to analyse possibilities for poorer markets. Some clarification of why Sanyour was so pessimistic would be welcome, as well as some feel for whether or not this is a common perception. Maybe the pessimism matters little in terms of NPV in non-private-sector poorer markets in the report, since value from these markets hardly impacts the NPV figures? Here, though, we find cases where these markets can still contribute to value, mainly because though prices may be low, quantities in such markets can be high to compensate.

None of the report's figures – either replacement, boost, or rich-world vaccine – describe a separate market in India (though China is listed in the sales figures for replacement vaccines). When the report's authors state that they ruled out some countries because of 'unstable' epidemiology, this also must have covered some countries experiencing growth of TB incidence. India has better ability to drive adoption via focused urban promotion than many other countries, and it is therefore not clear why India is left out – if it has been (since it may in part be captured in the private market figures). It would be useful to have this clarified. It would also be useful too to have some notion of the social value of a large public market in India if the report simply worked on the basis of only a private market in India.

This section does a few explorations of what happens if there are larger poor markets, and then explores what happens if COGS is lower, and speed of initial market penetration is higher, and so forth. The intuition is that if richer markets are less strong than first perceived, is it possible to make a return in poorer markets? If so, how should sponsors respond?

2.3.1. Some issues with the data

Before creating some further NPV scenarios involving changes in markets other than rich high-risk markets, we review some problems with the data. It was hoped that some of these problems would be clarified, but this did not prove possible.[20] Given the limited amount of original data to work with already, this is somewhat unfortunate. This section does the best it can with the data given, but may need still further alterations in light of better data.

BCG Figures for replacement vaccine sales:

A check was made of all market demand figures listed on the 'Replace Demand' spreadsheet provided by BCG to support the report (or conversely a check of the revenue figures on the 'Replace ROI' spreadsheet), simply by taking revenue from each listed area on the 'Replace ROI' sheet and dividing by price per dose as detailed in Table 1 in the report.

In the case of replacement vaccines, low income, middle income, and rich income market figures matched up exactly. The China figures matched to 2021, but then registered a discrepancy. The private sector did not match at all.

The discrepancies have been pulled out and listed in the following table.
Terms in table:
'Given' = figures given in 'Replace Demand' spreadsheet provided by BCG.
'adj' = figures derived from revenue as given by BCG spreadsheet adjusted for dose reported in Table 1 of report
Discrepancies colored pale orange.

[20] Several approaches were made to BCG to get simple clarifications of the data, in the hope of not drawing any attention to this issue. This did not prove possible.

	2016	2017	2018	2019	2020
India/China given:	0	0	5,437,606	7,864,721	10,066,173
India/China adj.	0	0	5,437,606	7,864,721	10,066,173
India/China discrepancy	0	0	0	0	0
Private market, given	772,890	3,091,559	5,410,229	7,728,899	10,047,568
Private market adj.	252,676	1,010,702	1,768,729	2,526,755	3,284,782
Private market discrepancy	520,214	2,080,857	3,641,500	5,202,143	6,762,786

	2021	2022	2023	2024	2025
India/China given	12,041,963	11,375,205	12,320,581	12,436,481	12,588,969
India/China adj.	12,041,963	14,219,006	15,400,726	15,545,601	15,736,211
India/China discrepancy	0	-2,843,801	-3,080,145	-3,109,120	-3,147,242
Private market, given	12,366,238	22,152,836	23,383,549	24,121,977	24,614,262
Private market adj.	4,042,808	18,460,696	19,486,291	20,101,647	20,511,885
Private market discrepancy	8,323,429	3,692,139	3,897,258	4,020,329	4,102,377

	2026	2027	2028	2029	2030
India/China given:	12,814,632	13,040,294	13,265,957	13,491,620	13,491,620
India/China adj.	16,018,290	16,300,368	16,582,446	16,864,525	16,864,525
India/China discrepancy	-3,203,658	-3,260,074	-3,316,489	-3,372,905	-3,372,905
Private market, given	24,614,262	24,614,262	24,614,262	24,614,262	24,614,262
Private market adj.	20,511,885	20,511,885	20,511,885	20,511,885	20,511,885
Private market discrepancy	4,102,377	4,102,377	4,102,377	4,102,377	4,102,377

As another attempted check, the COGS figure given by BCG for each year were divided by the number of calculated doses in each respective year; it was found that from 2022 onwards the calculated average dose cost was $1. This did not help identify the problem in the data, since after 2021 the positive discrepancy approximately equaled the negative discrepancy. The problem is that private sales after 2022 are being made at $4 per dose while India/China sales are at only $1 per dose. This discrepancy appears ten years into licensure and 17 years after the 2005 PDV of NPV, so will have had relatively little impact on NPV. But it still needs checking.

This COGS check, however, did more clearly show the discrepancy for the private market in the period 2016-2021. If the dose figures on the BCG 'Replace Demand' spreadsheet are right, then the private market has been undervalued in the 'Replace ROI' sheet. Alternatively, the dose figures on the BCG 'Replace Demand' sheet are wrong.

On the basis of the revenue figures BCG gave, we now do some changes to non-rich markets in replacement vaccine NPV calculations, holding the rich market the same (as always, that this is the base case needs to be factored into discussion of the results).

2.3.2. Some non-rich market scenarios (presuming rich market figures in report are unchanged and no change in costs)

Each of these scenarios starts afresh each time with the base case. Thus each is a change in one direction only.

SCENARIO:
Case of all else the same but no private (non-rich) replacement market

NPV at end 2012 at 20%	$28.44
Discounted to 2005 at 20%	$5.96
NPV at end 2012 at 15%	$187.50
Discounted to 2005 at 15%	$51.09
NPV at end 2012 at 10%	$431.67
Discounted to 2005 at 10%	$185.82

No India figures were present in the BCG files or detailed in the report. Given that one-third of all global cases of TB are in India and China alone, it would be good to have some notion of the size of the potential market in India. Some scenarios were done involving India (and presuming that in doing these scenarios there was no harm to the private market figures, which may be unreasonable).

SCENARIO:
India generates same replacement demand as China, and production costs are $0.5 (with no change in quantities demanded on account of lower cost). All else is held the same.

NPV at end 2012 at 20%	$214.70
Discounted to 2005 at 20%	$45.03
NPV at end 2012 at 15%	$471.66
Discounted to 2005 at 15%	$151.20
NPV at end 2012 at 10%	$884.78
Discounted to 2005 at 10%	$423.19

SCENARIO:
This is left in 'fuller form', since several things were done:[21]

Pull all low income, middle income, private market and China forward by three years
COGS all pulled forward by three years (adjusting for rich-world component)
Lower manufacturing costs to $0.5
China pays $1
Add India at same doses as China (noting the problems indicated above)

NPV at end 2012 at 20%	$414.33
Discounted to 2005 at 20%	$86.89
NPV at end 2012 at 15%	$703.44
Discounted to 2005 at 15%	$225.51
NPV at end 2012 at 10%	$1,155.79
Discounted to 2005 at 10%	$552.81

This shows both the value in pulling all poor market sales forwards, and the importance of low COGS as a way of turning those sales into NPV.

[21] The needs checking, since if there is a fault in the private market figures, this will all need adjusting.

Incidentally, these scenarios suggest that it is right to suggest that poor countries weaken the market for TB. But this is only part of the story. When designing pull instruments, emphasis should be on tackling this delay as a way of repaying R&D at the same time as maintaining good pressure on COGS.[22] If price pressure on COGS is weakened, so is the value of the pull instrument.

2.4. BOOSTER FIGURES

A test was done of the boost revenue figures. The revenues used in the base case spreadsheet to calculate NPV were divided by the prices that were quoted as applying in each year in Table 1, to work out the underlying quantities that these revenue figures imply. These were then compared to the quantities recorded on the BCG booster demand spreadsheet.

Similar to the replacement data, there seems a discrepancy in the number of booster doses accounted for in private market sales (the middle income and rich market figures add up 'correctly').

Top line: Figures given by BCG.

Second line: Calculation of private market booster doses sold by dividing revenue from private market booster sales in the BCG spreadsheet by price listed in the report at the time of sale per regimen. This is, in a sense, the 'implied' quantities.

Middle line: Private market booster doses sold as listed in BCG spreadsheet. The 'listed' quantities.

Bottom line: Discrepancy between the two.

Private market sales:

	2016	**2017**	**2018**	**2019**
Figures supplied by BCG	1,708,822	6,835,286	11,961,751	17,088,216
Calculated figures derived from quoted revenues	589,249	2,356,995	4,124,742	5,892,488
Discrepancies	1,119,573	4,478,291	7,837,009	11,195,728
Adjustment factor applied to original revenue figures	2.90000	2.90000	2.90000	2.90000

2020	**2021**	**2022**	**2023**	**2024**
22,214,680	27,341,145	30,758,788	32,467,610	33,492,903
7,660,235	9,427,981	13,701,642	14,462,844	14,919,566
14,554,446	17,913,164	17,057,146	18,004,765	18,573,337
2.90000	2.90000	2.24490	2.24490	2.24490

2025	**2026**	**2027**	**2028**	**2029**	**2030**
34,176,431	34,176,431	34,176,431	34,176,431	34,176,431	34,176,431
15,224,047	15,224,047	15,224,047	15,224,047	15,224,047	15,224,047
18,952,385	18,952,385	18,952,385	18,952,385	18,952,385	18,952,385
2.2448980	2.2448980	2.2448980	2.2448980	2.2448980	2.2448980

[22] So, for example, one might want to take care not to create concerns on the ground that sales are triggering large (prize) payments, and take care also not to use pull subsidies to cover high COGS (and not R&D costs).

The discrepancy is constant, suggesting some 'global' error. It also creates a dilemma. Do we do scenarios based on the original data, or do we 'correct' this discrepancy and then work out?

If left in (and presuming the sales figures are correct[23]), the private market boost revenues used in the calculations are about one third what they would be according to the quantities reported on the demand spreadsheet in the period 2015-2021 at the prices quoted, and less than half what they should be based on the quantities in the period 2022-2030 at the prices quoted for that period.

Middle income sales were also off but by a tiny amount. Again, the discrepancy is constant, suggesting a global error of some kind.

Middle income sales:

	2022	**2023**	**2024**	**2025**
Figures supplied by BCG	8,234,561	8,918,923	9,002,823	10,126,038
Calculated figures derived from quoted revenues	8,227,844	8,911,648	8,995,480	10,117,779
Discrepancies	6,717	7,275	7,343	8,259
Adjustment factor applied to original revenue figures	1.00082	1.00082	1.00082	1.00082

2026	**2027**	**2028**	**2029**	**2030**
11,268,626	12,329,612	13,308,995	13,880,366	14,288,378
11,259,435	12,319,555	13,298,139	13,869,044	14,276,724
9,191	10,057	10,856	11,322	11,654
1.00082	1.00082	1.00082	1.00082	1.00082

Furthermore, we could not presume that the COGS were correct, so it was necessary to adjust total COGS to reflect the higher quantities if making this correction (or at least to do a check on them). In this calculation, it was presumed that average COGS was $7 in the first year, falling by 30% in 8 years (to $5), stabilizing at this lower COGS. Using the 'correct' demand figures and price, generates the following NPV:

SCENARIO:

'Correct figures' for boost sales:

NPV at end 2012 at 20%	$1,280
Discounted to 2005 at 20%	$269
NPV at end 2012 at 15%	$2,134
Discounted to 2005 at 15%	$684
NPV at end 2012 at 10%	$3,569
Discounted to 2005 at 10%	$1,707

[23] We are presuming here that the sales levels are reported correctly and the revenue figures are off. Of course, it could be the other way around.

These booster NPV figures are much higher than those reported in the report, on account of the value of private booster vaccine markets being higher than that reported in the report.

We can then use this data to see what happens under various rich-world scenarios (and thus these figures are always questionable until this issue is resolved).

With no high income markets at all, booster vaccine NPV (based on these private sector revenue figures that are higher than those calculated by BCG) is as follows:

NPV at end 2012 at 20%	$77
Discounted to 2005 at 20%	$16
NPV at end 2012 at 15%	$555
Discounted to 2005 at 15%	$178
NPV at end 2012 at 10%	$1,405
Discounted to 2005 at 10%	$672

Observe how sensitive the NPV is when going from 10% to 15% and then from 15% to 20%. Looking closely at the figures, the reason is because the positive NPV is based on booster sales to private market and middle income markets, but especially private markets, with those sales starting to generate revenue only after some years of delay. The power of discounting is such that NPV is very different at just a few percent difference in discount rate given this pattern of sales.

SCENARIO:
50% high income booster sales (and including higher private market figures)

NPV at end 2012 at 20%	$695
Discounted to 2005 at 20%	$146
NPV at end 2012 at 15%	$1,362
Discounted to 2005 at 15%	$437
NPV at end 2012 at 10%	$2,507
Discounted to 2005 at 10%	$1,199

SCENARIO:
With 20% high income sales (and including higher private market figures)

NPV at end 2012 at 20%	$324
Discounted to 2005 at 20%	$68
NPV at end 2012 at 15%	$878
Discounted to 2005 at 15%	$281
NPV at end 2012 at 10%	$1,846
Discounted to 2005 at 10%	$883

All figures are adjusted to account for lower COGS.

It may be necessary to clarify some of the underlying cost issues, since none of the base scenarios ever goes above 54m sales per year for a plant size that is designed to supply 120m doses per year. This seemed rather puzzling.

Clearly, it needs to be clarified exactly what is going on in the figures supplied by BCG, since a straight removal of high income markets under the revenue figures given in the report yields:

NPV at end 2012 at 20%	($644)
Discounted to 2005 at 20%	($135)
NPV at end 2012 at 15%	($542)
Discounted to 2005 at 15%	($174)
NPV at end 2012 at 10%	($336)
Discounted to 2005 at 10%	($161)

While a straight removal of high income markets under the revenue figures just derived yields:

NPV at end 2012 at 20%	$77
Discounted to 2005 at 20%	$16
NPV at end 2012 at 15%	$555
Discounted to 2005 at 15%	$178
NPV at end 2012 at 10%	$1,405
Discounted to 2005 at 10%	$672

This is a very big difference, and all because of the power of private market sales.

It also suggests that under the NPV figures based on the revenue figures provided by BCG, the power to use differential pricing in the case of booster vaccines (and make a positive return on booster sales) is not present, while under the adjusted/corrected figures it is. If the adjusted figures are nearer the 'truth', what does it say about the ability to supply poorer markets with booster vaccine? The suggestion from the second set of data is that there is some ability to supply poorer markets while making profits in private markets (and richer markets), with a key issue being to keep COGS down.

Presuming that these 'new' figures are now correct (we cannot presume so, and this needs to be clarified), we can then explore what happens if private uptake is slow. It is striking that in this 'new' case, private market sales peak at about $800m per year in the base case (if one thinks about it, this is simple math on the quantities and prices given by BCG, and nothing terribly revelatory).

If we imagine that the private uptake given these 'new' figures is slowed at different rates per year, we get a range of NPV (assuming base case for high-income high-risk market as presented by BCG, and making adjustments for COGS to reflect the lower private market uptake, and also presuming the cost structure that BCG presume and thus making no adjustment for higher costs).

SCENARIO:
At 20% less private market uptake:

NPV at end 2012 at 20%	$1,085
Discounted to 2005 at 20%	$228
NPV at end 2012 at 10%	$3,090
Discounted to 2005 at 10%	$1,478
NPV at end 2012 at 15%	$1,835
Discounted to 2005 at 15%	$588

SCENARIO:
At 50% less private market uptake:

NPV at end 2012 at 20%	$792
Discounted to 2005 at 20%	$166
NPV at end 2012 at 10%	$2,372
Discounted to 2005 at 10%	$1,134
NPV at end 2012 at 15%	$1,386
Discounted to 2005 at 15%	$444

2.5. PRIME-BOOST FIGURES

From the start, there clearly was something wrong with the prime-boost data presented. Various checks were done on the prime-boost data, with interesting, and at times perplexing results. Over time, some interesting discovered were made. This section is a "who dunnit" of this discovery process before we turn to some prime-boost scenarios.

First, the data from the pages of BCG data for demand in each market category was put alongside each other, and the differences taken. A simple add was also done.

The total number of doses of Prime-Boost matched those reported in the BCG report, a figure of 140m. Low income, middle income, China and India are straightforward additions. The private market is straightforwardly added up to and including 2021; after that date the prime-boost figure given in the Prime-Boost spreadsheet is lower than a straightforward add. It appears that high income BCG replacement vaccine is excluded in the spreadsheet prime-boost figures.

Up to 2021 the total prime-boost doses are 'under-reported'. After 2021, the spreadsheet total figures then switch to 'over-reporting' the combined total of replacement and booster vaccine – by about 4m doses per year, even including the absence of replacement vaccine in richer markets.

Furthermore, looking at revenue figures, the Prime-Boost and the Boost revenue figures from the high income markets match exactly for all years out to 2030 indicating that, indeed, it would appear, revenue from the replacement vaccine sales in high-income markets is not being counted in the Prime-Boost figure.

The *way* the prime-boost sales figures were generated for each market segment from prime and boost data for that segment was also reviewed. In the BCG report, according to the spreadsheet provided, the prime-boost sales figures are calculated as follows:

Low income prime-boost figures consist of the replace vaccine figures only since low income markets use only replace and no boost vaccine.

The middle income prime-boost figure is an exact manual add every year of both replace and boost vaccine up to and including 2023. From 2024 on there are very slight differences, but in principle the two sets of data are simply added.

There is no India data prime-boost figure. Again, perhaps this is contained within the private data?

China uses no boost vaccine, so the China prime-boost figure is the straightforward replacement data.

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The private market figure is pretty much a straightforward add of both replace and boost till 2021 (with the simple addition slightly higher than the BCG figure). Then from 2022, a manual add of the two sets of original BCG prime and replace data gives a figure that is about 7 million per year lower than the BCG figure for private market prime-boost sales. There is no explanation for this. For example, prices fall in the year of the competitive event and, if anything, this would be expected to generate a rise in quantity demanded, but this should be captured already in the original replacement and boost data.

Regarding high income markets, the BCG figures for prime-boost sales are just straightforward booster sales, ignoring replacement sales. This seems inconsistent with the way the prime-boost demand data is derived for the other market segments. It seems odd that from 2022 the BCG figures for one market section is coming in larger than a simple add of the two underlying set of data, while for another it is coming in lower. Though all these discrepancies just about cancel out – 16 million sales on just over 1.5 billion sales – the timing and the market segments (and hence the prices) are different, impacting revenues and NPV at the same level of sales.

The discrepancies from a simple add of prime and boost data are as follows:

Discrepancies in BCG demand figures compared to simple add of prime and boost data per market segment	**2013**	**2014**	**2015**
Low income	0	0	0
Middle income	0	0	0
India	0	0	0
China	0	0	0
Private market	0	0	0
High income	-523,396	-1,373,914	-2,224,432
Total	-523,396	-1,373,914	-2,224,432

2016	2017	2018	2019	2020
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
0	0	0	0	0
-424	-1,698	-2,971	-4,244	-5,517
-2,682,404	-2,747,828	-2,845,965	-2,878,677	-2,944,102
-2,682,828	-2,749,526	-2,848,936	-2,882,921	-2,949,619

2021	2022	2023	2024	2025
0	0	0	48,899	79,567
0	0	0	0	-772
0	0	0	0	0
0	0	0	0	0
-6,790	6,470,696	6,830,179	7,045,869	7,189,662
-2,949,336	-2,949,336	-3,009,526	-3,009,526	-3,009,526
-2,956,126	3,521,360	3,820,653	4,085,242	4,258,931

2026	2027	2028	2029	2030
108,074	133,989	146,946	159,903	162,495
-772	-772	-772	-772	-772
0	0	0	0	0
0	0	0	0	0
7,189,662	7,189,662	7,189,662	7,189,662	7,189,662
-3,009,526	-3,009,526	-3,009,526	-3,009,526	-3,009,526
4,287,438	4,313,353	4,326,310	4,339,267	4,341,859

The issue then is what data was used in calculated revenue and hence NPV of prime-boost sales? In the cases of countries that use both prime and boost vaccine, it is not clear why a different way of 'adding' up is used for middle income (simple add), private market (add up but presume more sales of one or other of the vaccines, though we have no data to suggest which vaccine went up), and high income market (only count booster sales).

Since the model is a black box, how quantities respond to price was not available for this assessment. However, Table 1 in the report states that the cost of the combined prime-boost package simply adds up the price of each component on its own. Therefore, in calculating prime-boost revenues it seems that the methodology is a straightforward addition of the prime and the boost revenue data for all countries in turn except the high-income countries, with prices used according to each component of the package.[24] Nowhere in the report or follow-on literature was the notion of a mechanism to set price that was 'profit maximizing' (as reported in the report) explained. The methodology seems to be pretty rudimentary.

This also raises the issue of what to use as average manufacturing cost. Table 1 in the report reports an average cost of $1 for replacement and $7 for booster, and $8 for prime-

[24] That is, since the proportions are different across prime and boost, one does not take the average price and multiply the total quantities, but one treats each type of vaccine sale separately and then adds.

boost (which itself seems a straightforward addition of the two costs, with cost range to match the simple addition of the two cost ranges). But then it is puzzling why cost is modeled as experiencing decline in the case of booster vaccines of 30% over 8 years, and 40% over 8 years in the case of prime-boost vacceins; how can something that looks to be a simple straightforward addition, decline more than the combined decline on the parts separately considered?

The problem with using the raw prime-boost data provided by BCG is that we only have the overall totals of prime-boost sales. One cannot simply take these figures and multiply by the average prime-boost price, since this would ignore the composition of sales at different prices.

The first task therefore was to do a simple check of the NPV calculation in the spreadsheet provided by BCG to see where the NPV came from. Since no equations are left in the spreadsheet, the easiest thing to do (though still laborious) was to redo the figures according to both the sales data reported in the spreadsheet (prime-boost page) and using a set of revenue figures that treats the high income markets the same as the middle income and private markets – i.e. that simply adds up country sales across boost and prime-boost vaccines.

On the presumption that one can simply add sales – as seemed to be the logic of how BCG had done this – this was done, and it yielded the following revenue figures, based on the price figures in Table 1, and with COGS adjusted across all categories (and no adjustment to R&D cost figures).

Table of prime-boost revenues based on Table 1 prices:

	2013	**2014**	**2015**	**2016**	**2017**	**2018**
Low income	0	0	0	0	0	40
Middle income	0	0	0	0	0	64
India	0	0	0	0	0	0
China	0	0	0	0	0	5
Private market	0	0	0	70	279	488
High income	111	291	471	568	582	602
TOTAL REVENUES	111	291	471	637	860	1199

	2019	**2020**	**2021**	**2022**	**2023**	**2024**
Low income	58	74	88	35	38	38
Middle income	93	119	142	53	57	58
India	0	0	0	0	0	0
China	8	10	12	11	12	12
Private market	697	905	1114	765	808	833
High income	609	623	624	322	329	329
TOTAL REVENUES	1464	1731	1981	1187	1244	1271

	2025	2026	2027	2028	2029	2030
Low income	39	40	41	42	43	43
Middle income	69	81	92	102	107	112
India	0	0	0	0	0	0
China	13	13	13	13	13	13
Private market	850	850	850	850	850	850
High income	329	329	329	329	329	329
TOTAL REVENUES	1300	1313	1325	1336	1343	1348

Observe the difference between these revenue figures (based on the Table 1 prices), and the figures quoted by BCG as the prime-boost revenue figures.

The next table lists the differences, which are substantial in places (a surprise when I first set out, given the insistence that BCG were "making an investment case"). These are the levels of underreported prime-boost revenue from a simple add (which seemed to be what BCG had done) based on the quantities and prices that BCG themselves propose:

	2013	2014	2015	2016	2017	2018
Low income	0	0	0	0	0	0
Middle income	0	0	0	0	0	0
India	0	0	0	0	0	0
China	0	0	0	0	0	0
Private market	0	0	0	43	174	304
High income	39	103	167	201	206	213
TOTAL REVENUES	39	103	167	245	380	517

	2019	2020	2021	2022	2023	2024
Low income	0	0	0	0	0	(0)
Middle income	0	0	0	0	0	0
India	0	0	0	0	0	0
China	0	0	0	(3)	(3)	(3)
Private market	434	565	695	327	345	356
High income	216	221	221	59	60	60
TOTAL REVENUES	650	785	916	383	402	412

	2025	2026	2027	2028	2029	2030
Low income	(0)	(1)	(1)	(1)	(1)	(1)
Middle income	0	0	0	0	0	0
India	0	0	0	0	0	0
China	(3)	(3)	(3)	(3)	(3)	(3)
Private market	363	363	363	363	363	363
High income	60	60	60	60	60	60
TOTAL REVENUES	420	419	419	419	419	419

Observe that the removal of the replacement sales from the high income data had a very big impact. But, equally interesting, the private market sales are considerably higher than the original figures in the BCG spreadsheet.

With prices:

Price per dose, taken from Table 1	**2013-2021 inc**	**2022-2032**
Low income replace	3.00	1.25
Low income boost, no uptake	0.00	0.00
Middle income replace	14.00	1.25
Middle income boost	15.00	6.13
India/China replace	1.00	1.00
India/China boost, no uptake	0.00	0.00
Private replace	26.00	4.00
Private boost	29.00	22.00
High income replace	75.00	20.00
High income boost	75.00	49.00

NPV is:

NPV at end 2012 at 20%	$1,691.41
Discounted to 2005 at 20%	$354.72
NPV at end 2012 at 10%	$4,727.11
Discounted to 2005 at 10%	$2,260.96
NPV at end 2012 at 15%	$2,837.42
Discounted to 2005 at 15%	$909.61

This is considerably higher than in the BCG report, and had this author scratching his head for a day. How could working with the same raw data regarding quantities and prices, and approximately the same methodology, produce such a dramatically different result?

As well as the quantities possibly being different, another thing to watch is that the math is done properly. The correct way is to multiply each sale of each type of vaccine by price at time of sale and for the type of vaccine, and then add up, and not to add the number of sales and then multiply by the simple un-weighted average price. As can be seen in the quantity tables, in the case of private markets, there are considerably more booster sales than replace sales, approximately 8m-10m more per year. These have a very high profit margin and need to be correctly weighted in the total prime-boost revenue.

Similarly, these higher figures reflect the inclusion of high income replacement vaccine sales, which also carry a very high profit margin.

It is not clear what is going on here.

Clearly though, the same range of sensitivities exist for prime-boost sales as for replacement and booster sales. Some further NPVs were calculated using this table.

SCENARIO:
High income replace and high income boost now $50 in the initial period, falling to $20 and $30 respectively after competitive event.
Such that price is: replace $50, $20 / boost $50, $30
All quantities kept the same.

NPV at end 2012 at 20%	$1,039.79
Discounted to 2005 at 20%	$218.06
NPV at end 2012 at 15%	$1,993.32
Discounted to 2005 at 15%	$639.01
NPV at end 2012 at 10%	$3,589.66
Discounted to 2005 at 10%	$1,716.92

SCENARIO:
Case of high income market replace $50, $20 / boost $50, $30
Private market replace $16, $4
Private market boost $19, $12

NPV at end 2012 at 20%	$450.09
Discounted to 2005 at 20%	$94.39
NPV at end 2012 at 15%	$1,092.88
Discounted to 2005 at 15%	$350.35
NPV at end 2012 at 10%	$2,153.37
Discounted to 2005 at 10%	$1,029.95

SCENARIO:
Case of high income $30, $20
Private market replace $16, $4
Private market boost $19, $12

NPV at end 2012 at 20%	($49.03)
Discounted to 2005 at 20%	($10.28)
NPV at end 2012 at 15%	$456.13
Discounted to 2005 at 15%	$146.22
NPV at end 2012 at 10%	$1,312.82
Discounted to 2005 at 10%	$627.92

On closer inspection, one thing that holds the NPV back is the slow (in terms of quantities) private market uptake. These sales peak at high levels according to these figures, but pulling that forward by a few years, would greatly impact the NPV.

SCENARIO:
Removing high income replace vaccine:

NPV at end 2012 at 20%	$1,048.40
Discounted to 2005 at 20%	$219.86
NPV at end 2012 at 15%	$2,022.37
Discounted to 2005 at 15%	$648.33
NPV at end 2012 at 10%	$3,660.76
Discounted to 2005 at 10%	$1,750.93

One sees at this point that the prime-boost figures for revenue generated from rich markets underlying this set of figures is exactly the same as those produced in the BCG spreadsheet. Therefore the difference between these figures and the NPV figures produced by BCG must be on account of either the way the private market is treated, or in the prices presumed. But since the private market figures by manual add are actually lower than the BCG private market prime-boost figure, the revenues should not have come out higher than the BCG figures if the same prices are being used across comparisons. With most other quantities held the same, there must be different (lower) prices or weighting issues in the way the BCG figures were calculated (such that an average price was used on total prime-boost demand, ignoring the fact that more prime than boost is contained in the overall purchase, and should have been weighed more highly in the revenue and NPV calculations done by BCG).

Yet in the early years of the private market, there is only a tiny discrepancy in quantities, so differences in quantities cannot be driving such a big difference in revenues. There has to be something in the pricing instead. In years 2022 onwards, it might be possible to generate some revenue discrepancies by simply taking the average price of prime-boost and multiplying the total sales, because there is a quantity difference between replace and boost; there is lower level of sales of replace than boost, such that using an 'average' price will undervalue boost vaccines. However, a quick check shows that this is not going to be big enough to generate such a big revenue difference. The only explanation would appear to be that low prices were used in the BCG calculations.

If one takes sales for a particular market segment, there are two ways to add up revenues. 1) ([quantity of replace demand in year X times replace price in year X] + [quantity of boost demand in year X times boost price in year X]).

2) ([quantity of replace demand in year X + quantity of boost demand in year X] times average price of replace and boost weighted by quantity).

Observe that in the second approach one can also work backwards from revenues and quantities to find what the average price must have been. Importantly, this average price should move around because of the change in the weighting between replace and prime vaccine if the laws of motion on replace and boost are independent. Even tiny changes in the ratio of prime to boost should show up in a change in this average price.

What do we observe for private market sales? The private market prime-boost revenues from BCG were divided by the total of private market prime-boost sales recorded by BCG. This produced two astonishing findings. First, the average price in the years 2016-2021 was 10.57 and in 2022-2030 it was 7.39. This means that the average price in the earlier period, when read out from revenues and quantities, was much lower than the $26 and $29 given in Table 1 for replace and boost respectively for this private market. This is not possible. In the later period, 7.39 is higher than $4 but much lower than $22 – in a period when more than half of sales are at the higher $22 price. Again this is not possible. Second, and more surprising, instead of moving about as relative quantities of the two types of vaccine changed, the price is found to be identical across 2016-2021 and 2022-

2030. This could only have happened if an identical average price was used in the original BCG revenue figures, that is a price that did not change as the relative quantities changed.

This suggested that it was worthwhile checking the average price for all markets by simply dividing the revenue listed by BCG by the sales also listed by BCG.

	2013	2014	2015	2016	2017	2018
Low income						3.00
Middle income						14.80
China						1.00
Private market				10.57	10.57	10.57
High income	75.00	75.00	75.00	75.00	75.00	75.00

2019	2020	2021	2022	2023	2024
3.00	3.00	3.00	1.25	1.25	1.26
14.80	14.80	14.80	5.16	5.16	5.16
1.00	1.00	1.00	1.25	1.25	1.25
10.57	10.57	10.57	7.39	7.39	7.39
75.00	75.00	75.00	49.00	49.00	49.00

2025	2026	2027	2028	2029	2030
1.26	1.27	1.27	1.27	1.27	1.27
4.38	3.90	3.63	3.46	3.39	3.32
1.25	1.25	1.25	1.25	1.25	1.25
7.39	7.39	7.39	7.39	7.39	7.39
49.00	49.00	49.00	49.00	49.00	49.00

This not only shows the way the prime-boost figures missed off any replace vaccines for high income markets (reflected in the $75 and $49 average price calculated via this route for high income markets, in line with the booster vaccine price schedule), but it also reveals that China (only ever taking replace vaccine) is modeled as facing $1 till 2021 and $1.25 from 2022 (the year of the competitive event), which is clearly wrong.

The only other possibility is that the ratio of prime to boost did not change over significant periods of time regardless of how the revenue figures were calculated. This suggested checking this ratio, yielding another astonishing result:

	2013	2014	2015	2016	2017	2018
Middle income						4.07
Private market				2.21	2.21	2.21
High income	1.82	1.82	1.82	1.82	1.82	1.82

	2019	2020	2021	2022	2023	2024
Middle income	4.07	4.07	4.07	4.07	4.07	4.07
Private market	2.21	2.21	2.21	1.39	1.39	1.39
High income	1.82	1.82	1.82	1.82	1.82	1.82

	2025	2026	2027	2028	2029	2030
Middle income	1.79	1.19	0.95	0.83	0.78	0.74
Private market	1.39	1.39	1.39	1.39	1.39	1.39
High income	1.82	1.82	1.82	1.82	1.82	1.82

Strikingly – since it was not expected, and the very notion of dividing prime by boost figures would not ordinarily have suggested itself – the boost figures turn out to be simple multiples of the prime figures. In the case of high income markets, the ratio is a constant 1.82 for all years 2013-2030. For private market sales it is 2.21 for years 2016-2021, and then 1.39 for years 2022-2030. For middle income markets it is 4.07 for years 2018-2024, followed by some variance in the closing years. Incidentally, this 4.07 persists through the competitive event, and through a change in price that was disproportionate across the two types of vaccines (and should have generated a reaction in quantities if there had been a 'profit maximizing' equation at work).

Could it be that the boost demand figures (for all the epidemiological thinking) are simply scaled up versions of the replace demand figures?

There is no evidence here for much thinking behind what drives the figures. Prime and boost figures have certainly not been derived independently as one might expect, and do not seem to be based on any modeling of the epidemiological impact of the two kinds of vaccine. Furthermore, if there is an equation driving quantities in response to price in order to 'profit maximize', it is not much in evidence: It does not act on the high income markets; it seems strange if applying to middle income markets, since the ratio does not change over the competitive event; and if operating on the private market it does so in the year 2022 only.

At this point, there did not seem much point in interrogating the prime-boost data further since they seemed to have been derived in some rather odd, and even primitive, ways. It does however suggest extreme caution in interpretation of the base case prime-boost financial returns in Table 2 of the report, if based on the spreadsheet figures.

2.6. COVERAGE AND PATTERN OF BUILD UP FOR BOTH REPLACE AND BOOST

The revenue figures going into the NPV calculations are based on the following assumed coverage rates "necessary to accrue full benefits":
BCG replacement: 85%
Booster (where booster used): 66%

It is not clear to this reviewer what this means. Did rates build to these levels, thus *eventually* accruing full benefits, so that 85% is the long-term *steady state*? The backup material says that the adoption curve was "patterned on *average*[25] *Hepatitis B adoption curve* (Source: WHO tracking 2005)," (italics added) suggesting so. Or are high rates

[25] It would be good to see the data for this averaging, just to check that averaging was done with correct weighting for country sizes, etc.

presumed at the start? It needs to be spelled out a bit more what the phrase 'patterned on' means exactly. Furthermore, what is the justification for presuming that the Hep B case will be repeated in the case of TB?

Now we take a close look at BCG replacement data on dose sales (and it turns out the same pattern for booster sales too since, as we just discovered, booster sales are linked to replacement sales figures by constant ratios that differ by country but are constant over long stretches of time):

Doses	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**
Low income	0	0	0	0	0	13,293,065
Middle income	0	0	0	0	0	855,009
India	0	0	0	0	0	0
China	0	0	0	0	0	5,437,606
Private market	0	0	0	772,890	3,091,559	5,410,229
High income	523,396	1,373,914	2,224,432	2,682,404	2,747,828	2,845,965

Doses	**2019**	**2020**	**2021**	**2022**	**2023**	**2024**
Low income	19,223,933	24,609,174	29,448,787	27,962,664	30,273,962	30,569,485
Middle income	1,238,624	1,582,146	1,885,574	2,021,037	2,189,002	2,209,595
India	0	0	0	0	0	0
China	7,864,721	10,066,173	12,041,963	11,375,205	12,320,581	12,436,481
Private market	7,728,899	10,047,568	12,366,238	22,152,836	23,383,549	24,121,977
High income	2,878,677	2,944,102	2,949,336	2,949,336	3,009,526	3,009,526

Doses	**2025**	**2026**	**2027**	**2028**	**2029**	**2030**
Low income	31,273,543	32,150,590	33,000,019	33,821,830	34,505,549	34,643,641
Middle income	5,655,004	9,453,317	12,938,446	16,110,390	17,716,408	19,282,333
India	0	0	0	0	0	0
China	12,588,969	12,814,632	13,040,294	13,265,957	13,491,620	13,491,620
Private market	24,614,262	24,614,262	24,614,262	24,614,262	24,614,262	24,614,262
High income	3,009,526	3,009,526	3,009,526	3,009,526	3,009,526	3,009,526

Total Doses	
Low income	374,776,242
Middle income	93,136,886
India	0
China	150,235,820
Private market	256,761,315
High income	48,195,597
TOTAL	923,105,859

There are certain features to this pattern (that apply also to booster sales, which are exactly patterned on this data):

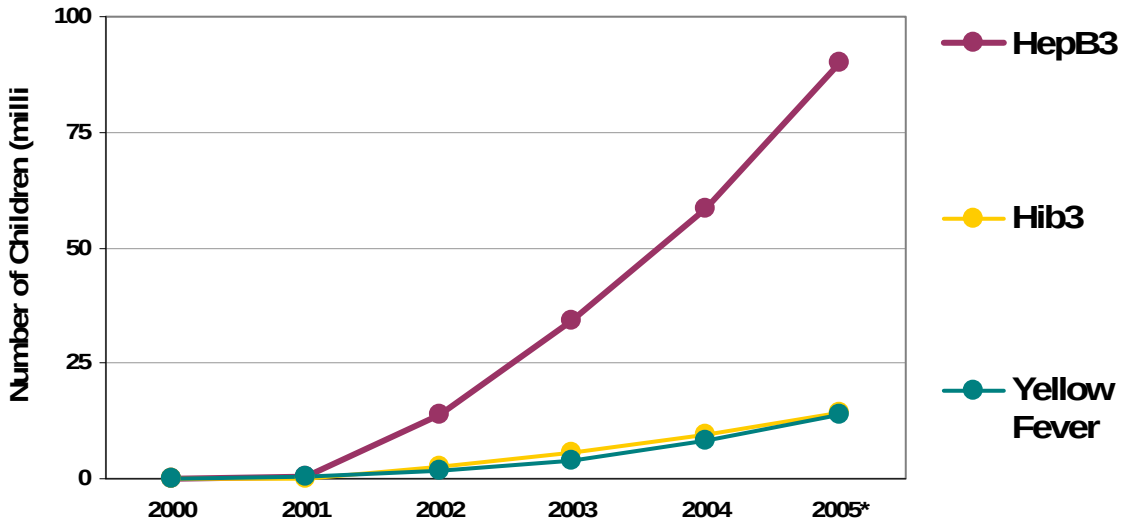
1) Low income market levels build up to steady state in just 3-4 years (no catch-up period it would appear);

2) Middle income seems to take much longer, with a big take-off in the period 2025-2030;
3) India does not register at all (though may be being picked up in private market sales);
4) China reaches steady state in about four years (with a big surge in the third to fourth year);
5) Private market grows strongly till 2021, then jumps following the competitive event.

Are all these trajectories realistic? On the one hand, is this a generous interpretation for a 70% efficacious vaccine in some cases? What specific role does efficacy have in dictating the adoption curve, since here it is not clear? On the other hand, why is there (apparently) such a limited catch-up phase?

2.6.1. Some points about Hep B levels and rate of adoption

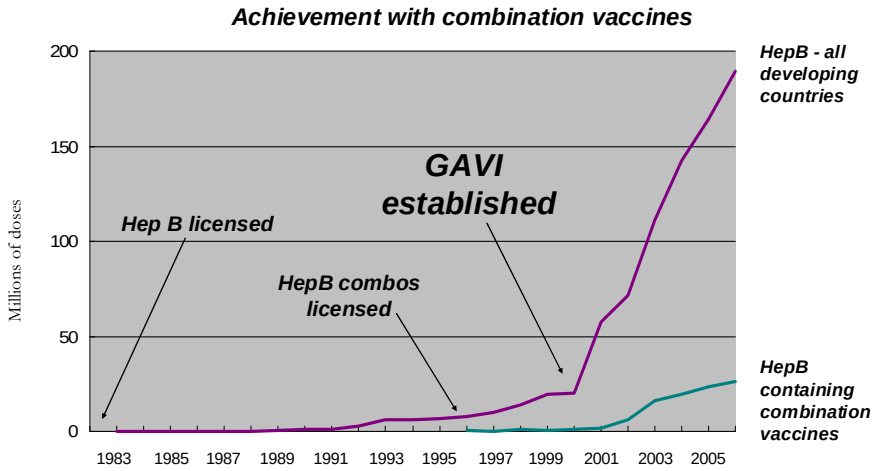
Given the heavy reliance on the "average Hepatitis B adoption curve", we are beholden to consider that curve in some detail.
The Hep B adoption curve in terms of millions covered is impressive:



Cumulative Number of Children Reached in GAVI-Supported Countries
*projected
Source: WHO/UNICEF

But it also shows the importance of GAVI emphasis on Hep B roll out compared to other vaccines (c.f Hib and yellow fever):

GAVI and Hep B

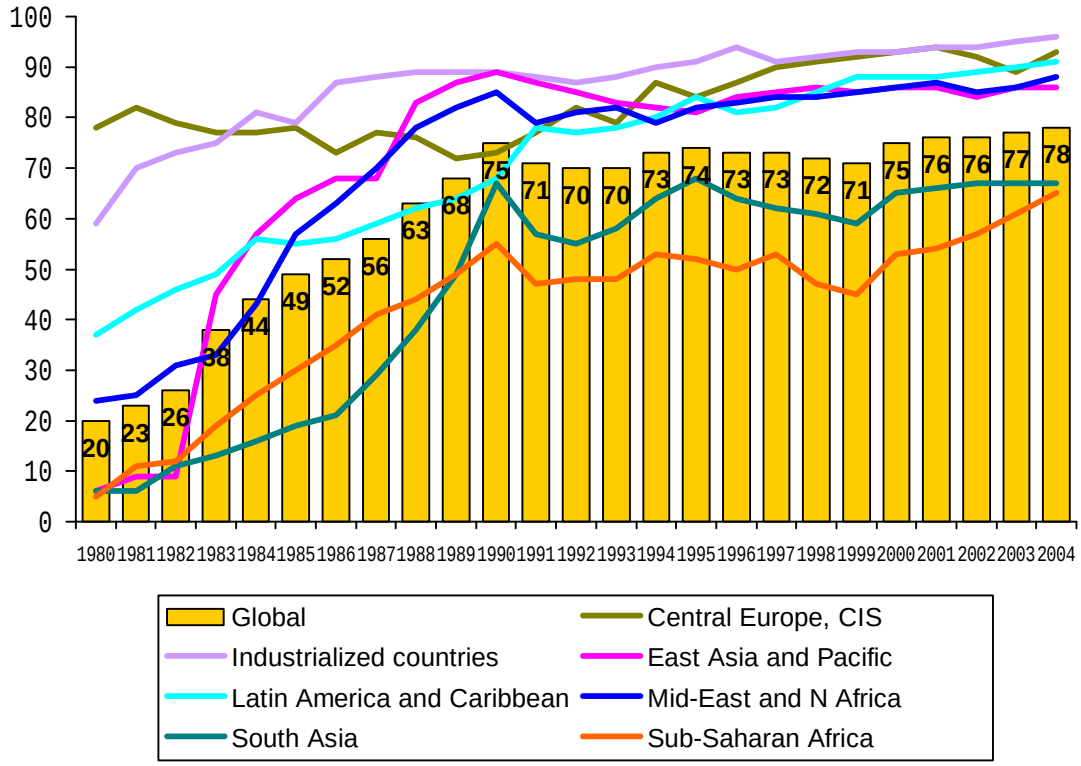


In 2005, coverage of hepatitis B vaccine in GAVI-eligible countries was 45%; this was a dramatic improvement on 20% in 2000, but it is still much lower than 85%.[26] Was the rate of *increase* in the BCG calculations based on the *rate of increase* of HepB, even if not the levels? Or is there some other explanation?

2.6.2. A note about EPI levels

If achieving levels "necessary to accrue full benefits" presumes that 85% is the market penetration level for BCG-replacement vaccine, does this also cover poorer countries? Many of the countries experiencing the highest impact from TB (and hence key poor markets) face much lower rates of EPI coverage than 85% (though some key markets for TB vaccines do reach 85% plus).

[26] SOURCE: WHO/UNICEF coverage estimates 1980-2005 as of august 2006.



Source: WHO, 2005

The issue here would be how realistic it might be to achieve similar speed of uptake and coverage to Hep B in the case of TB, given the record in general and the more nuanced interpretation of the case for Hep B. The product profiles are very different, and the issues on the ground in getting uptake are likely to be very different too.

Some replacement vaccine scenarios for non-rich markets

Assumptions for scenarios:

1) It is assumed that it is possible to adjust for less than perfect coverage all the way through a typical spreadsheet by simply re-weighting all the figures and appropriately adjusting COGS figures downwards. For replacement vaccine we simply assume $1 for COGS, so this is pretty simple to do.

2) No adjustment is made for R&D, facilities and maintenance (one might imagine the latter two might be scaled, but it is not obvious[27]).

[27] But maybe not? It depends on what is the minimum efficient scale of production. It may not be able to scale down according to coverage. Here, to simplify, no adjustment is made to scale.

SCENARIO:
High-income market the same as BCG case. Other markets only ever reach 50% of the presumed BCG optimistic case in each year. COGS worked out (because of lack of clarity about private market quantities) as US market size COGS taken off total COGS, then halve that, then add US back in. No adjustment for facilities, R&D or maintenance.

NPV at end 2012 at 20%	$53.80
Discounted to 2005 at 20%	$11.28
NPV at end 2012 at 15%	$227.55
Discounted to 2005 at 15%	$62.01
NPV at end 2012 at 10%	$498.20
Discounted to 2005 at 10%	$214.46

Even halving the non-US market left overall NPV positive. This just goes to show how key the rich-world market is in terms of: i) revenue, and ii) early pay-back to investors. This is in spite of, no doubt, massive social benefit in these poorer markets (not worked out here). Again, this shows how little poorer markets matter for financial return in the report's figures.

SCENARIO:
Pull all low income, middle income, private market and China forward by three years. COGS pulled forward three years (adjusting for rich-world component).[28]

NPV at end 2012 at 20%	$296.78
Discounted to 2005 at 20%	$62.24
NPV at end 2012 at 15%	$533.57
Discounted to 2005 at 15%	$171.05
NPV at end 2012 at 10%	$897.56
Discounted to 2005 at 10%	$429.30

This demonstrates how valuable sales even in poorer markets can nevertheless be; in this case, the key is the removal of delay in uptake.

SCENARIO:
Pull all low income, middle income, private market and China forward by three years. COGS pulled forward three years (adjusting for rich-world component). Lower COGS from $1 to $0.5.[29]

NPV at end 2012 at 20%	$395.13
Discounted to 2005 at 20%	$82.87
NPV at end 2012 at 15%	$675.75
Discounted to 2005 at 15%	$216.63
NPV at end 2012 at 10%	$1,113.86
Discounted to 2005 at 10%	$532.75

[28] Needs checking, may depend if there is a fault in private market figures.
[29] Needs checking, may depend if there is a fault in private market figures.

Here we add a lower COGS (a cut of just 50cents on original COGS of $1) to the above poorer market 'early' scenario. The impact is large because though the sales are at a much lower price than richer markets, the volumes are so much greater.

SCENARIO:
Pull all low income, middle income, private market and China forward by three years. COGS pulled forward three years (adjusting for rich-world component).[30] Lower manufacturing costs to $0.5. China pays $1. Add India at same doses as China.

NPV at end 2012 at 20%	$414.33
Discounted to 2005 at 20%	$86.89
NPV at end 2012 at 10%	$1,155.79
Discounted to 2005 at 10%	$552.81
NPV at end 2012 at 15%	$703.44
Discounted to 2005 at 15%	$225.51

The key to large NPV here is to boost the uptake of poorer markets earlier. The reader may note that a different mechanisms is at work to a large prize-like mechanism to "repay R&D costs." The needed incentive is to generate higher NPV via large purchases, early, at low COGS in poorer markets.

Some booster vaccine scenarios

An assumption of 66% market penetration for booster vaccines seems high. It is not clear how robust the reasoning for this is, especially given the need to develop sustainable delivery mechanisms targeting older age groups, and given the importance (and limitations) of diagnostics. These surely are very big unknowns, and will require a great deal of extra funding. Again, the size of NPV depends heavily on how the phrase "necessary to accrue full benefits" was interpreted. Given the power of discounting, what assumptions are being made about the speed of uptake as well as the ultimate level of uptake?

The BCG report does not try to explore what the fully burdened costs for adoption will be. This (and the risks that provisions for the costs of such regimen will be lacking) has not therefore been factored into expected returns to investors (apart from excluding poorer markets in the case of booster vaccine).

The BCG report presumes that COGS of booster vaccines will put them out of the reach of poorer markets. It would be interesting to analyze what might happen if booster vaccines can be made cheaper to produce and thence to purchase, if this then opens up poor markets. There is poor information here to do this, but the pricing figures used suggest some ability surely to use differential pricing.

[30] Needs checking, may depend if there is a fault in private market figures.

BASE BOOSTER SCENARIO FROM BCG:

NPV at end 2012 at 20%	$538
Discounted to 2005 at 20%	$113
NPV at end 2012 at 15%	$1,006
Discounted to 2005 at 15%	$323
NPV at end 2012 at 10%	$1,779
Discounted to 2005 at 10%	$851

2.7. EFFICACY AND COVERAGE/PENETRATION

The report says that to work out "the potential return on industry investment, the target product profiles needed to capture those market opportunities" need to be derived (p 7). However, there appears to be no analysis in the report or background material of the relationship between 'target' product profile, coverage/market penetration, and price, since only one profile per vaccine type was speculated. It would be interesting to see some modeling of this. If nothing else, it would help reveal the value of investments in achieving higher or lower rates of product efficacy (e.g. if more up-front funding leads to more candidates and increased chance of higher efficacy). It is difficult to use the report therefore to guide investments towards specific target product profiles.

In general, it is not clear how meaningful are the figures of 70% (replacement/prime), 70% (Booster), 80% (Prime-Boost). What are the probability distributions around these probabilities (if it is possible to think in this way about these figures)? How sensitive are all the demand figures to percent efficacy, and hence to any guesswork that went into these figures? What explains the fact that adding a booster vaccine to a replacement vaccine adds only 10%, yet the booster on its own is capable of accounting for 70%? What is the data on which the relationship between coverage rates and percentage efficacy of product were established, since this then feeds into the revenue figures?

It is not clear yet what the evidence is for the efficacy gains above the existing established vaccines for the recombinant BCG and for the combination prime-booster strategy. How do we capture the durability of response which is not captured in the efficacy measure, and what is the evidence for the impact of rBCG vs prime-booster from a durability point of view?

Once we know more about response of coverage to efficacy, we can explore different NPVs according to needed efficacy and coverage. Intuitively there ought to be a model showing higher NPV of costs related to higher average efficacy (presuming that, on average, higher R&D expenditure leads to higher expected efficacy) and higher NPV of revenues; the issue will be whether the latter exceeds the former.

Similarly, willingness to expand delivery mechanisms (especially amongst adult populations) and to change organizational practice (e.g. to provide vaccine to LTC and the homeless in the US, etc.) is a function of efficacy. Would this be especially the case in rich markets (this author hypothesizes that it is the case), where the marginal incentive to change current practice (say in prevention strategies in LTC) must surely be very

sensitive to efficacy. Is there a floor, a discontinuity in market size if efficacy falls short? Some experts have explained to this reviewer that there is a discontinuity in the target product profile that will be acceptable in rich markets, and maybe also *across* rich markets given different decision-making processes. The implicit assumption in the way NPV is calculated in the report is that there is a continuous uptake-probability distribution over efficacy with no discontinuity. Similarly, is there a big upside if efficacy is higher? None of this is capable of being explored in the report.

This issue potentially affects price too, as well as likely coverage at a price given a particular level of efficacy. Admittedly, this is difficult to explore.

2.8. IMPACT OF 'WILLINGNESS TO PAY' QUESTIONAIRRE ON REVENUE MEASURES

In order to work out 'willingness to pay', a questionnaire was used. This raises a few separate issues bearing on the revenue figures (mainly via revision in expected prices used in calculations). Willingness to pay is always relative to expectations of product impact, efficacy, immunological memory, costs, etc. Without further explanation from those who carried out the questionnaire:

1) What was the questionnaire protocol w.r.t. explanation of efficacy and impact on lives saved of different vaccines and vaccine combinations? For example, 70% is described as the "minimal target threshold for vaccine efficacy" (p11) but is also described as "observed efficacy" (Table 1);
2) The analysis seems to suggest that efficacy and lives saved are very non-linearly related, as evidenced in Figure 6 of the report. For example, one 70% efficacy figure relates to 17% lives saved, another 70% figure relates to 40% lives saved, and the 80% figure relates to 62% lives saved (all based on the assumptions the report makes regarding duration of immunological memory). How was this (and the limitations of this) communicated in the questionnaire protocol? To the extent it was poorly communicated, what can be read into the figures claimed for willingness to pay in different settings?
3) If questions had been framed in terms of lives saved, would this have changed the claimed willingness to pay for different vaccines (or not), especially for those vaccines having greatest impact on lives saves at the population level, i.e. booster vaccines?
4) In terms of 'lives saved', the report suggests high value to booster technology. Figure 6 shows that the booster vaccine does a lot on its own to save lives. In particular, it is saving 500,000 more deaths per year compared to the BCG replacement scenario at the 2030 horizon, though both are described as 70% efficacious. This is because of the power of boosting at ten yearly intervals. It would be nice if some of this value could show up in some way. The booster vaccine saves a further 400,000 more per year at the 2030 horizon when combined with the BCG replacement vaccine. Again, this prime-boost value (based on a '10% efficacy gain' over either prime or boost on their own) is not well captured in this simple 'efficacy' description. There seems to be a very big population effect in here not being easily picked up when respondents are simply

asked to respond to 70% and 80% efficacy rates. If the questions were framed in lives saved, would this change the responses of claimed willingness to pay? At the 2030 horizon, the BCG replacement strategy saves 300,000 lives, yet combined with the booster strategy (and presuming this is even under the assumption of poor take up too) 1.2m lives are saved (= 2.00m - 0.8m). Perhaps this correspondent is not fully understanding this, but the value of the booster seems very high, and may have been poorly communicated in questionnaires based simply on efficacy. This suggests we also look at the questionnaire protocol. Did those being asked fully understand 'effective' efficacy (against the costs too) outside of the 70% listed?

5) This is heavily dependent on (the certainty of) an average 10 years duration of immunological memory. How reasonable is this assumption? How well was this communicated in the questionnaire protocol?
6) There seems some confusion regarding what various consumers are willing to pay. On the one hand, we hear that "In fact, we found that India and China are particularly sensitive to price, suggesting that they would be unwilling to purchase any vaccine unless it is less than $1" (p13). On the other hand, footnote 9 (p23) observes that 70% of all Chinese households bought the Hep B vaccine for their newborns at a cost of $3 per dose. When facing the very real choice and $3 price tag we are told that a large portion of Chinese households paid it. When facing the hypothetical choice, it is reported that they (or officials on their behalf) claimed a $1 maximum threshold. It is very difficult to do controlled experiments in this area, but are claimed limits to be taken as seriously as findings based on actual choices? If 1$ was used across the analysis of low-income sections of the market, it would be nice to see the justification for this. Is this floor too low compared to actual experience? How did this impact NPV and IRR (and presumed take-up of booster vaccines, etc.)?

2.9. IMPACT OF DELAY TO LICENSURE ON REVENUES

All the BCG figures are based on licensure *by 2013*. The BCG report however, clarifies that "With most vaccine candidates in pre-clinical or Phase I trials, interviewees generally agreed that the first successful product is unlikely to be licensed before 2013-2015." This suggests a necessary condition (that we need to wait at least until 2013-2015) but not a sufficient condition (that if we wait till 2013-2015 we will get a vaccine by then). Though "at least one new vaccine will successfully complete Phase III testing and be licensed by 2013-2015," (p11) this is no certainty. Neither is there any guarantee that an early success will meet any of the profiles suggested in the report.

The NPV figures produced by BCG show that even a one or two year delay to licensure significantly harms NPV. This is because of the extra delay imparted to revenue streams from sales, especially from richer markets, that are then heavily discounted in the NPV calculation. Similar logic would seem to apply to slow achievement of market penetration, and slow provision for new fully burdened costs.

2.10. IMPACT OF OTHER INTERVENTIONS AND UNCERTAINTIES ON NPV OF REVENUES

The presumption underlying all the figures in the report is that there will be no new drug interventions between now and 2030 to 'upset' vaccine sales patterns. In 'Appendix II: Methodology' of the report, it is observed that "no new drug to fight TB has been developed in the past 40 years," (p9) and public markets in poor countries are valued relative to costs (and efficacy) of non-vaccine treatment, and this is presumed to be the current state of play vis a vis DOTS. So there *is* a presumption underlying all the figures that there will be no new drug interventions between now and 2030. How realistic is this? What risks does it pose and benefits does it suggest? If there are any new drugs, this will impact on vaccine revenues – especially of less than 100% efficacy vaccines – and hence NPV for vaccine investors.

The recent TB drug development report, "Pathways to Patients: Charting the Dynamics of the Global TB Drug Market", reveals a very low level of market for new TB drugs in richer countries, but also argues that the progression of MDR-TB and XDR-TB may be an important factor in persuading richer markets to both adopt new drugs and switch funding into vaccine-based prevention strategies. Paradoxically, the earlier investment and earlier success in tackling MDR-TB and XDR-TB, the lower the value of vaccine-based investments.

These two issues are a big uncertainty that financial markets must be factoring into their evaluation of the NPV of investment in TB vaccines. Again, this is hard to evaluate in the report – and no doubt hard to estimate in general.

Observe also that there must be some option value in waiting to see how these two issues resolve over time. This suggests that we i) Should try to get a handle on this option value ii) there may be value in sponsors investing early in terms of compensating for this option component.

At this level, different interventions have the ability to both 'complement' and 'compete'. Some exploration of this issue, and its impact on investors, would be useful.

2.11. SOME EPIDEMIOLOGICAL ISSUES

The effect of a vaccine or vaccines on the TB epidemic – and hence the value of a vaccine or vaccines – depends on the epidemiology of TB. For example, because of the latent nature of much disease in very resource-poor setting, while "The path to reducing the epidemic levels of TB infection, particularly in the poorest countries of the world, is through a TB vaccine," a vaccine strategy to eradicate TB is a long process. This process should also feed into the value of, say, booster vaccines compared to replacement vaccines. Latent infection in certain population sub-groups will also affect the rich market component of revenues.

In spite of mentioning one technical paper on the epidemiology of TB, the pattern of behavior of the data – for example, the way in which booster vaccine quantities are

simply scaled up versions of replacement vaccine quantities in spite of them having a very different epidemiological impact – indicated that the use of this was fairly minimal, particularly in composing revenue figures and NPV. It seems to have been partially used to derive Figure 6. But the complexities of that technical work are not part of the BCG model itself.

The replacement vaccines are designed to replace the existing BCG vaccine with improved duration of immunologic memory (more than 20 years) for newborns and will be live attenuated strains. It would have been interesting to see more surrounding the issues that arise for different degree of immunological memory achieved. What would the impact on NPV be of different possible cases?

The booster vaccines are to be given to children, adolescents, and adults as a boost to the neonatal BCG vaccination (typically subunit vaccines or viral vectored vaccines). It would have been interesting to have seen more of the NPV impact of the need to provide the delivery mechanisms for this.

With a prophylactic vaccine, to be given prior to TB infection, several other issues arise that will impact NPV:

1) Use is more limited in those countries that actually have high infection rates already;
2) There are issue about the ability to diagnose and separate out those who get from those who do not;
3) It is not clear what the trajectory for adult take up is (if any). One cannot easily compare this with other situations;
4) There is a need to keep alternatives treatment and prevention strategies going. This was not well factored into the analysis underlying the report. A long-term pandemic control strategy with goal of (near) eradication requires all interventions working together over very long periods of time and over very diverse settings.

Active pulmonary TB is the leading cause of death in HIV/AIDS patients in the developing world and has spiraled in the last decade or more. There was no inclusion of any modeling relating to this.

3. COST IMPACT ON NPV

As the NPV equation at the start of this assessment makes clear, NPV will be sensitive to R&D and production costs, and not just to revenues. Indeed, the more the underlying figures in the report are explored, the more apparent it becomes that the cost issues need much more careful consideration.

Wide uncertainty over development costs creates widely varying measures of NPV. Yet, while reference is made in the report to "wide opinion" over R&D costs, little analysis was done on this side of the NPV/IRR equation.

A few scenarios performed (above) showed that production costs too – even in the case of the hypothesized much cheaper replacement vaccine – were found to positively impact NPV if the circumstances are right (especially if contributing to early bulk sales). The next section turns attention to R&D costs.

3.1. R&D COSTS

In conversations with Aeras this author has voiced strong reservations about the way the R&D cost figures seem to have been derived in the report and the way this is then allowed to feed through into NPV (and IRR) figures.

3.1.1. 'Probability adjusted' R&D cost figures

One particular concern is the way a 'probability adjusted' R&D cost figure was derived for each of the vaccine cases. According to BCG, "Non-attrition-adjusted development costs (that is, the cost to bring a single, successful product to market) are estimated at $194 million for a BCG-replacement vaccine and $203 million for a booster vaccine. (See Table 1 and Appendix II.) From the perspective of a single, successful vaccine candidate, this suggests that a total investment of several hundred million dollars is necessary when the costs of manufacturing capacity are included." Furthermore, "based on a wide range of interviews and *current industry benchmarks*, we assumed that attrition-adjusted research and development costs to get one vaccine to market (given a 35 percent chance that at least one candidate will be successful) would be in the range of $600 million to $800 million, although opinions varied widely." [31]

Furthermore, "ROI calculations weigh development costs against expected money earned *from the perspective of one company investing in TB vaccines*. We calculated cash inflows (R&D funding and product sales) and cash outflows (development costs, manufacturing scale-up, cost of goods sold or COGS, and sales and marketing expenses) for each year, each product type, and each market scenario. We then discounted these cash flows by the probability of occurrence and by the cost of capital (discounted value of all future cash flows). When the NPV is positive, the project is a financially sound investment." (p14).

[31] P12, italics added.

It is not clear how results derived *from the perspective of one company* can be straightforwardly extrapolated to the population level. Nor is it clear how "probability of occurrence" is treated. The figures seem quite rudimentarily calculated.

The report argues that there is a 35% chance of *at least one* success and that this has been used to attrition-adjust the figures. This seems to have entailed multiplying all base figures by about three (figures derived from Table 1, p12).

	$m	$m	Ratio
Prime	194	563	2.90
Boost	203	638	3.14
Prime-Boost	397	1201	3.03
Average			3.02

No R&D funding inflows are listed in the spreadsheet and no sales and marketing data, so it is hard to see how this was done. It seems rudimentary. And if simply multiplied by three, it is actually the wrong way to work out such figures.

3.1.2. 'One' or 'at least one'?

It is not made clear if this is "the cost to bringing a single, successful product to market" or the cost of bringing "at least one single, successful product" to market. In both cases there is no notion of 'expectation' of outcome or of any distribution around an expected outcome. Some fairly basic notions of uncertainty are missing.

It would seem very odd in the case of such a major killer for us to be only interested in the costs of achieving *35% chance* of at least one successful product. We might rather be interested in, for example, the expected costs of generating "95% chance of getting at least one vaccine" to market (controlling for vaccine characteristics). The only way really to analyze this – and it is still a somewhat imperfect approach given all the informational limitations – would be to use portfolio analysis. Intuitively, we would expand the pool of vaccine candidates till we got this 95% figure and would accept the consequent increase in costs. This latter interpretation has several major implications:

1) The cost of achieving a particular percent probability of "at least one success" is not linear. One can't simply add up the costs of three 1/3 chances; the underlying probabilities over outcomes don't work like that. Intuitively, as the pool of vaccine candidates increases in size, at first new additions to the pool have a big and initially growing positive impact on the probability of "at least one success." At some point however, the addition of new candidates to the pool, while increasing the percent chance of success, starts to do so at an ever-decreasing rate. Assuring 95% chance of "at least one success" can be expensive, since within that range of probability that act of raising the chance of "at least one success" is getting ever harder (and more expensive) to do.

2) This is only the percent chance *of at least one success*. The portfolio will produce a range of possible numbers of outputs. When there is 95% chance of at least one success, the average number will be more than one. For example, in the case of TB drug

development (an issue with which the author is familiar[32]), given attrition rates, achieving 95% probability of at least one success produces nearly three products on average. While this is good in one respect (average cost to develop each new product is lower than if there was just one new drug/vaccine), nevertheless the overall cost of achieving this still has to be extracted from the overall market for *all* of these products, with some of these products having little market in order to generate the few that do. Hence, if this 95% thinking generates a cost much greater than that calculated by BCG, this will swamp any market figures they generate, even under their most optimistic assessment. This is why it is so important for BCG to clarify exactly how they derived their R&D cost figures, and to do so in a way that makes sense economically.

Getting a better fix on early attrition rates will have a big impact on the figures. If there is need for many more early phase trials than the scientific understanding in the BCG report presumes, this will have to be compounded to create a larger measured R&D cost in the year of licensure. To the extent BCG have been overly optimistic about these rates, NPV is lower, potentially much lower, and increasingly likely to be negative.

This also begs the question of how phase III trial costs are handled. On the one hand, these are usually the heaviest single out-of-pocket cost. On the other hand, the advantage of costs falling later in time, and closer to licensure, is that they have lower impact on discounted NPV.

It would be really good to see the impact on costs of shorter phase II trials (on account of biomarkers). Intuitively, one would imagine a potentially big impact on the NPV.

Given the apparently very simple way that R&D cost has been calculated, none of these issues has been explored in the report, and we should have correspondingly less confidence in the NPV figures derived.

3.1.3. Attrition rates

In an ideal world we would use attrition rates specific to the vaccine challenge at hand, and given the underlying state of the science. Given high uncertainty about what the rates must be, we might also want to vary attrition rates and see the impact on NPV. Instead, trial attrition rates (converse of success probabilities) were fixed throughout the analysis underlying the report.

The only source quoted for attrition/success rates is Struck, M., "Vaccine R&D success rates and development times", Nature Biotechnology, vol. 14, May 1996, pp. 591-593. This does not seem to reflect modern understanding of the case in hand, or the range of opinion the report concedes.

In related material supplied by Aeras and prepared by Applied Strategies, for AMC calculation, each compound finishing the Preclinical phase has a 15% chance of going the whole way to licensure. The probabilities of phase success used were:

[32] http://www.economics.ox.ac.uk/members/andrew.farlow/FarlowTBPortfolio.pdf

Phase 1	45
Phase 2	50
Phase 3	70
Licensure	95
Post-License R&D	-

From end preclinical to licensure: 0.45*0.50*0.70*.95 = 0.15

In the backup material to the report,[33] three cases of probabilities of success are reported:

1) Pharma vaccine (Top pharma company,[34] from BCG interviews)

Discovery/Preclinical	57
Phase 1	72
Phase 2	79
Phase 3	71
Licensure	96
Post-License R&D	Not given

This yields:

Discovery to launch	22%
Phase 1 to launch	38%

Candidates needed at discovery/preclinical: 4.5
Candidates needed at Phase 1: 2.6

2) 'Alternative'

Discovery/Preclinical	50
Phase 1	80
Phase 2	60
Phase 3	70
Licensure	96
Post-License R&D	Not given

This yields:

Discovery to launch	16%
Phase 1 to launch	32%

Candidates needed at discovery/preclinical: 6.2
Candidates needed at Phase 1: 3.1
The 3.1 figure was highlighted in the background paper, since there are currently 3.1 candidates in phase 1.

It is not clear how this has been read (and if it has been read) to generate expected R&D costs.

[33] Background material "TB Vaccine Development Ranges to Test," p4.
[34] It seems singular.

3) Pharma/biotech drug	
Discovery/Preclinical	60
Phase 1	60
Phase 2	45
Phase 3	68
Licensure	95
Post-License R&D	Not given

This yields:	
Discovery to launch	10%
Phase 1 to launch	17%

Candidates needed at discovery/preclinical: 9.6
Candidates needed at Phase 1: 5.7

In this author's opinion, the value of some of these rates is unclear. Neither is it clear how one goes from this to the calculated R&D cost figures used in the report. Are the attrition rates used in the analysis plausible? Do "current industry benchmarks" apply to this case?

This begs the question of what sensitivity analysis over attrition rates would do to the range of NPV/IRR. We don't do this here. But we can do the next best thing, and simply explore what happens if R&D costs are higher.

3.1.4. Impact of extra costs

It is possible to create a 'ready reckoner' for the impact of higher R&D costs on to any of the NPV figures derived in this assessment.[35]

Capitalized extra R&D costs, where capitalized to *end* launch year 2013[36]	Impact NPV in 2005 at 20%	Impact NPV in 2005 at 15%	Impact NPV in 2005 at 10%
(100)	(16.78)	(27.25)	(43.05)
(200)	(33.55)	(54.50)	(106.29)
(300)	(50.33)	(81.75)	(159.43)
(400)	(67.11)	(109.00)	(212.58)

It is worth observing the obvious: That just $200m or so of extra (amortized) development costs in 2013 (hence derived from much lower flows of costs in earlier years) has potential to destroy the positive NPV in many of the scenarios in the report.

The following are performed on the BCG base case.

[35] Note, as elsewhere, this all needs checking after clarifying how the 2013 figures were worked out by BCG.

[36] This is the figure on the BCG 2013 cost column. Hence, until confirmed otherwise, all figures are based on 8, and not 7, years of discounting.

SCENARIO:
R&D rises by $300m *as measured at end 2013*

NPV at end 2012 at 20%	($100.75)
Discounted to 2005 at 20%	($21.13)
NPV at end 2012 at 15%	$107.46
Discounted to 2005 at 15%	$34.45
NPV at end 2012 at 10%	$441.13
Discounted to 2005 at 10%	$210.99

SCENARIO:
R&D costs $300m higher, Facility cost of $250m. No other changes.

NPV at end 2012 at 20%	($154.05)
Discounted to 2005 at 20%	($32.31)
NPV at end 2012 at 15%	$51.84
Discounted to 2005 at 15%	$16.62
NPV at end 2012 at 10%	$382.98
Discounted to 2005 at 10%	$183.18

Thus, combinations of lower than expected high-income high-risk uptake, delayed licensure (compared to 2013, which was already starting to look optimistic), and higher costs, can easily make investment in this case not at all financially attractive.

3.1.5. Cost of development issues, including biomarkers and trial site limitations

There are many other scenarios that would be interesting from a practical policy perspective:

1) For potential sponsors, it would be extremely useful to break down this 'aggregate' cost figure into the costs needed to get to each stage of development, and hence the 'remaining costs' and expectations to get to product at each point in the chain of product development, and NPV from that moment onwards.
2) A better calculation of the cost of 95% of "at least one success".
3) A better calculation of the average costs of each new product based on this 95% thinking.
4) It would be interesting to see some exploration of the relative chances of which will come first (BCG replacement or booster), and hence what cost/capacity issues will have to be tackled first. The issue would be how much attention we should put on affordability issues now. The possible suggestion is that if boosters are 'ahead' now, then there should be more attention to affordability issues now (e.g. tech transfer, role of emerging suppliers, timing of 'competitive event', etc.). Also, is it worth exploring any option value issues if there is any risk of the 'other' product arriving first? Is this high for booster vaccine developers for example?
5) The report acknowledges serious bottlenecks in trial sites (p19). On p11, those candidates going into phase III in the next few years are listed. It would be worth exploring the impact on costs and delay to those candidates in the pipeline

arriving later on account of restrictions on trial sites once these 'early' candidates have absorbed much of the trial capacity.

6) It is explained that the lack of surrogate markers means that trial sizes need to be large and long. The creation of predictive biomarkers, it would appear, has the potential to greatly reduce costs and hence (greatly?) increase NPV and IRR (all other assumptions held fixed). What is the private and social value of investment in investing in developing such biomarkers? It would be worth exploring what 'market failure' there is if insufficient investment is going into the development of biomarkers (incidentally, this is another case where 'risk' and 'cost' seem to be mixed up in the wording of the report, see p6).
7) How does the lack of clinical biomarkers relate to the shortage of clinical trial sites? If trial sizes and lengths can be shorter on account of better biomarkers, the effective availability of trial sites rises for any given actual trial sites in existence.
8) How does the development of biomarkers impact cost and risks (see p18)?
9) Can the value of some of these options be transferred into cost savings and hence value to sponsors of such activities, and NPV/IRR, etc.? For example, there are no costs scenarios looking at what happens if there is much better trial infrastructure and biomarkers, pushing costs down, it is claimed, heavily. This should have a big payoff in terms of NPV.
10) The value of reducing delays in use of trial sites could be big. The value of the $10m investments each in trial sites and cross country regulation (RHS p 20) are not calculated but would be worth doing since this is an alternative way to spend funds.
11) Diagnostic and better targeting of the booster vaccines (it enables targeting of those who have not been infected with TB already). Impact of diagnostics on improving cost-effectiveness of booster vaccine.
12) Some of these alternatives (regulatory improvements, shorter delay in getting access to trial sites, ability to run more trials, etc.) would reduce cost and increase value. Are these better value than an AMC-style subsidy for example (also when factoring in price pressures)? It would be good to put possible interventions side by side to work out marginal effectiveness.
13) A better treatment of sponsor funds. It is not clear exactly how sponsor funding is treated in the R&D cost figures in the report. Is it treated as an R&D cost subsidy or as lowering costs of capita? There seems some confusion over this. 'R&D funding' (from sponsors, including the Bill and Melinda Gates Foundation) and product sales are factored into positive cash flows (p14 bottom RHS) on which risk analysis is then performed. But, sponsor funding appears later as outside of these cash flows (such as in the guise of AMC funding). However, on p15 of the report, sponsor funding towards R&D is described as lowering the cost of capital, and on p17 it "lowers the discount rate." Usually one would visualize such funding as lowering R&D costs. There may also be a risk-reduction element (for example, such funding may have some option or insurance value), but that would be separate from (and additional to) the cost reduction issue. What are the assumptions made regarding these sources of R&D funding' as positive cash-flows in the 'base case'? For example, on p15, NPV is based on expected returns over development costs and cost of capital, yet development costs had been

defined as that part of costs *not* covered by inflow of R&D funding from non-private sources. This compounds a general mixing up of costs, attrition rates and risk in the analysis.

14) In treating sponsor contributions, sometimes sponsors prefer to take payout in terms of contractual conditions (like lower prices and access) in return for their financial contributions. How are all these contractual obligations factored into returns to private players? We are told here that this funding 'reduces risk', but do they also have obligations impacting NPV and IRR to firms?

3.2. PRODUCTION COSTS/COSTS OF GOODS

The BCG report presumes low take-up of booster vaccines, entirely because of the cost of goods, COGS, of such vaccines, and not because of the R&D costs of developing such vaccines (under the assumptions here at least). This then feeds uptake/market penetration and NPV/IRR.

The BCG spreadsheet presumes $1 COGS for replacement vaccines.[37] Therefore, several scenarios were done in this assessment on the notion of $2 and $0.5 COGS, and on the basis that nothing else changed (same revenue and costs figure as presented in the report, and no change in quantities demanded). Interestingly, whether COGS is $0.5 or $2 makes a big difference to the NPV in the-base case outcome.

SCENARIO:
$0.5 production costs, replacement case, no change in quantities demanded

NPV at end 2012 at 20%	$204.27
Discounted to 2005 at 20%	$42.84
NPV at end 2012 at 15%	$455.02
Discounted to 2005 at 15%	$145.87
NPV at end 2012 at 10%	$857.09
Discounted to 2005 at 10%	$409.94

SCENARIO:
$2 production costs, no change in quantities demanded

NPV at end 2012 at 20%	$39.20
Discounted to 2005 at 20%	$8.22
NPV at end 2012 at 15%	$194.95
Discounted to 2005 at 15%	$62.50
NPV at end 2012 at 10%	$427.40
Discounted to 2005 at 10%	$204.42

[37] An average COGS of $0.5-$2 is quoted in the tables, but the spreadsheet figures are calculated on the basis of dose manufacturing costs of $1.

3.2.1. COGS and LDC sales brought forward

Given this impact, this suggested exploring what might happen if sales in less developed countries were brought forward under COGS of $2 and $0.5 (and, since the base assumption was the same COGS till 2030, this assumption is also kept). The results are as follows.[38]

SCENARIO:

Pull all low income, middle income, private market and China forward by three years.
COGS pulled forward three years (adjusting for rich-world component, since the timing of that has no changed).
Lower COGS to $0.5.
China pays $1.

NPV at end 2012 at 20%	$395.13
Discounted to 2005 at 20%	$82.87
NPV at end 2012 at 10%	$1,113.86
Discounted to 2005 at 10%	$532.75
NPV at end 2012 at 15%	$675.75
Discounted to 2005 at 15%	$216.63

SCENARIO:

Pull all low income, middle income, private market and China forward by three years.
COGS pulled forward three years (adjusting for rich-world component).
COGS raised to $2.
China pays $1 (so is subsidized in the $2 case, something that may be questioned).

NPV at end 2012 at 20%	$100.08
Discounted to 2005 at 20%	$20.99
NPV at end 2012 at 10%	$464.98
Discounted to 2005 at 10%	$222.40
NPV at end 2012 at 15%	$249.20
Discounted to 2005 at 15%	$79.89

Note though that the figures provided by BCG had no demand from India (to the extent these are not covered in the private market data provided). And China is paying only $1 per dose at all times, so is, in effect being subsidized at any price above $1.

WITH INDIA:

A scenario was done with India entered paying $1 when costs are $0.5. This would positively enhance NPV. We need some India data to do the figures, since this is too rough to treat with a high degree of confidence.

[38] The following scenarios need checking, after it is clarified if there is a fault in the private market data provided.

SCENARIO:

$0.5 COGS, no change in quantities demanded.	
Imagine India generates same demand as China.	
NPV at end 2012 at 20%	$214.70
Discounted to 2005 at 20%	$45.03
NPV at end 2012 at 10%	$884.78
Discounted to 2005 at 10%	$423.19
NPV at end 2012 at 15%	$471.66
Discounted to 2005 at 15%	$151.20

Lower COGS hardly impact cost of supply to rich markets, since number of doses sold is very low. At the same time, though sales to less developed countires are further off, potentially their quantities are such that they can have a big impact on NPV. Pull those sales forward and they have a big impact on NPV.

3.2.2. Booster COGS

Recent progress in science has enabled progress in effective subunit vaccines with several under development, including fusion protein vaccines and viral vectors for key antigens. Indeed, all three vaccines described here as being in clinical trials are these booster vaccines. Yet, we are also told that these are the more expensive type of vaccine to manufacture (p6 “estimates of the cost of certain booster vaccines suggest that current technology for producing these vaccines may be too expensive for developing countries to afford”). This is then fed into presumptions about market uptake (essentially that poorer markets do not take up booster technology), and hence NPV. The presumed high cost of booster technology means those who need booster vaccine the most do not get them under either the booster vaccine scenario or the prime-boost vaccine scenario.

However, predicting the future direction of the cost/price of any ‘new and novel’ technology is inherently difficult (think of chip memory, plasma and LCD screens, etc.). What are the assumptions that went into the cost thinking of the manufacture of this technology? What is the thinking about the costs of different boosters?

The reason here for little take-up on the booster vaccine is because the cost per DALY averted and cost per death averted is high (Table 7). This seems to be all down to the cost of making the vaccine, and not the R&D costs (under the assumptions here). A very detailed rigorous analysis of how to push production costs lower would seem to be key to the use of booster technology, at least according to this report. This, at the very least, suggests that work on analyzing the costs of manufacture of this technology should be a high priority.

BCG ran off some COGS analysis of booster vaccine costs from their Base 1 case (that is, assuming good coverage in high-income high-risk groups).

	Base 1		
COGS for Booster Vaccine	**IRR**	**NPV**	**Doses in 2021**
$5	**33%**	**$128.7**	**50.8M**
$3.5	**33%**	**$131.2**	**50.9M**
$2	**34%**	**$124.2**	**53.0M**
$1	**33%**	**$104.4**	**74.5M**

With lower COGS, BCG expected manufacturers to reduce prices in the low and middle income markets. With this price change, the number of doses demanded rises (we are told that the BCG model has a built-in feature where price is automatically set in each market segment to maximize profitability[39]). However, as the figures above show, the quantity responses are very insensitive until dose cost is as low as a dollar or so (though this is conditioned on willingness to pay evidence stating that vaccines would not be purchased at much above a dollar, and so this may be open to change if this is not the case for certain kinds of vaccines and certain kinds of efficacies).

With COGS at $1, we begin to see significant uptake of the booster vaccine in low income countries in both the public and private markets – with adoption beginning in 2016 and rising to 35M doses by 2021 (more than half of all doses sold) and 65M doses by 2030.

Interestingly, in the report, NPVs decline with lower COGS, although the return on investment remains fairly constant. This is because the model underlying the report assumes facility capacity sufficient to produce 120M doses, such that as demand rises in response to lower COGS, the number of doses demanded eventually exceeds the threshold to incur the cost of another plant. Thus, NPVs decline with lower COGS.

It is not clear what this is supposed to demonstrate. If the notion is to achieve greater developing country sales from the start (rather than sales that are added once plant size is set 'too low' already, as here), one might build a plant size commensurate with this. A bit more exploration of optimal plant size in light of this possibility would be useful. What, for example, might happen if plant is built ready to satisfy the much higher level of demand from the start? This needs a proper industrial economics model.

Given this behavior of NPV, and given the importance of COGS, it would also be worth exploring scenarios/incentives/policies that might be adopted to make this technology more affordable. More precise answers to the following might be of interest:

[39] It would have been interesting to see how this works, since this is very much a 'black box' component of the thinking. Other bits of evidence seem to suggest that it is not always working.

1) How might lower booster manufacturing costs on their own stimulate more uptake? And how does that feed in to NPV and IRR?
2) What are the calculations underlying the increased IRR/NPV on page 17? Reducing the cost of the initial booster to $3.50 per dose and increasing efficacy to 85% should lead to changes in quantities sold and market prices (and a need for greater capacity etc.). How were these issues modeled? In general, the report seems to have little by way of analysis of factors driving changes in prices of vaccines.
3) What are the presumed dynamics of the 'competitive event'?
4) What is the social welfare – but also impact on NPV and IRR – of pulling this 'competitive event' earlier so as to drive lower COGS[40] (perhaps as a condition of sponsor funding) or pushing it off to later? Intuitively, one might imagine a cost-benefit tradeoff.
5) What is the underlying assumption about plant size, and hence plant costs?
6) What are the presumed drivers of the 30% or 40% decline in costs over time? For example, why does the combined prime-boost production cost fall by 40% when neither component falls at greater than 30%, and one does not fall at all?
7) Footnote 8 of the report observes that "More recent information from developers suggests that the cost of goods sold (COGS) for the different subunit vaccines may, in fact, be lower than originally modeled." If this sort of information can change in just a few months (and maybe for quite accidental reasons, like conversations during the writing of a report) what does it say about making critical long-term investment decisions based on NPVs based on these hypothesized costs?
8) How are the contractual obligations stipulated by PDPs/sponsors factored into the returns scenarios facing private players?

The AMC tables provided by Aeras indicate a COGS assumption of $1.75 for biotech 1, $1.00 for biotech 2, and $1.5 for emerging supplier. This suggests that different groups analyzing the same problem are coming to quite different conclusions regarding COGS. With COGS feeding into NPV, different groups are therefore coming to quite different conclusions about NPV.

3.2.3. COGS scenarios on booster vaccines

Within the limitations of the evidence provided, some scenarios were done.

SCENARIO:

Same demand figures but half COGS

NPV at end 2012 at 20%	$752
Discounted to 2005 at 20%	$158
NPV at end 2012 at 15%	$1,327
Discounted to 2005 at 15%	$425
NPV at end 2012 at 10%	$2,285
Discounted to 2005 at 10%	$1,093

[40] If that is the effect, given that this should be explored further given the need to commit to plant size for a significant period of time.

Observe that way that lower COGS make a sizeable impact, even if most of the value of sales is driven by the high income market.

SCENARIO:
50% high income market. COGS adjusted to remove part accounted for by 50% high income market. 50% of original COGS. Note that capacity and maintenance costs are kept the same.

NPV at end 2012 at 20%	$136
Discounted to 2005 at 20%	$29
NPV at end 2012 at 15%	$517
Discounted to 2005 at 15%	$166
NPV at end 2012 at 10%	$1,175
Discounted to 2005 at 10%	$562

The underlying assumption about plant size, and hence plant costs, also seem a bit unclear. In Table 1 (p12, the base case assumption), production plant cost is quoted on the basis of 120m doses. In Figure 3, p13 (presumably the base case underlying Table 2 figures) shows that 120m is never used in a year. Indeed, booster vaccine sales are about 50m max in a given year; average yearly doses sold in the base case over the period 2013-1030 are 54.3m, 35.35m, and 90.60m respectively. This is largely because of the very slow initial number of sales. Is capacity presumed fully utilized or not? If not, then how is the cost factored in to unit costs? Indeed, base (expected) case uptake is described on p15 of the report as *peaking* at 60m for replacement and *peaking* at 40m for booster vaccine. It is not clear how this relates to the assumption of costs of 120m doses (and underlying assumptions about plant size). Only the prime-boost combination comes to 100m combined doses, but the costs of capacity in that case still seem to be based on two lots of 120m.

4. NPV WHEN RETURN SCENARIOS ARE NOT INDEPENDENT

If we stick to the report's figures (since the above analysis revealed some inconsistencies that make it hard to know how to treat these figures) the three Financial Returns scenarios listed in the report (Table 2, replacement, boost, prime-boost) do not appear to be independent of each other.

That is, according to Table 2, the expected payoff to replacement vaccine R&D is not independent of the payoff w.r.t. booster vaccine R&D and vice versa. If both approaches 'succeed', the expected payout to those investing in each approach is, according to the Table, lower than just looking at the payoffs scenarios for each approach treated separately. For example, the negative NPV prime-boost outcome that BCG create and list on p17 (and not the other NPVs) will weigh heavily on investors, the more likely it is that developers will succeed in producing *both* replacement and booster vaccines.

Furthermore, a policy framework targeting a 95% chance of at least one success, as discussed above, will raise the chances of this joint outcome. Scaling up to hit this 95% target will inflict much heavier costs, and while it may increase revenues if it increases the average expected efficacy and if there is a market response to that, nevertheless the average number of products means that the average revenues per product are lower at any given level of efficacy. The better our endeavors, perversely the lower the financial value of some of our investments. None of this is possible to see in the methodology of the report. But, without doing complicated calculations, according to the figures in the report (and presuming they can be taken at face value) there would appear to be a high chance that a target of a 95% chance of "at least one success" will take us into negative NPV territory.[41] But none of this subtlety has been worked out.

Let us look in more detail at the prime-boost scenario based on the figures in the report (and not any of our own created figures):

PRIME-BOOST OPTIMISTIC SCENARIO:

NPV at end 2012 at 20%	$176.77
Discounted to 2005 at 20%	$37.07
NPV at end 2012 at 15%	$724.86
Discounted to 2005 at 15%	$232.37
NPV at end 2012 at 10%	$1,648.50
Discounted to 2005 at 10%	$788.47

[41] It would generate a NPV 'surface' relating probabilities of success of each individual vaccine into the probabilities of returns scenarios and hence expected payoffs for all vaccine developers.

However:

	NPV in $ discounted to 2005 at:		
	10%	15%	20%
Replacement vaccine	341.43	118.08	31.30
Booster vaccine	850.92	322.55	112.93
Sum valued separately	1192.36	440.63	144.23
Prime-boost = sum valued together	788.47	232.37	37.07

This indicates that the NPV of each potential outcome – replace or boost – as calculated in all the tables above, is the wrong way to think about the investment decision facing each player. In the figures used in the report, the value of both outcomes happening together is always much lower than the value of their happening separately.

We see this also in Table 2, p14, of the report. At 20%, NPV in 2005 in Table 2 in the report is $41m for Prime-Boost, $35m for Replacement only and $125m for Booster only. Instead of getting $160m ($125m = $35m) NPV to split between both sets of investors, they have just $41m to split.[42] This is reflected in the IRR too. Combined IRR is 22% in this case, compared to separate IRRs of 25% and 32%. Booster vaccine developers are modeled by BCG as being particularly harmed by the joint outcome. Observe also that this $41m to split was based on the optimistic BCG scenario (though, still on the basis of poor prime-boost uptake in poor countries). When combined to generate a prime-boost scenario 3, the peak value of sales is also seen to be always lower than the combined peak value of the first two scenarios. In the base/expected-case, the peak value of scenario 1 is $450m, and the peak value of scenario 2 is $800m (see p6), but it is "about $1bn" when combined. This is a 20% 'loss' over the simple summing of the two values ($1,250m). This seemed even odder later once it was realized how the prime-boost figures seem to have been calculated.

Incidentally, there is no pessimistic prime-boost scenario in the table relating to optimistic and pessimistic scenarios. It is not clear why this should not be included. After all, if both vaccines are developed but in pessimistic territory, this will generate negative NPV.

Observe that the 22% combined IRR is based on a NPV of $41m. Under the cost section above, we showed how easy it was to create negative NPV with extra costs.

[42] In the 21 November BCG figures in the backup material, this is also seen with slightly different figures. Market NPV in 2005 at 20% is $39m for replacement, $108m for boost, and $30m for Prime-Boost, and Market IPR in 2005 dollars is 26%, 30% and 22% respectively. Again, the combined outcome 'punishes' both types of investors. And, again, this is based on best case outcome.

Capitalized extra R&D costs, where capitalized to *end* launch year 2013: This is the figure on the report's 2013 cost column (hence 8 not 7 years discounting)	Impact NPV in 2005 at 20%	Impact NPV in 2005 at 15%	Impact NPV in 2005 at 10%
(100)	(16.78)	(27.25)	(43.05)
(200)	(33.55)	(54.50)	(106.29)
(300)	(50.33)	(81.75)	(159.43)
(400)	(67.11)	(109.00)	(212.58)

This means that it is especially difficult to read into the returns for the two respective groups of investors (Replacement or Booster) in isolation from each other without figuring out their expectations about the chances of the joint outcome and their expectations of the true level of costs of development, and the risks posed to each 'type' of vaccine developer from the success or failure of the other 'type' in terms of expected payoff. Paradoxically, in the way BCG have calculated return to investors in the prime-boost scenario, the higher the chance of getting a prime-boost outcome, the worse off all investors are.

The follow-up BCG analysis indicates this again:

Assumptions	**Base 1**	**Base 2**	**Pessimistic 1**	**Pessimistic 2**	**Optimistic**
Adoption curve	Patterned on average Hepatitis B adoption curve (Source: WHO tracking 2005)				
Pricing	Model calculates profit maximizing price balancing adoption price thresholds with revenue potential within user-defined upper bounds				
Efficacy	Efficacy in children and adults				
General Population Coverage	US + non-EURO: high-risk populations only(1); EURO: High-income countries using BCG now(2) would adopt BCG replacement and booster vaccines for children under 14 + high-risk populations				
High-Income Market High-Risk Population Coverage	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide; lower penetration than base 1	Use in targeted populations limited to high-burden areas (e.g. NYC, TX, FL, CA)	Recommended for high-risk populations country wide	Recommended for high-risk populations country wide
High Income Markets Adoption % (High-Risk Pops)					
Healthcare workers	75%	60%	38%	38%	90%
LTC residents	75%	60%	38%	38%	90%
Homeless	40%	25%	20%	20%	60%

Correctional officers	75%	60%	38%	38%	90%
Prisoners	72%	60%	36%	36%	85%
Immigrants	25%	0%	0%	0%	40%
High-income markets	US + non-EURO: high-risk populations only; EURO: High-income countries using BCG now(1) would adopt BCG replacement vaccine for its birth cohort + high-risk populations				
COGS*	$3.5	$3.5	$3.5	$3.5	$3.5
Results					
IRR	25%	19%	13%	16%	29%
NPV ($M) @20%	$82	$(24)	$(113)	$(68)	$159

(1) High income countries: 34 countries including US, Australia, Canada, UK, Korea, Singapore and Japan.
(2) Includes Finland, France, Greece, Ireland and Portugal (Note that non-EURO countries that currently administer BCG to infants now and have higher rates of TB, such as Korea and Singapore, are assumed under these scenarios to only adopt for their high-risk populations, not for children.)

At 20%, Base 2 and both pessimistic scenarios are negative. In the report, negative Prime-Boost scenarios were not reported. This table yet again shows the importance of achieving high take-up in high-income high-risk markets of combined prime-boost vaccines.

5. SOME OTHER ISSUES

There are a range of other issues that would welcome some clarification:

1) It is not clear whether discount rates / rates of return used are real or nominal. The presumption in this assessment is that everything is nominal.
2) NPV/IRR has been calculated for different types of players on the basis of the whole product development chain (c.f. top p17). However, different players do not go the 'whole way', but account for different parts of the product development chain. It would be interesting to see NPV/IRR calculated over a combination of public/sponsor funded entities and biotechs and big pharma under realistic scenarios of their involvement along the product development chain. For example, it would be useful to 'peal off' portions of the chain and review NPV from that point forward (under the assumption that certain earlier costs are already sunk and hence a great deal of NPV of those costs is removed from the data). Timing of involvement matters when even one year of delay heavily destroys value.
3) For example, even if the overall size of NPV is negative, what is the NPV when having several candidates reaching phase III? We ideally need a measure of NPV going forward at each point in time. For example, such a calculation may reveal sufficient NPV exists if reaching phase III, even if not enough NPV exists when looking at the whole product development process (as done here and in the report). In which case we can obsess too early about the level of potential sales and size of incentive instruments needed to add to the pull of the market.
4) The report presumes that the average time to licensure is 2013-2015. A large chunk of that is phase III. One strategy to get costs down is to maximize the number of possibilities of products at phase II to draw off at phase III. This is not an angle the report or this assessment studies. For example, a sponsor funding structure that is willing to take as far as phase III, and maybe then just one phase III, may leave enough residual NPV to attract private players, and may also avoid the need to calculate a 'prize' value to offer well in advance.
5) It would also be useful to work out the value of specific R&D costs extrapolated back to 2005 (at 2005 values).
6) Positive NPV/IRR requires several events coming together. It would be useful to rank these events by probability of occurrence and some suitable time-frame.

6. CONCLUSION

BVGH argue that "By shining a spotlight on viable markets that otherwise might not have been noticed, BVGH can illuminate the potential return on industry investment, the target product profiles needed to capture those market opportunities, and the regulatory and distribution pathways that will bring safe and effective products to the developing world. Where the markets are insufficient to attract industry investment, or where there are significant challenges and hurdles to development or market entry, BVGH aims to point to areas where public-sector intervention can improve the likelihood that industry will invest." (p7).

An implicit assumption in this reasoning is that industry has not spotted a big opportunity, and that if only industry had better information it would spot this opportunity and invest. This is, incidentally, also a comment on the failure of equity investors (in the case of 'big pharma') and more specialist investors (such as biotechnology funds) in the case of biotechs, either because they are not being 'rational' investors, or because, though rational investors, they suffer from a free rider problem in analyzing information such that there is underinvestment since nobody has the incentive to gather the information to know about the investment opportunity. One would usually be skeptical of such arguments. First, industry, and especially the financial industry, puts a lot of resources in to trying to work out the value of markets. Second, it is hard to believe that stock market investors regularly fail to spot such profitable opportunities. If investors are not investing, this tells us something about their information that reports, and analysis like that above, are somehow not capturing.

Interestingly, one potential clue worth collecting would be stock market response to the release of such reports. To the extent that there is not so much as a financial ripple, this would suggest no fundamentally new piece of information has been released and no revision of estimated value of this investment opportunity.

This is not as nihilistic as it sounds. Such reports, for all their limitations, can help to find blockages and lead to suggestions of ways to boost the value of the market to make it more attractive. At the same time, it is crucial not to get too obsessed about these figures. Whatever use the report and the above analysis have, it is not to justify spending regardless of the more important issue of getting the science right.

Hopefully this assessment has indicated that the level of NPV measured is not a precise science, and one must be mindful of, and debate and explore, the range of possibilities, and, in sponsor funding decisions, to treat it as secondary to getting the science right.