TB Vaccine Scoping Study:
Evidence and Methodology

Part 1:

Epidemiology, cost effectiveness and socioeconomic issues

Demand, revenue, adoption, pricing and cost issues

Including:
Global market frameworks
Rate of adoption and mechanisms of uptake
Pricing, tiered pricing strategies: rich, middle income, and poor segments
Policy processes for driving faster and wider uptake
R&D and production cost issues

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Task Force on Economics and Product Profiles
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INTRODUCTION

The mission of the recently established Task Force on Economics and Product Profiles of the Stop TB Working Group on New Vaccines is to support the rapid development and deployment of improved TB vaccine(s) in the world by gaining an understanding of the associated economic issues and consequences, identifying the major economic incentives and constraints, and identifying mechanisms to increase these incentives and decrease these constraints.

The rationale of this project is to support a well-informed discussion by the Task Force of a range of issues critical to the rapid development and deployment of improved TB vaccine(s), to identify existing resources and gaps in knowledge, and to help the Task Force to focus its activities on areas where value can be added. The intent is to help the Task Force plan the construction of an integrated economic, cost effectiveness and epidemiological evidence base and formulate a research action plan over different horizons (immediate, two-year, five-year, and distant).

Section 1 reviews a range of evidence on the epidemiology of TB and efforts to set targets and measure progress. It reviews evidence about current control and vaccine (BCG) strategies, the socioeconomic impact of TB and the cost-effectiveness of new TB vaccines. On route it identifies the consequences of the well-know complexities of TB, including the role of latent infection, HIV and drug resistance (MDR-TB and XDR-TB). It identifies the now well-understood need to have all interventions, and not just vaccines, working harmoniously and effectively together. It casts an eye over some of the limitations identified when handling cost-effectiveness and socioeconomic evidence. It gathers a select bibliographic list.

Section 2 reviews the competing frameworks that have been developed for calculating the potential market for TB vaccines, both in terms of doses and revenues. It first compares the basic frameworks, before going through different vaccine scenarios. Many of the details are left to the original treatments.

One purpose of the Working Group is to 'identify the major economic incentives and constraints, and identifying mechanisms to increase these incentives and decrease these constraints'. This can be achieved by sponsor R&D and fund 'push' and 'pull' mechanisms of various sorts. One way to do this is to support and nurture the market. Section 3 reviews how the rate of adoption might be modeled and how mechanisms of uptake might be encouraged. Increasingly these days, interventions are competing for tight resources; increasingly new vaccines in particular risk competing against each other.

Section 4 is largely an extension from Section 3. An important market-building technique is the use of tiered/Ramsey pricing to increase the present discounted value of a global market – while serving the poor. This section also overlaps with issues discussed in Section 1, since the ability for tiered pricing to work is a function of the incentives for different markets to adopt solutions, e.g. replacement, booster and prime-boost vaccines, given current prevention and treatment strategies. Some review is done of how 'catch-up' has been treated in the current market and investment case models. A lot of

manipulations of market data are done to explore whether certain markets (middle income, private sector, India, China, etc.) and certain strategies for encouraging use of affordable vaccine(s) might help support vaccine R&D. The conclusion is that this may be so and it is worth further exploration. Recent 'willingness to pay' analysis is questioned.

Section 5 explores policy making processes. One question is whether research on policy decision-making processes can improve decision making at the country and regional level, help vaccine launch efforts, and improve the quality of marketing frameworks and investment case analysis. Another is whether using empirical evidence from past vaccine introductions can give launch and investment case analysis more 'predictive power' in the case of improved TB vaccine(s). This section does a basic review of the vaccination and health policy literature and political science and public policy literature. A select bibliography is presented and the possible next steps discussed.

One way to identify 'mechanisms to increase incentives and decrease constraints' is to deal with costs at many levels. If one can be more efficient with costs and achieve more affordable outcomes, by definition markets can be enhanced and markets made more appealing to sponsors and investors. Section 6 reviews a range of cost issues. It concludes that we still have a very poor grasp of the probable costs needed to achieve certain probabilistic vaccine goals. Better portfolio analysis is clearly needed. It shows that lots of other cost issues need to be better thought through, including relating to Cost of Goods Sold, booster vaccine production costs, biomarkers, trial sites, licensure, plant size and production capacity.

In a follow-on Part 2, 'lessons' for TB – both positive and negative – are drawn from the launch of five other vaccines – Hepatitis B, Haemophilus influenzae type B (Hib), rotavirus, pneumococcal, and human papillomavirus (HPV). Many other previous vaccine launches could be added to this list, but these happened to be the ones the author had spent more time analysing. The intention is to further explore ways to improve thinking about market and launch issues for TB vaccines – by imbedding the analysis of TB vaccine launch in a comparative framework.

The report's author would like to especially thank Sarah Miller (HM Treasury) and Senthuran Bhuvanendra (Department of Economics, University of Oxford) for their erudite and perceptive contributions, especially towards Sections 1 and 5, and for their encouragement and support throughout the preparation of this report.

1. REVIEW OF EVIDENCE ON EPIDEMIOLOGY, SOCIOECONOMIC IMPACT OF TB AND COST-EFFECTIVENESS OF NEW TB VACCINES

1.1. Introduction

Despite a targeted campaign to increase treatment and control of *M. tuberculosis* (TB), and the most widely used vaccine in the world, Bacillus Calmette-Guerin (BCG), TB continues to be a major cause of morbidity and mortality. An extremely high level of latent TB infection (affecting around one-third of the world's population), and the relatively recent problems of coinfection with HIV/AIDS and increasing multi-drug resistance to treatment, have led to the high incidence of active tuberculosis. TB is particularly burdensome in developing countries in Asia and Africa, and is often regarded as a "disease of poverty", affecting resource-poor countries disproportionately.[1,2]

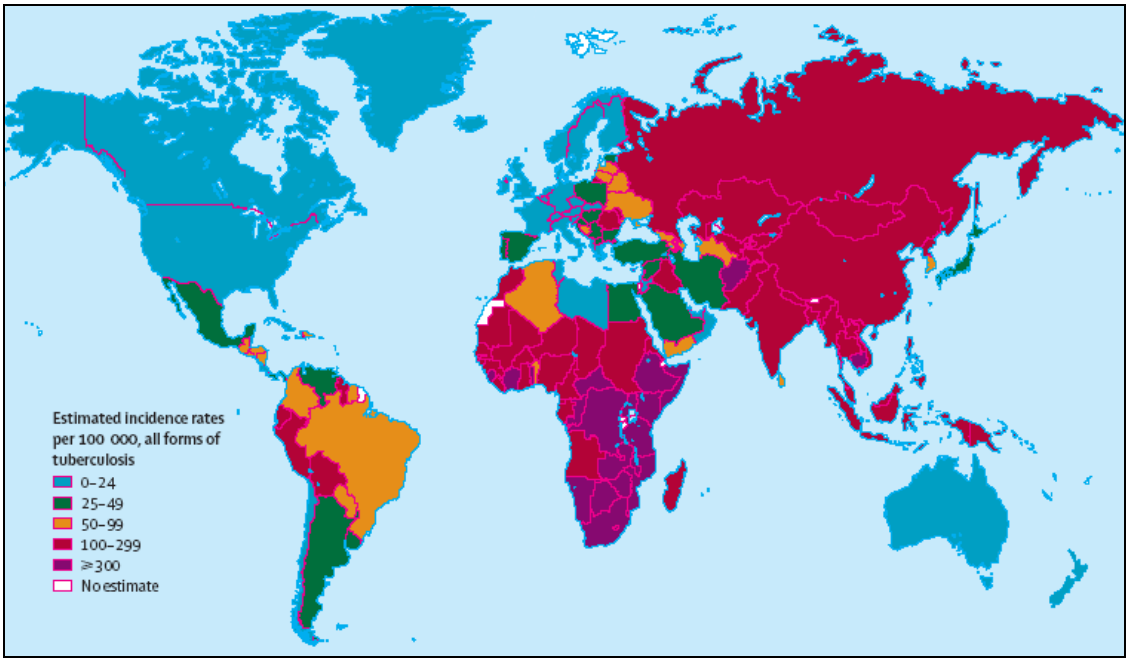

Figure 1.1: Distribution of tuberculosis in the world in 2003. Estimated incidence rates per 100,000, all forms of TB.[3,4]

[1] WHO Factsheet, April 2008 http://www.who.int/tb/publications/2008/factsheet_april08.pdf.
[2] Hussey G, T Hawkridge and W Hanekom "Childhood tuberculosis: old and new vaccines" *Paediatric Respiratory Reviews* (2007) 8, 148-154.
[3] Taken from Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. JAMA 2005; 293: 2767–75.
[4] A note on diagrams: This report was originally prepared for only the Working Party on New TB Vaccines. In the interests of open discussion, the report has been placed on the net with the caveat that diagrams, though in the public domain, are the property of others (and original authorship is indicated). Should any group or author wish a diagram be removed, please consult the lead author and he will be happy to oblige.

Recent data suggests 9.2 million new cases of TB in 2007 and 1.6 million deaths (137 cases/100,000 population, 25 deaths per 100,000 population), 31% of which occurred in the African Region, and 55% of which occurred in South-East Asia and the Pacific.[5]

During the 1990s case rates rose globally, and are now stable or falling. This masks some notable regional differences. In Europe case rates rose 40% during the 1990s, and are now falling slowly; mainly this was the consequence of the collapse of the Soviet Union. In Africa case rates rose over 200%, and are now stabilizing; this is largely the consequences of the rise of HIV in Africa.

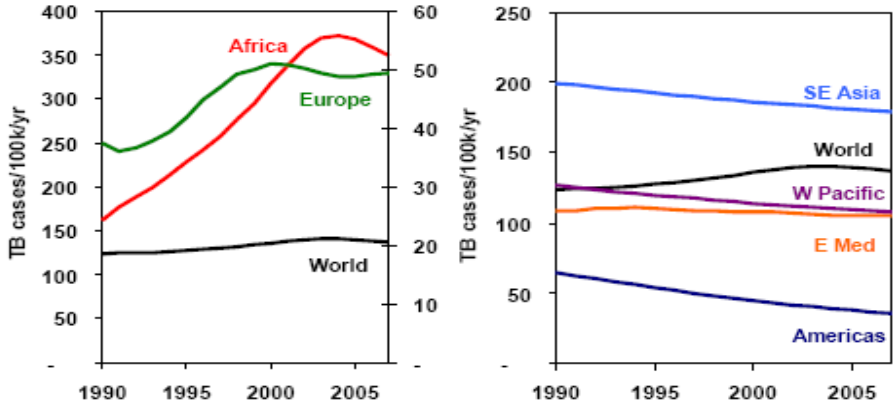

Figure 1.2: After peaking in Africa and Europe, case rates are now stable or falling.[6]

The impact of HIV is highlighted in the diagram below, with a sharp difference between trends in incidence rates between Africa (high HIV) and Africa (low HIV)

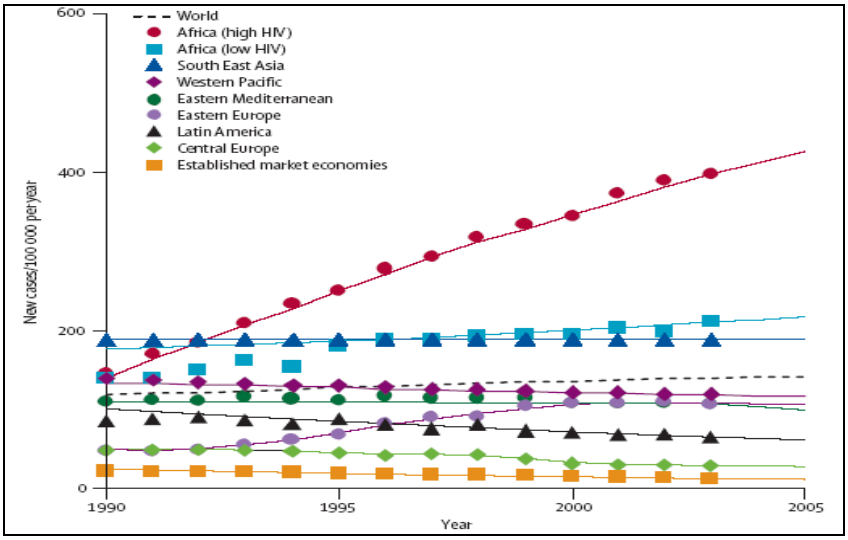

Figure 1.3: Trajectories of tuberculosis epidemic for nine epidemiologically different regions of the world. Points mark trends in estimated incidence rates.[7]

[5]Global tuberculosis control: surveillance, planning, financing: WHO report 2008. (WHO/HTM/TB/2008.393). Page 19.

[6] Taken from presentation of Dye, C. in Oxford in November 2008.

The following shows estimates of the percentage of children that die from lower acute respiratory infections (ARI) by country in 2000.

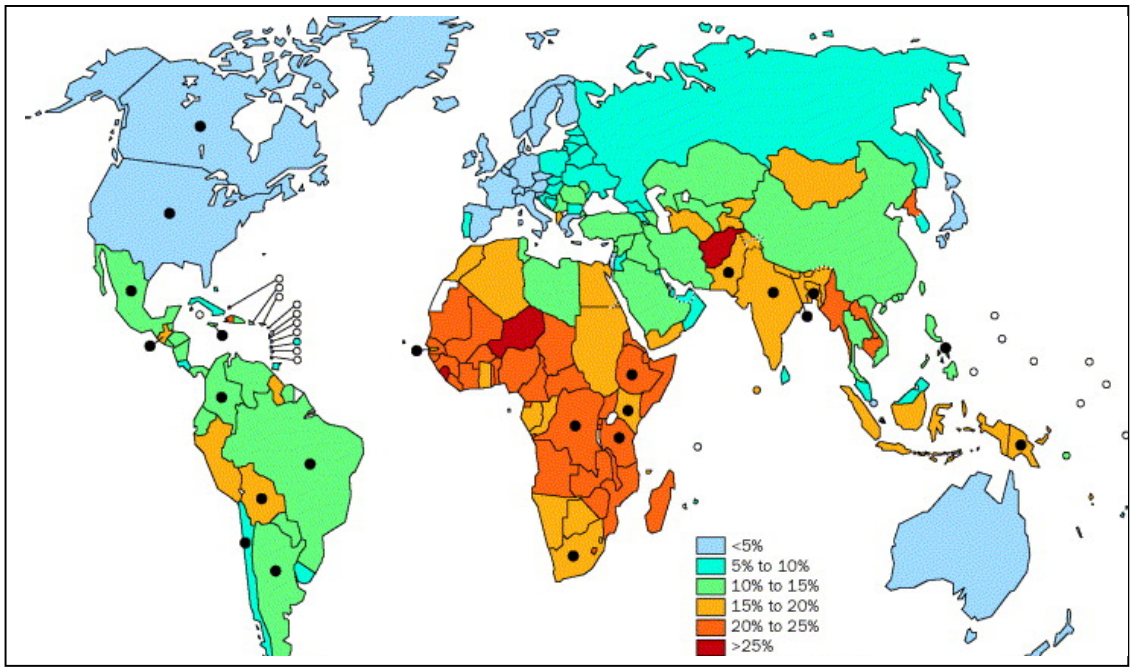

Figure 1.4: Estimates of the percentage of children that die from lower ARI, by country in 2000. The last category includes values up to 26·0%.[8]

Current targets for TB control centre around expanding Directly Observed Treatment Strategy (DOTS) and on achieving reductions in TB incidence, prevalence and death rates. The Millennium Development Goals (MDGs) set out the impact target of halting and reversing TB incidence by 2015 – and the WHO's Stop TB Strategy (launched in 2006) has set further targets:

- By 2005 – At least 70% of people with sputum smear-positive TB will be diagnosed (i.e. under the DOTS strategy), and at least 85% cured. These are targets set by the World Health Assembly of WHO (first set in 1991).
- By 2015 – The global burden of TB (per capita prevalence and death rates) will be reduced by 50% relative to 1990 levels.
- By 2050 – The global incidence of active TB will be less than 1 case per million population per year.[9,10] Observe that as an epidemiological measure of success,

[7] Points mark trends in estimated incidence rates, derived from case notifications for 1990–2003. Groupings of countries based on WHO regions. High HIV=incidence ≥ 4% in adults aged 15–49 years in 2003; low HIV= <4%. Established market economies=all 30 OECD (Organisation for Economic Cooperation and Development) countries, except Mexico, Slovakia, and Turkey, plus Singapore. Countries in each region listed in full at WHO. Global tuberculosis control: surveillance, planning, financing. Geneva: World Health Organization, 2006: 242. Adapted from Dye C "The global epidemiology of tuberculosis" *Lancet* (2006) 267, 938-940 (original with permission of the American Medical Association).

[8] Taken from Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C.. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003 May 12;163(9):1009-21.

incidence usually changes more slowly than prevalence or deaths in response to control efforts.[11]

The principal WHO measure of case detection is the rate of case detection for new smear-positive cases in DOTS programmes.

1.2. Measurement of progress

Several of these ambitious targets have not yet been achieved[12] in spite of the existence of effective interventions to diagnose tuberculosis and the existence of strongly recommended and successful tuberculosis control strategies. There is also significant inconsistency across countries in the delivery and support of control strategies, as Frothingham et al comment: "Despite attempts to standardize TB control strategies, there remains wide variation in the selection and implementation of control strategies within and among countries."[13] National estimates suggest that 77 countries met the 70% target for case detection rates by the end of 2006.[14] Although some countries have indeed met the target according to this data, progress has been much slower in the African, Eastern Mediterranean and European regions. Nevertheless, the fall in incidence has been slow and projected incidence will still be 100 times the elimination threshold in 2050:

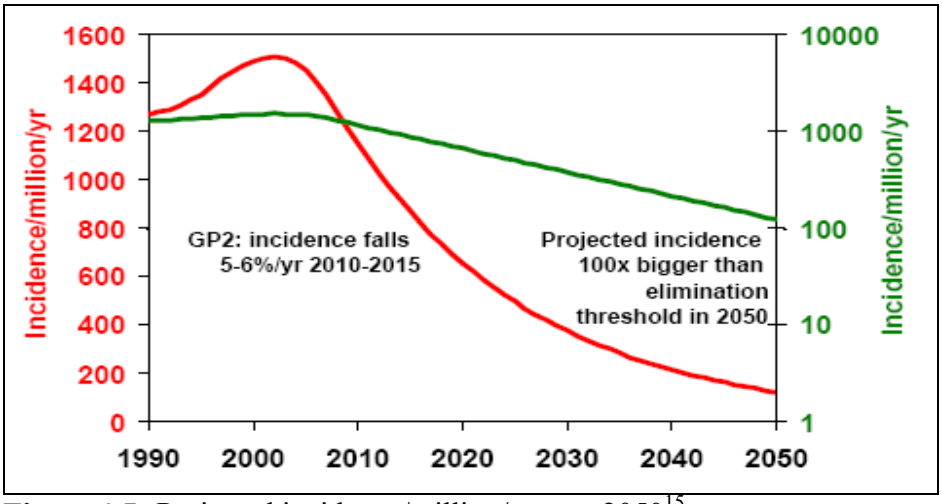

Figure 1.5: Projected incidence/million/year to 2050[15]

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[9] The Global Plan to Stop TB, 2006–2015. Geneva, Stop TB Partnership and World Health Organization, 2006 (WHO/HTM/ STB/2006.35).

[10] Global tuberculosis control: surveillance, planning, financing : WHO report 2008. (WHO/HTM/TB/2008.393). Page 18.

[11] C Dye, Tuberculosis 2000–2010: control, but not elimination, *Int J Tuberc Lung Dis* **4** (2000), pp. S146–S152.

[12] WHO Factsheet, April 2008 http://www.who.int/tb/publications/2008/factsheet_april08.pdf.

[13] Frothingham R, J E Stout, C D Hamilton "Current issues in global tuberculosis control" *International Journal of Infectious Diseases* (2005) 9, 297-311.

[14] Global tuberculosis control : surveillance, planning, financing : WHO report 2008. (WHO/HTM/TB/2008.393). Page 27.

[15] Taken from Dye. C. presentation, Oxford November 2008.

The variation in DOTS delivery has serious implications. As the WHO 2008 report notes, this is a matter of concern – "Variation in treatment outcomes among regions raises important questions about the quality of treatment, the quality of the data and how quickly these will improve in future."[16] There are also concerns over the extent to which DOTS can continue to deal with TB, which have been voiced across the scientific and academic community. As noted in Dye (2003),[17] rates of improvement have to some extent been limited by the quality of health systems in countries:

> "The principal difficulty is that DOTS programmes have, up to now, mostly recruited patients who would have been detected and treated anyway in the public health system…. DOTS has failed in some countries to reach deeply into the private sector, and in others to provide access to patients living in areas with inadequate health services."

More broadly speaking, has the momentum slowed? Bloom et al comment that the task of reaching populations inevitably gets harder after the first waves of an intervention. This is the case whether the intervention is preventative such as a vaccine, or a treatment or control strategy. The implications for new tuberculosis vaccines are complex. DOTS expansion could complement a new vaccine, acting as a bridge – or identifying gaps and difficulties in access to populations. However the links between prevention and control strategies can be complicated. It is important for existing strategies not to 'crowd out' new strategies for dealing with a disease. Interventions may have a common aim in dealing with tuberculosis disease, but slightly different intermediate goals or success metrics; and may be aimed at people in different demographic groups. Any new vaccination strategy would need to operate in parallel with existing treatment and control strategies, so it is crucial that any new strategy considers benefits and limitations of any integration and implications for infrastructure and costs.

There are also limitations in the figures associated with the targets, for example case detection, which relies on an estimation of the total number of new smear positive cases to provide a denominator. It is always risky to use big numbers to illustrate progress for complex problems. It is important to have a clear picture of the disease burden and detection. In fact in order to achieve the targets outlined above, the first step can be seen as the effective detection and surveillance of disease. This in itself is a huge task. A recent publication by Dye et al re-emphasizes the difficulties of tuberculosis surveillance, which (like many diseases) is hampered by poor quality data and potential bias in incidence estimates. Dye considers the advantages and disadvantages of various approaches to understanding a full picture of tuberculosis incidence, prevalence and mortality in a country:[18]

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[16] Global tuberculosis control : surveillance, planning, financing : WHO report 2008.(WHO/HTM/TB/2008.393). Page 31.

[17] Dye C, C J Watt, D M Bleed, B G Williams "What is the limit to case detection under the DOTS strategy for tuberculosis control?" *Tuberculosis* (2003) 83: 35-43.

[18] Dye C, A Bassili, AL Bierrenbach, JF Broekmans, VK Chadha, P Glaziou et al "Measuring tuberculosis burden, trends, and the impact of control programmes" *The Lancet Infectious Diseases* 8(4): 233-243.

	Advantage	Disadvantage
Disease incidence	Measure of denominator of WHO case detection rate; MDG indicator	Falls slowly after reductions in transmission
From prospective cohort studies	Direct measure of incidence; more feasible for cohorts of individuals at high risk of developing tuberculosis (eg, people infected with HIV)	Costly; logistically complex; requires two or more surveys with large cohort and carefully judged survey period and follow-up of individual patients
From case notifications	Absolute incidence can be obtained from routine case reports, most accurately if case detection is estimated to be complete; trends can be judged from series of routine case reports if measured consistently; every country has a surveillance system, reporting annually or sub-annually, which should become the standard method for assessing tuberculosis incidence and its trend	Case detection is low in many high-burden countries (underestimates incidence), and may vary through time (inaccurate trends) because of changes in case identification
Disease prevalence	Component due to duration changes relatively quickly in response to drug treatment; MDG indicator	Component due to incidence falls slowly after reductions in transmission
From population-based surveys	Unbiased measure of bacteriologically confirmed disease; should change quickly in response to drug treatment; surveys useful if routine surveillance data are poor; serve as a platform for related investigations (eg, risk factors for tuberculosis, and interactions between patients and health system)	Costly; large sample size needed; logistically complex (especially with radiography); cannot easily be measured annually or with a precision better than ±25%; surveys usually exclude children and extrapulmonary disease; without bacteriological confirmation, diagnosis is unreliable; does not lead to a precise estimate of tuberculosis incidence (denominator of WHO case detection rate) because duration cannot be measured accurately
Tuberculosis mortality	Direct measure of tuberculosis burden accounting for a high proportion of years of life lost; case fatality falls quickly in a new drug treatment programme; MDG indicator	Component due to incidence falls slowly after reductions in transmission; case fatality may already be low in low-incidence countries and not easily reduced further
From prospective cohort studies	Direct count of deaths in sample cohort	As for measuring incidence, but more costly; not generally feasible
From observations on patient cohorts	Direct count of number of patients dying; approaching total deaths if case notifications complete and all patients monitored throughout treatment	Deaths observed are those in cohort only, not in the population at large, and not beyond the period of cohort follow-up; deaths among defaulters and transfers usually unknown; tuberculosis not always the cause of death for patients on tuberculosis treatment
From product of incidence and case-fatality rate	Simple and widely applicable	Relies on accurate measures of incidence (above) and case-fatality rate; case fatality measurable in observed DOTS cohorts, but not among patients treated elsewhere or untreated
From routine death reports (vital registration)	Direct measure of tuberculosis deaths and trends; can be reported annually or sub-annually; the ultimate method for evaluating tuberculosis deaths nationally	Vital registration does not yet exist in most high-burden countries, notably in Africa and Asia; sensitivity and specificity mostly untested
From verbal autopsy in conjunction with sample vital registration	Review of registered deaths can improve accuracy of cause of death statistics	Sensitivity and specificity of verbal autopsy not fully evaluated; where no vital registration system exists, laborious to compile deaths from a rare disease, and requires large sample sizes
Infection prevalence	Risk of infection changes relatively quickly in response to treatment of active tuberculosis (but prevalence, from which risk is calculated, changes slowly)	Measures infection, not disease burden; not an MDG indicator
From population-based surveys	Tuberculin surveys relatively cheap and logistically straightforward; can be used to assess time trends and geographical variation in risk of infection; IGRAs have high specificity, and might be used to calibrate tuberculin	Recommended procedures must be followed rigorously to avoid pitfalls, including digit preference; low specificity means that results may be hard to interpret if infection rates are low and if BCG coverage or exposure to environmental mycobacteria are high; measures average risk of infection over past 5–10 years; IGRAs not yet fully evaluated, relatively costly and require blood by venepuncture; Styblo's[15] 1:50 rule for indirectly estimating disease incidence no longer generally applicable

IGRAs=interferon-γ release assays. MDG=Millennium Development Goal.

Table 1.1: The strengths and weaknesses of various indicators and measures of tuberculosis burden and trends[19]

[19] Taken from Dye C, A Bassili, AL Bierrenbach, JF Broekmans, VK Chadha, P Glaziou et al "Measuring tuberculosis burden, trends, and the impact of control programmes" *The Lancet Infectious Diseases* 8(4): 233-243.

It is important to fully understand the burden of disease, both in order to achieve targets and also to inform any further analysis (whether through an economic evaluation or a different approach). The need for good incidence data is really a key part of building robust analysis of cost and effectiveness of any new or existing treatment approach.

1.3. The complexities of TB – latent infection, HIV and MDR- and XDR-TB

Tuberculosis is a complicated disease and not fully understood, particularly the development of the disease beyond the normal human response. Whilst several risk factors for TB have been identified, their role in its pathogenesis remains unclear.[20] In particular, it is largely unclear why infection mostly remains latent.[21,22] Less than 10% of those infected with TB develop active disease (around 5-15% in HIV-negative individuals[23]) and it is not entirely clear what prompts active disease. In Sierra's analysis of lessons learned from the BCG vaccine[24] he comments that:

> "Protection against a very complex disease has been attempted with a very incomplete understanding of the pathology and the intervening elements."

The complexity of TB implicates detection and treatment of the disease. The difficulties of diagnosis, treatment adherence, multidrug resistance and the HIV pandemic are all discussed widely in the existing literature.

Much of the increase in global tuberculosis incidence since 1980 is attributed to the spread of HIV in Africa.[25,26,27] In 2006, Dye estimated that about 40% of adults with TB aged 15-49 years are co-infected with HIV.[28] It has also been widely suggested that the HIV epidemic will lead to continuous increase in the incidence of TB in developing countries. However, it is currently unclear what the effect of co-infection with HIV will

[20] Nagelkerke NJD, SJ deVlas, Y Mahendradhata, THM Ottenhoff and M Borgdorff "The search for a tuberculosis vaccine: an elusive quest?" *Tuberculosis* (2006) 86, 41-46.
[21] G.R. Stewart, B.D. Robertson and D.B. Young, Tuberculosis: a problem with persistence, *Nat Rev Microbiol* **1** (2003), pp. 97–105.
[22] J.M. Tufariello, J. Chan and J.L. Flynn, Latent tuberculosis: mechanisms of host and bacillus that contribute to persistent infection, *Lancet Infect Dis* **3** (2003), pp. 578–590.
[23] Nagelkerke NJD, SJ deVlas, Y Mahendradhata, THM Ottenhoff and M Borgdorff "The search for a tuberculosis vaccine: an elusive quest?" *Tuberculosis* (2006) 86, 41-46.
[24] Sierra VG "Is a new tuberculosis vaccine necessary and feasible? A Cuban opinion" *Tuberculosis* (2006) 86, 169-178.
[25] EL Corbett, CJ Watt and N Walker et al., The growing burden of tuberculosis: global trends and interactions with the HIV epidemic, Arch Intern Med 163 (2003), pp. 1009–1021.
[26] WHO, Global tuberculosis control: surveillance, planning, financing, World Health Organization, Geneva (2006), p. 242.
[27] C Dye, CJ Watt, DM Bleed, SM Hosseini and MC Raviglione, Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally, JAMA 293 (2005), pp. 2767–2775.
[28] Dye C "The global epidemiology of tuberculosis" *Lancet* (2006) 267, 938-940.

be on TB vaccine effectiveness. It can also be difficult to understand the effects of these various issues within TB control compared to any success in case detection and control strategies – as noted by the WHO:[29]

> "It has been difficult to disentangle the effect of better programme performance leading to better case-finding, and the impact of the HIV epidemic, on increases in case notifications."

The latent stage of TB infection (LTBI) is without symptoms and may last for many years[30] and can be detected, generally through a positive reaction to a tuberculosis skin test (TST) and can be treated to decrease the chance that TB infection will progress to active TB. The interpretation of TST can be complicated if a person has had the BCG vaccine. Therefore:[31]

> "Societies have tended to choose either the BCG vaccination or the strategy of TST and treatment of LTBI."

Treating latent tuberculosis infection is most relevant in populations where repeated exposure to live TB is not of great concern. Although it is possible to have a dual strategy of BCG vaccination at birth and selective use of screening and treatment of LTBI in high risk populations, there is evidence that the test is also confounded by HIV and other forms of mycobacteria and that the skin test results can be misleading even for those without HIV or other complications.[32]

For this literature review, the limitations, costs and benefits of the different diagnostics strategies have not been considered in detail. However it is clear that this is an important part of any analysis – whether directly considered in cost-effectiveness through coverage and cost variables or whether examined with respect to different country and/or cohort characteristics in a discussion section.

[29] Global tuberculosis control : surveillance, planning, financing : WHO report 2008. (WHO/HTM/TB/2008.393). Page 28.
[30] Dietrich J, C Vingsbo Lundberg, P Andersen "TB Vaccine Strategies – What is needed to solve a complex problem?" *Tuberculosis* (2006) 86, 163-168.
[31] Frothingham R, JE Stout and CD Hamilton "Current issues in global tuberculosis control" *International Journal of Infectious Disease* (2005) 9, 297-311.
[32] Frothingham R, J E stout, C D Hamilton "Current issues in global tuberculosis control" *International Journal of Infectious Diseases* (2005) 9, 297-311.

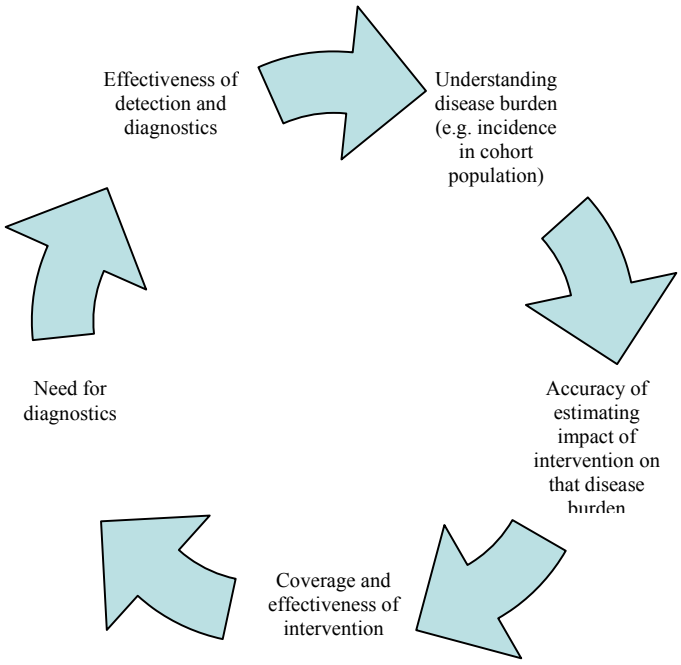

Figure 1.6: Interdependencies

1.4. Existing vaccination strategies – the BCG vaccine

The need for a new TB vaccine is widely recognised[33,34,35] and would be expected to significantly improve control of TB. This need has been formalised through international commitments to the development of a new TB vaccine as a priority, and the Bill and Melinda Gates Foundation alongside other international bodies including the European Union and the National Institutes of Health have demonstrated their support of this objective. The Aeras Global TB Vaccine Foundation was set up "to ensure the development of safe and effective vaccine regimens that will prevent TB in all age groups and will be affordable, available and adopted worldwide."[36]

The current vaccine for TB, BCG, is the most widely used vaccine in the world. However, it provides only partial protection of the disease and has failed to control TB. This fact is indisputable, but there is a no consensus as to the effectiveness of BCG vaccination strategies. In fact, the protective effect of BCG against tuberculosis estimated in randomised controlled trials and observational studies ranges from negative to close to

[33] Dietrich J, C Vingsbo Lundberg, P Andersen "TB Vaccine Strategies – What is needed to solve a complex problem?" *Tuberculosis* (2006) 86, 163-168.
[34] Hussey G, T Hawkridge and W Hanekom "Childhood tuberculosis: old and new vaccines" *Paediatric Respiratory Reviews* (2007) 8, 148-154.
[35] Girard M, U Fruth and M-P Kieny "A review of vaccine research and development: Tuberculosis" *Vaccine* (2005) 23, 5725-5731.
[36] Aeras Annual Report 2008, www.aeras.org/newscenter/downloads/pubs/Aeras%202008%20Annual%20Report_Final_9.29.08.pdf.

100%,[37] although many agree that BCG is ineffective in providing complete protection for TB – "BCG is at best credited with a 50% overall protective efficacy."[38] Meta-analysis of the results of a large number of trials estimate an average efficacy of 50%.[39,40] There is also a range of opinion over how long protection lasts.[41,42] Some even suggest that there is no obvious benefit in having large-scale BCG vaccine strategies, referring to countries such as The Netherlands and the USA that did not introduce these strategies, and that have managed to avoid (relatively speaking) high disease burden.[43] However, there are several factors which may contribute to the relative ineffectiveness of a vaccination strategy for TB – which may differ in developed countries. Later in this review, the socio- cultural factors associated with TB are discussed in more detail.

It is generally accepted that BCG has proven to be effective in protecting against TB meningitis and miliary TB in children.[44] In addition, it has been suggested that BCG vaccines may have beneficial effects in addition to protection against tuberculosis in a similar way to the non-specific survival benefit of measles vaccines. This is particularly the case for children in resource-poor countries. Results have shown that BCG has more beneficial effects for girls[45] and young children. Analysis notably includes studies in West Africa, some of which also suggested that the positive effect was not mitigated by the presence of HIV infection in children.[46,47] The overall effect of BCG on morbidity and mortality remains unclear, and indeed there are strong counter arguments to suggest natural bias and the role of other factors in assessing those vaccinated and non-vaccinated individuals.

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[37] Rodrigues L, V Diwan and J G Wheeler "Protective Effect of BCG against Tuberculosis Meningitis and Miliary Tuberculosis: A Meta-Analysis" *International Journal of Epidemiology* 1993, 22, 1154-1158.

[38] Girard M P, U Frith and M Kieny "A review of vaccine research and development: Tuberculosis" *Vaccine* (2005) 23, 5725-5731.

[39] Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. JAMA 1994;271:698–702.

[40] Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study. JAMA 2004;291:2086–91.

[41] Girard M P, et al. ibid.

[42] Sierra V G "Is a new tuberculosis vaccine necessary and feasible? A Cuban opinion" *Tuberculosis* (2006) 86, 169-178.

[43] Nagelkerke N, S Vlas, Y Mahendradhata, T Ottenhoff and M Borgdorff "The search for a tuberculosis vaccine: An elusive quest?" *Tuberculosis* (2006) 86, 41-46.

[44] Bourdin Trunz B, Fine P E, Dye C. "Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost effectiveness" Lancet 2006; 367: 1173-1180.

[45] Veirum JE, M Sodemann, S Biai, M Jakobsen, ML Garly, K Hedegaard et al "Routine vaccinations associated with divergent effects on female and male mortality at the paediatric ward in Bissau, Guinea-Bissau." *Vaccine* (2005) 23 (9) 1197-1204.

[46] Kristensen I, P Aaby and H Jensen "Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa" *British Medical Journal* (2000) 321, 1435.

[47] Garly ML, CL Martins, C Bale, MA Balde, KL Hedegaard, P Gustafson et al "BCG scar and positive tuberculin reaction associated with reduced child mortality in West-Africa. A non-specific beneficial effect of BCG?" *Vaccine* (2005) 23, 3991-98.

As discussed in Roth et al (2006),[48] the evidence that BCG has non-targeted beneficial effects should be incorporated into research and the development of future vaccines. It will be important to evaluate new vaccine candidates against BCG and to analyse the impact of new vaccines on survival and morbidity. However, as Fine comments, these issues are multi-faceted and should be investigated carefully, ideally through studies which avoid selection bias.[49]

This literature should be taken into consideration both in assessing cost-effectiveness and in assessing implications for policy. When assessing a new vaccine strategy, it is important to consider the interrelation with BCG and both direct and indirect effects of a new vaccine candidate.

1.5. New vaccination strategies and the health impact of new TB vaccines

The debate over the best strategy to improve immunisation against tuberculosis has been discussed in detail.[50,51,52,53] In general there are two main approaches that are being given substantial consideration – new pre- or post-exposure vaccines, or a combination of vaccines and boost strategies. Building on the existing vaccination strategy, this could mean an improvement to the BCG pre-exposure vaccine, or a supplemental vaccine designed to be given as a 'booster' vaccine at a certain age after a child has received BCG. Alternatively, it may be sensible to focus on vaccinating post-exposure to TB.

Ziv et al (2004), extending the work of Lietman and Blower,[54,55] analyze the effectiveness of a pre- or postexposure vaccination strategy in developing countries with high incidence and prevalence of disease. At first, postexposure vaccines have a greater impact in reducing the number of cases of disease. However, this effectiveness declines over time (even with continuous vaccination campaigns) while the effectiveness of preexposure vaccines rises. Preexposure vaccination strategies are ultimately nearly twice as effective compared to postexposure vaccines in reducing the number of new infections. Over a 20-30 year horizon, the cumulative TB cases prevented under post- or preexposure vaccination campaigns would be roughly equal. However, even with a widely deployed and highly effective vaccine, whether pre- or postexposure, the number of cases of TB in high-incidence countries is likely to remain high:

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[48] Roth A E, LG Stensballe, ML Garly and P Aaby "Beneficial non-targeted effects of BCG – Ethical implications for the coming introduction of new TB vaccines" *Tuberculosis* (2006) 86, 397-403.
[49] Fine P "Commentary: an unexpected finding that needs confirmation or rejection" *British Medical Journal* (2000) 321, 7274.
[50] Girard M P, U Frith and M Kieny "A review of vaccine research and development: Tuberculosis" *Vaccine* (2005) 23, 5725-5731.
[51] Frothingham R, J E stout and C D Hamilton "Current issues in global tuberculosis control" *International Journal of Infectious Diseases* (2005) 9, 297-311.
[52] Gupta UD, VM Katoch and D N McMurray "Current status of TB vaccines" *Vaccine* (2007) 25, 3742-3741.
[53] Hussey G, T Hawkridge and W Hanekom "Childhood tuberculosis: old and new vaccines" *Paediatric Respiratory Reviews* (2007) 8, 148-154.
[54]Lietman T, Blower SM. The potential impact of tuberculosis vaccines as epidemic control agents. Clin Infect Dis. 2000;30:S316–22.
[55] Lietman T, Blower SM. Tuberculosis vaccines. Science.1999;286:1300–1.

"Even widely deployed and highly effective (50%–90% efficacy) pre- or postexposure vaccines would only be able to reduce the number of TB cases by one third."

In the case of *M. tuberculosis*, unlike for example the pathogens for measles and smallpox, a 70%-80% reduced infection rate does not translate into 70%-80% reduced disease rate. Incidence of TB disease is driven by two sources: susceptible persons who become infected and quickly progress to disease, and latently infected persons who slowly progress to disease often with a long time lag. Preexposure vaccines, given to uninfected individual, act mainly by reducing the first of these routes, but with little impact on the second. Postexposure vaccines, given to latently infected persons, act mainly on the second route with little impact on the first. This leads to a strong case for developing vaccines that function both as a pre- and a post-exposure vaccines. Indeed Ziv et al argue:[56]

"We suggest that to achieve global control of TB, developing a single TB vaccine that functions as both a pre- and a postexposure vaccine is necessary."

Two flow-diagrams show the basic pathogenesis of postexposure and preexpossure TB (states and processes relating to a vaccine are shown in red).[57] Efficacy of postexposure vaccines is defined by the reduction in the rate of latently infected individuals progressing to disease. Efficacy of preexposure comes via three different mechanisms of action: by reducing the risk for infection in the uninfected; by allowing infection but reducing the probability of fast progression to disease; and by allowing infection but reducing the rate of progression of latent infection to clinical disease.

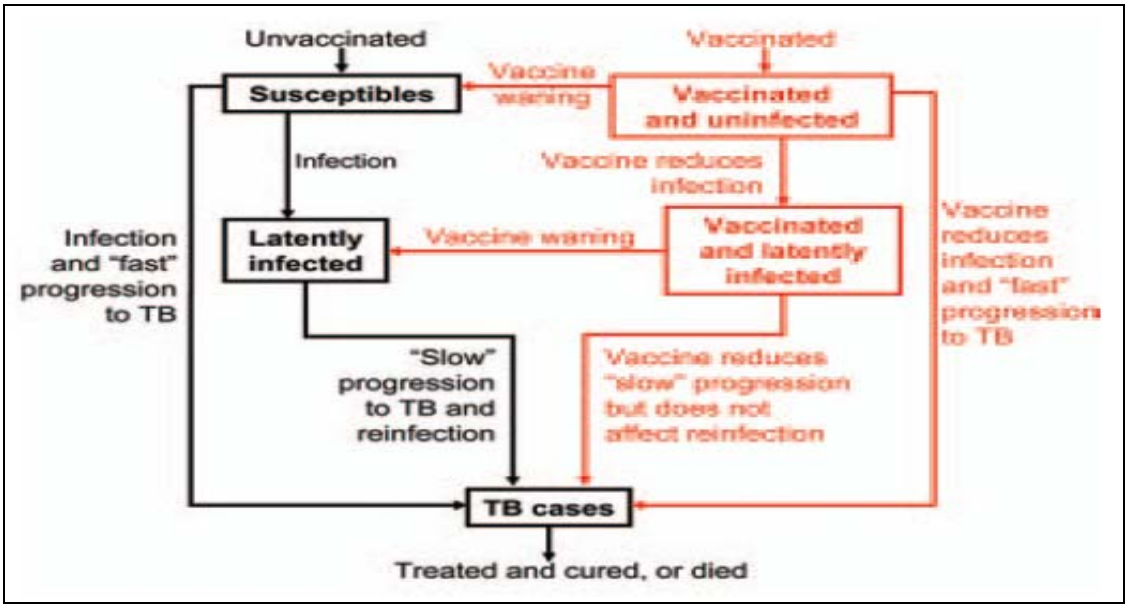

Figure 1.7: Flow diagram for postexposure TB vaccine

[56] Ziv E, Daley CL, Blower S. Potential public health impact of new tuberculosis vaccines. Emerg Infect Dis [serial on the Internet]. 2004 Sep [*date cited*]. Available from: http://www.cdc.gov/ncidod/EID/vol10no9/03-0921.htm.

[57] All the following diagrams are from Zif et al. Equations in Appendix of Ziv et al.

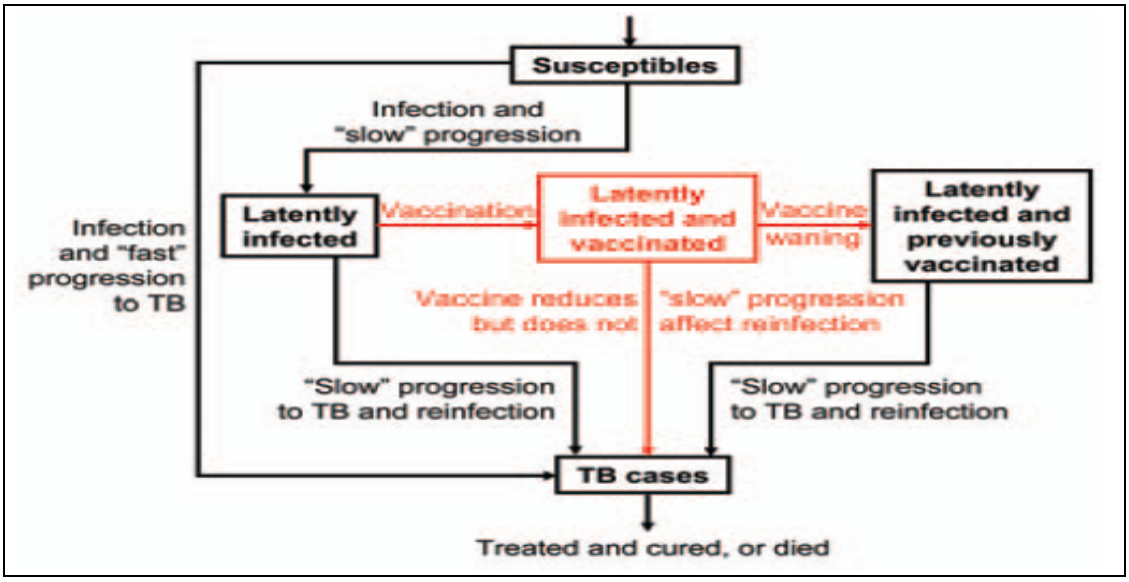

Figure 1.8: Flow diagram for preexposure TB vaccine

Zif et al simulate these frameworks under various assumptions about incidence, treatment rates, vaccine efficacy, vaccine coverage and duration[58] using Monte Carlo simulation (1000 simulated vaccines) to generate cumulative percentages of infections and TB cases prevented at horizons up to 40 years:

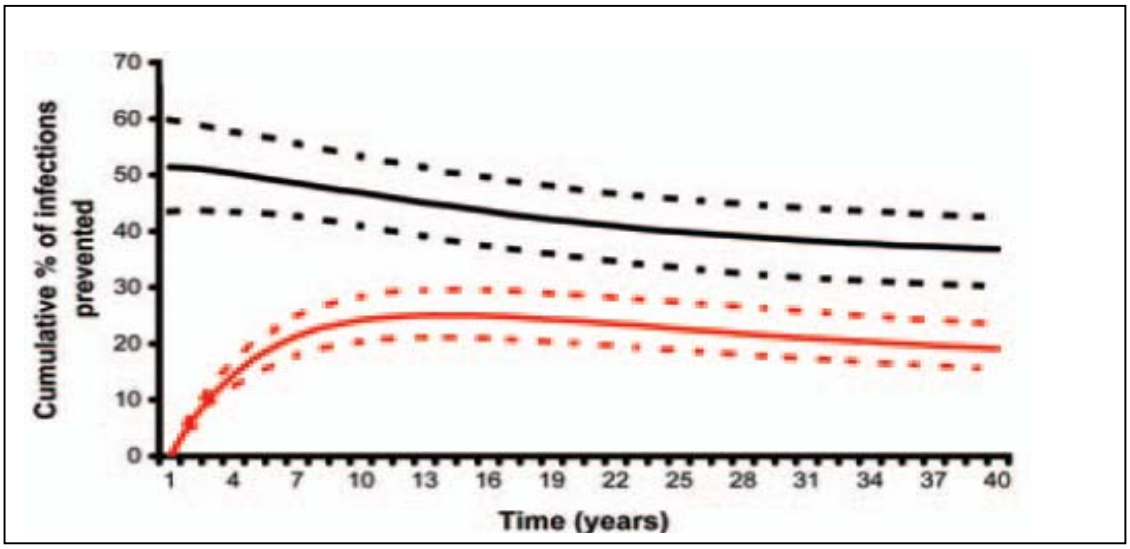

Figure 1.9: Predicted cumulative percentage of new infections with *Mycobacterium tuberculosis* prevented (preexposure = black, postexposure = red) under different uncertainty analysis.

[58] Simulated incidence ranged from 100 to 200 new TB cases per 100,000 persons per year. 28%–50% of the population was presumed latently infected with *M. tuberculosis*. Treatment rates were low to moderate (40%–60% of TB patients treated and cured). High vaccine efficacy was defined as 50%–90%. High vaccine coverage was defined as 60%–90%. Average duration of vaccine-induced immunity was 10–30 years. The model extended previous models by including the possibility of reinfection of a latently infected person with a new strain of *M. tuberculosis*.

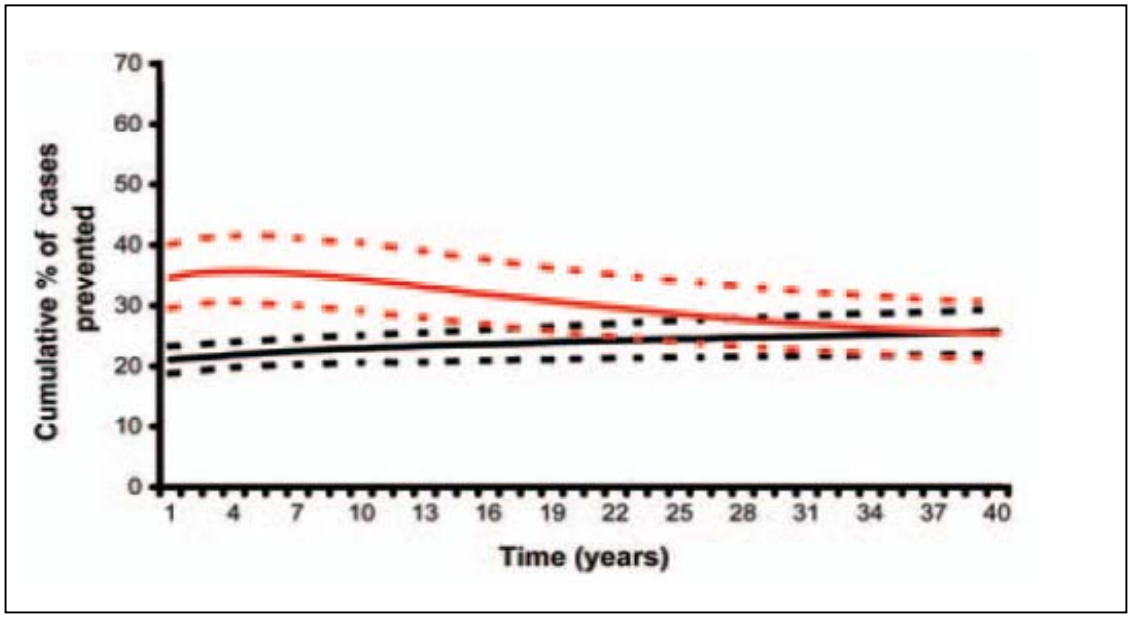

Figure 1.10: Predicted cumulative percentage of tuberculosis cases prevented (preexposure = black, postexposure = red) under different uncertainty analysis.

Zif et al perform multivariate sensitivity analysis on coverage rates, duration of immunity and vaccine efficacy to understand the impact on cumulative percentage of TB cases prevented after 20 years of continuous vaccination, concluding that there are large impacts as coverage rates go from 60% to 90% (especially for postexposure vaccines), as average duration of vaccine-induced immunity increases from 10 to 30 years (especially for postexposure vaccines), and, in the case of postexposure vaccines, as vaccine efficacy went from 50% to 90%. For preexposure vaccines, the impact according to coverage rate and duration was much less dramatic at 20 year horizon, with cumulative percentage of TB cases prevented around the 20% to 30% figure. For preexposure vaccines, the impact of efficacy depends on the mechanism by which a preexposure vaccine works.[59] In brief: If the mechanism was via allowing infection but reducing the probability of progression of latent infection to disease, then the impact was low. If the mechanism was via allowing infection but reducing the probability of rapidly progressing to disease, then the impact was much better. If the mechanism was by reducing the risk for infection in the uninfected, the impact was the greatest of these the three mechanisms.

We saw above how HIV has had a dramatic effect on the incidence of TB in developing countries. It is not yet fully understood, though it is very likely that HIV co-infection will reduce vaccine effectiveness in the very population most at risk of TB. This is an extra dimension of the product profile needed for TB vaccines:

[59] Please see the original file for details.

"The ideal TB vaccine should be affordable, even in the poorest countries of the world, and should be more cost-effective than BCG vaccine. It should be easily administered at or soon after birth, and be safe, immunogenic and effective at all ages and in all populations.[1] The latter would include persons who have received BCG vaccine before, and persons infected with TB, atypical mycobacteria or HIV. The vaccine should be effective in preventing primary TB, reinfection and reactivation disease, as well as extrapulmonary and disseminated disease. It is unlikely that a single new vaccine candidate will meet all or even most of these requirements, and it is likely that more than one new vaccine will be needed."[2]

Quote taken from Hussey et al.[60] (Reference 1 and reference 2)[61,62]

1.6. Drugs and vaccines working together

One major upshot of the above would seem to be that vaccines on their own will not have the impact desired. Yet, the presumption underlying all the figures in all investment case analyses is that there will be no new drug interventions between now and 2030 to 'upset' vaccine sales patterns. For example, in 'Appendix II: Methodology' of the BVGH/BCG report, it is observed that "no new drug to fight TB has been developed in the past 40 years," (p9). Furthermore, 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. Therefore, there *is* a presumption underlying all the TB vaccine investment case figures that there will be no new TB drug interventions between now and 2030 and analysis is done relative to currently imperfect performance of DOTS.[63] However, as the diagram below shows, meeting the target of global incidence of active TB at less than 1 case per million population per year will require both vaccine and drug (and diagnostic) interventions working together. A long-term strategy with goal of near or eventual eradication requires maintaining high detection rates, treatment and vaccination strategies over very long periods of time and over very diverse settings.

[60] Hussey G, T Hawkridge and W Hanekom "Childhood tuberculosis: old and new vaccines" *Paediatric Respiratory Reviews* (2007) 8, 148-154.
[61] C.F. Von Reyn and J.M. Vuoya, New vaccines for the prevention of tuberculosis, *Clin Infect Dis* **35** (2002), pp. 465–474.
[62] A. Ginsberg, What's new in tuberculosis vaccines, *Bull WHO* **80** (2002), pp. 483–488.
[63] The BVGH/BCG investment case report mentions one technical paper on the epidemiology of TB. However, the pattern of behavior of the BVGH/BCG 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 analysis was fairly limited, particularly in composing revenue figures and NPV. It seems to have been partially used to derive Figure 6 in that investment case. But the complexities of the epidemiological work are not part of the BVGH/BCG model itself.

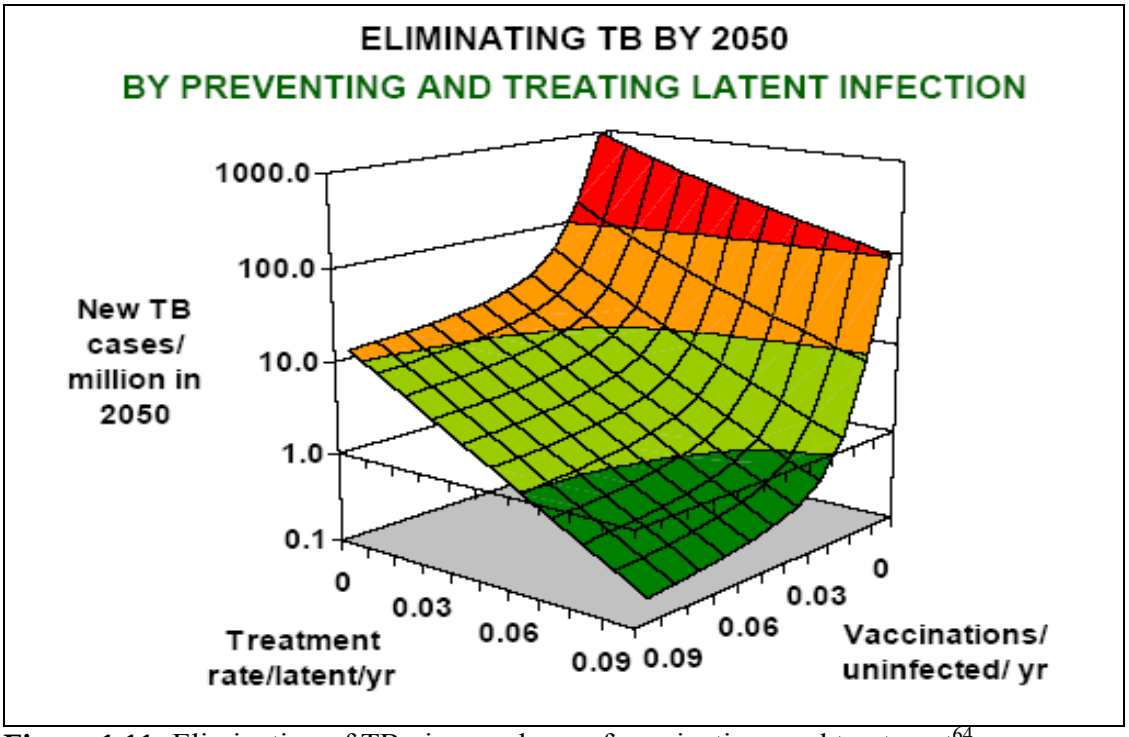

Figure 1.11: Elimination of TB via a package of vaccinations and treatment[64]

The recent 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. But the situation is quite complex. Paradoxically, the earlier investment and earlier success in tackling MDR-TB and XDR-TB via drugs, the lower the value of vaccine-based investments – and one would imagine that this impact should be related to efficacy of vaccines – and hence NPV for vaccine investors. Meanwhile the combination of new pre- and postexposure vaccines could substantially reduce the risks of emergence MDR-TB and XDR-TB.[65, 66] One would imagine a similar force working in the opposite direction.[67] The economic/investment incentive effects of all of this remain relatively under-explored, and clearly there are combinations of negative and positive investment externalities across different possible interventions.

[64] Taken from Dye presentation in Oxford November 2008.
[65] Blower SM, Small PM, Hopewell PC. Control strategies for tuberculosis epidemics: new models for old problems. Science. 1996; 273:497–500.
[66] Porco TC, Blower SM. Quantifying the intrinsic transmission dynamics of tuberculosis. Theo Pop Biol. 1998; 54:117–32.
[67] 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.

1.7. Cost-effectiveness of TB control and vaccination

Cost-effectiveness analysis can be used to determine the relative cost of an intervention, such as vaccination, and the outcome or effect compared to no intervention (or another alternative). In global health, cost-effectiveness analysis which produces outcomes of the cost of a health intervention per unit of outcome e.g. healthy life year averted (usually presented in Disability or Quality Adjusted Life Years - DALYs or QALYs), can be used to illustrate the economic impact of the disease and potentially to support the case for investment in that intervention or any other policy decisions. Cost-effectiveness analysis can also lead to the identification of knowledge gaps and the need for further research – particularly when setting up necessary assumptions for the full analysis to be carried out, and when results from sensitivity analysis indicate certain variables more or less significant than previous research might suggest.

Estimates of averted DALYs are a key part of calculating incremental cost-effectiveness ratios in conjunction with comprehensive cost data. DALYs can be estimated at the country level as the sum of the years of life lost due to premature mortality (YLL) in the population and the equivalent healthy years lost due to disability (YLD) for cases of tuberculosis. As recognized by others[68] it is important to show the robustness of DALY results by conducting well-defined sensitivity analyses for the effects of varying age weighting, discounting, and DALY input parameters, and to apply local life expectancies where possible. Ideally estimates of averted DALYs should also incorporate any transmission effects of the disease, to support any predictions of how disease incidence may change in the future and therefore provide a more substantiated claim on the effectiveness of a new intervention.

Cost benefit analysis can also be used. This makes a direct comparison of interventions by monetising costs of e.g. an illness, and benefits of prevention of that illness. It may not be practical to monetise the benefits of an intervention directly.

There are few existing studies which consider the cost-effectiveness of control strategies for TB, and very few which thoroughly consider economic evaluations or impact of vaccination strategies. As previously described, to date most economic studies of tuberculosis interventions in developing countries have evaluated screening as a method of detection, community based care, and the comparative effectiveness of short course chemotherapy treatment. Studies suggest that DOTS is cost-effective in Africa and in South East Asia despite differences in interventions across countries "Treatment of smear-positive, smear-negative, and extra-pulmonary cases in DOTS programmes and treatment of multidrug resistant cases in DOTS-Plus programmes are cost effective in both regions."[69]

There is a relatively small proportion of studies that have been conducted in high burden countries – in the analysis of existing studies by Floyd (2003) she identified 66 cost-

[68] Fox Rushby JA and K Hanson "Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis" *Health Policy and Planning* (2001) 16:3, 326-331.
[69] Baltussen R, K Floyd and C Dye "Cost effectiveness analysis of strategies for tuberculosis control in developing countries" *British Medical Journal* (2005) 331, 1364.

effectiveness studies on TB (some of which covered more than one topic of evaluation) but only 28% of these were looking at high-burden countries. The Floyd study covered the years 1982-1002, and could usefully be updated, given the surge in number of studies in the latter period. Further, as Baltussen et al discussed – most economic studies of tuberculosis in high burden countries did not assess the impact of interventions on transmission, and most used indicators of effectiveness that are specific to tuberculosis control, rather than generic measures. This can prevent the results on cost-effectiveness of tuberculosis control being compared with that of interventions for other diseases.[70] In turn, this limits the usefulness of these studies in decision-making at the policy level; as Floyd notes – most studies cannot inform cases for resource allocation or investment across the health sector, which is a key end use of rigorous cost-effectiveness analysis.

Highlighting one study in particular for interest, Rahman et al considered the cost-effectiveness of revaccination of BCG for school-age children in Japan.[71] This analysis relied on an estimation of the proportion of TB cases averted by vaccination. The authors carried out a thorough sensitivity analysis across all parameters. It is important in cost-effectiveness analysis of any new vaccine to consider efficacy (and indeed coverage) across a range of parameters to account for the difficulties in making risky assumptions, which are inherent to any economic analysis where there are still uncertainties.

The authors accounted for the direct benefits of vaccination in terms of treatment costs saved, and also made an estimate of indirect costs – loss of work from parents who might have to care for their children, and since averted cases at an older age would mean that those children would not have to miss work, the authors used the average length of treatment for a TB patient (70 days) to calculate the economic loss from not working. The indirect costs of morbidity should be included in cost-effectiveness analysis where possible. However, caution must be taken in assigning indirect costs relating to economic productivity and earnings through work. These factors may differ significantly both within and between countries.

Bishai and Mercer observe that "There have been no global estimates of the potential monetary benefits of improved TB vaccines".[72] They list the following potential benefits to different institutions of an improved vaccine or vaccines:

[70] Baltussen R, K Floyd and C Dye "Cost effectiveness analysis of strategies for tuberculosis control in developing countries" *British Medical Journal* (2005) doi:10.1136/bmj.38645.660093.68 (published 10 November 2005).
[71] Rahman M, M Sekimoto, K Hira, H Koyama, Y Imanaka and T Fukui "Is Bacillus Calmette-Guerin Revaccination Necessary for Japanese Children?" *Preventative Medicine* (2002) 35, 70-77 doi:10.1006/pmed.2002.1043.
[72] Bishai, D. M., and Mercer, D., 'Modeling the economic benefits of better TB vaccines' (2001) Int J Tuber Lung Dis (11):984–993.

Institution	Costs of vaccine	Benefits of vaccine
Susceptible unvaccinated hosts	Small increases in insurance premiums or tax rates	Prevented medical costs Prevented disability Prevented pain and suffering
Individual vaccine recipients	Out of pocket vaccine charges Side effects of vaccine reactions	
Insurance institutions	Insured portion of vaccine charges	Prevented medical costs
Individual clinicians	Storage and administration fees	Improved patient health
National vaccine policy boards	Sum of all of the above	Sum of all of the above
Pharmaceutical companies	Years of investment in research and development	Expected revenue on sales
Public research centers	Time in scientific research	Publicly funded research grants

Table 2: Costs and benefits of an improved TB vaccine[73]

Bishai and Mercer calculate the benefits of better TB vaccines by modeling the value of prevented TB medical spending and lost productivity. Given that the determinants of demand for a TB vaccines are likely to change by the time a vaccine becomes available, Bishai and Mercer reference their economic benefits to the year 2000, and divide the world into the standard World Bank groupings so as to generate benefits from vaccines dependent on local economic factors. Their baseline model assumed that 75% of individuals who complete a course develop 100% protective immunity, and that protection is for at least ten years. Their analysis yields the following results:

Age (years)	Men			Women		
	0–15	15–64	65+	0–15	15–64	65+
EME	$0.67	$5.38	$12.58	$0.54	$2.16	$4.77
FSE	$1.81	$38.47	$32.56	$3.19	$10.57	$11.71
SSA	$0.53	$2.87	$2.62	$0.65	$1.98	$0.94
LAC	$1.33	$2.57	$3.09	$1.43	$1.76	$1.54
MEC	$1.24	$5.42	$5.88	$1.74	$3.97	$3.76
Asia	$0.23	$2.24	$4.41	$0.31	$1.26	$1.52

EME = established market economies; FSE = former socialist economies; SSA = sub-Saharan Africa; LAC = Latin American countries; MEC = Middle Eastern countries including North Africa; Asia = India, China, other Asia and islands.

Table 3: Dollar value of medical benefit from 1 year of complete elimination of TB risk for one individual (and successive contacts) by age, sex and region of propositus (taken from Table 4 of Bishai and Mercer)

[73] From Bishai, D. M., and Mercer, D., ibid.

Age (years)	Men			Women		
	0–15	15–64	65+	0–15	15–64	65+
EME	$1.72	$14.00	$14.97	$1.83	$5.62	$5.67
FSE	$2.82	$60.89	$33.70	$6.03	$16.73	$12.12
SSA	$15.49	$86.74	$4.43	$30.22	$59.79	$1.59
LAC	$14.93	$29.81	$4.58	$24.86	$20.41	$2.29
MEC	$61.19	$278.50	$13.00	$138.28	$203.84	$8.31
Asia	$9.99	$99.48	$9.51	$21.11	$55.83	$3.29

EME = established market economies; FSE = former socialist economies; SSA = sub-Saharan Africa; LAC = Latin American countries; MEC = Middle Eastern countries including North Africa; Asia = India, China, other Asia and Islands.

Table 4: Dollar value of productivity and medical benefit from 1 year of complete elimination of TB risk for one individual (and successive contacts) by age, sex and region of propositus (taken from Table 5 of Bishai and Mercer)

Age (years)	Men			Women		
	0–15	15–64	65+	0–15	15–64	65+
EME	$1.72	$14.00	$14.97	$1.83	$5.62	$5.67
FSE	$10.34	$225.33	$87.14	$24.43	$61.90	$31.34
SSA	$97.86	$538.63	$224.47	$159.81	$371.28	$80.88
LAC	$67.90	$133.66	$73.43	$97.50	$91.51	$36.73
MEC	$63.13	$282.34	$139.93	$118.79	$206.65	$89.44
Asia	$30.61	$299.77	$269.87	$54.01	$168.24	$93.24

EME = established market economies; FSE = former socialist economies; SSA = sub-Saharan Africa; LAC = Latin American countries; MEC = Middle Eastern countries including North Africa; Asia = India, China, other Asia and islands.

Table 5: Equity model: societal benefit from 1 year of complete elimination of TB risk for one individual by age, sex and region assuming TB costs globally equal those of established market economies (taken from table 6 of Bishai and Mercer)

Whilst aware of the dangers of using monetary measures, Bishai and Mercer plot the cumulative number of vaccine users at different prices on the basis of the decision rule "vaccinate groups of people for whom the dollar value of the benefit exceeds the cost of the vaccine" from a 'health sector perspective'("Purchase vaccine for group *j* if benefit of vaccine to health sector > cost to health sector") and from a societal perspective ("Purchase vaccine for group *j* if benefit of vaccine to society > cost to society"). They perform some sensitivity analysis on the results.

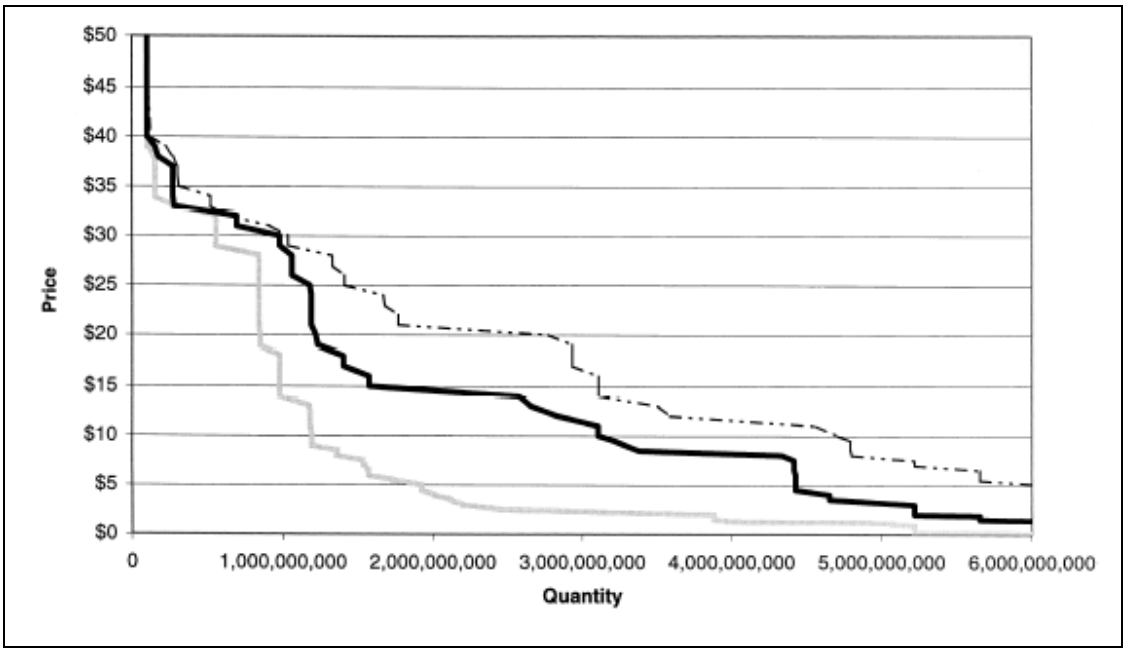

Figure 1.12: Health sector perspective on global benefits of TB vaccine. (From Figure 1, Bishai and Mercer)

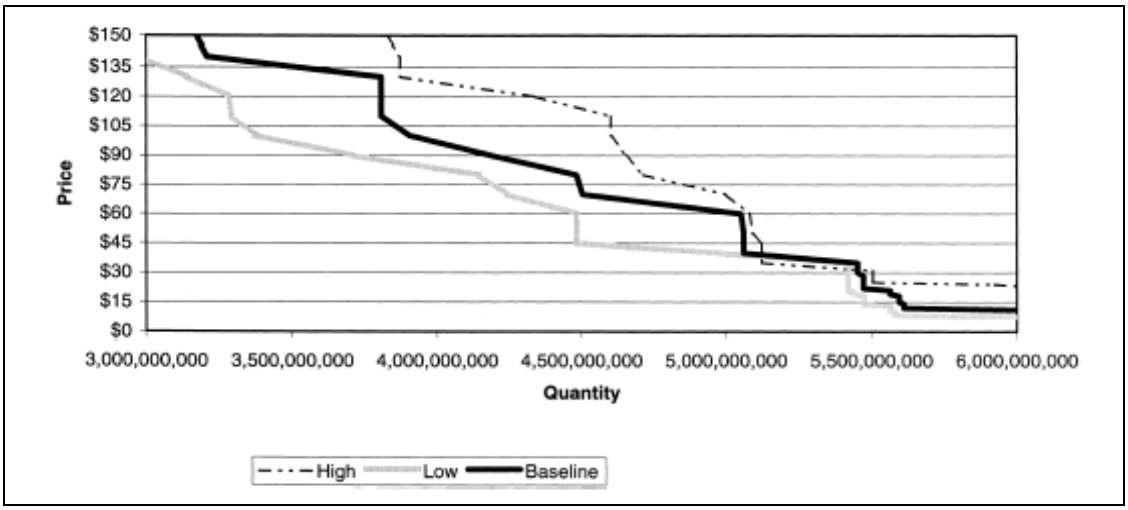

Figure 1.13: Societal perspective on global benefits of TB vaccine (From Figure 2, Bishai and Mercer)

Direct costs of an intervention or existing management of a disease are obviously a key part of cost-effectiveness analysis. Evidence on the current costs of treatment and control for TB as well as the areas of growing concern such as treating HIV-TB coinfection are relatively well documented and available as part of national health budgets and expenditure. Overall, DOTS is relatively expensive – the 2008 WHO report suggested that "DOTS accounted for easily the largest proportion of NTP budgets between 2002

and 2006, and in 2008 continues to account for much the largest share of the NTP budget in all of the 22 HBCs except the Russian Federation."[74] There are also high costs of MDR-TB diagnosis and treatment, particularly in certain countries – with the Russian Federation and South Africa accounting for just over US$500 million of the total of US$540 million. Collaborative TB/HIV activities remain a comparatively small component of NTP budgets for the HBCs as a whole, but account for a relatively large proportion of the budgets reported by several other African countries.[75]

In summary, key components of a thorough cost-effectiveness analysis include:

- A strong evidence base on disease burden in each country that is being considered, in order to create a suitable range of DALY values

- Information on existing direct costs of the disease (or the alternative intervention) – most obviously sourced through data on treatment and control, and costs of accessing that treatment or control.

- Information on broader impact of the disease. These could include direct costs of loss of productivity, costs to carers, etc.

- Guidelines for estimating cost of introducing new vaccines into the national immunisation system
    - Capital Costs e.g. vehicles, equipment, training, social mobilisation
    - Recurrent Costs e.g. vaccines, wastage, safety, transport/cold chain operation

An important consideration is of course the vaccination strategy that is chosen – and the population groups that it implicates. The modeling methodology will be dependent upon the desired mechanism through which the vaccine is delivered – this will impact significantly on the design of any costing model (e.g. incremental costs of vaccinating in each country through EPI vs. initiating a vaccination campaign). This must then be compared to existing treatment for those population groups – and should take into account any indirect costs. For example, when considering the costs of preventative treatments for those at working age, the implications are far beyond direct cost. As discussed, economic impact should consider costs of not working (or production for the economy) and impact on carers who may also have to stop working or incur extra costs. It should be possible to quantify these costs either through a detailed set of survey information, or through conducting an econometric analysis which can investigate the impact of, for example, x days lost due to illness on the economic productivity at the household or country level.

[74] Global tuberculosis control : surveillance, planning, financing : WHO report 2008, (WHO/HTM/TB/2008.393), Page 63.
[75] Global tuberculosis control : surveillance, planning, financing : WHO report 2008, (WHO/HTM/TB/2008.393), Page 64.

1.8. Limitations of cost-effectiveness analysis

It is important to note that sound cost-effectiveness analysis really goes hand in hand with sound epidemiological analysis/evidence. As the Disease Control Priorities Project comments, disease burden estimates are by nature limited by the data supporting assumptions – the "susceptible fraction of the population, infectivity rates of disease, sequelae of the disease, and estimates of local case fatality rates". Therefore the disease burden must be represented by a range of values reflecting this uncertainty. A full assessment of burden of disease in each country is also crucial and it is important to understand any assumptions made in calculating disease burdens at a country level such as corrections for underreporting. In an ideal situation, there would be any number of local cohort studies to inform disease burden and existing vaccination or treatment coverage. This could then be used to inform estimates on surveillance.

The DCPP project also noted that even for considerations of the costs per fully immunized child in EPI programs, estimates do not take into account household costs, the direct and indirect costs of acute illness prevented by vaccinations, the costs of long-term complications from disease, or benefits from partial immunization.[76] These are important factors. For a useful and rigorous cost-effectiveness evaluation it really is important to ensure a through understanding of the disease and the existing strategies – to integrate with existing evidence and any ongoing efforts to improve surveillance and detection.

Bloom et al consider the limitations of both cost-effectiveness and cost-benefit analysis in their recent publication on vaccination. They highlight in particular, the importance of considering disease prevention beyond the immediate costs. The impact of good health on economic progress and development can be substantial. It can even change the age structure of the population (via impacts on fertility rates and lower mortality rates) and improve the prospects for economic growth.[77] However, whilst it may be possible to account for broader economic impact to some extent – by the methods described in the section above, it is unlikely to be possible to link to any full model of economic growth. Indeed, such a strategy would also be limited, as broader economic models inevitably depend on a wide range of assumptions – either using past behaviour or behaviour in different countries to predict growth, or relying on economic theory, whose ability to explain behaviour in practice is inevitably limited. There is always more uncertainty and risk when attempting to explain the economic impact of an intervention more fully.

1.9. Socioeconomic analysis and cultural issues

As asserted previously (Floyd 2003), economic studies are not only about costs and cost-effectiveness, and indeed can play a valuable part in broader evaluations of the need for interventions and the best way to cover different populations. It is important, whether directly through particular economic evaluation or through parallel studies, to take into account the socioeconomic and cultural factors that are integral to the genetics of

[76] Brenzel L, L Woldson, J Fox-Rushby, M Miller and N Halsey "Vaccine-Preventable Diseases" *Disease Control Priorities Project* (2006) Chapter 20 http://files.dcp2.org/pdf/DCP/DCP20.pdf
[77] Bloom DE, D Canning and M Weston "The Value of Vaccination" *World Economics* (2005) 6:3, 15-39

societies and which play a crucial part in the success and effectiveness of any treatment or intervention.[78]

Kim et al criticise over-emphasis on cost-effectiveness, retelling the history of MDR-TB treatment drugs and the case made against them by international health policy to conclude that treatment of MDR-TB was not feasible in resource-poor settings before 1999. They suggest that cost-effectiveness analyses can be short-sighted and, because they often do not pay sufficient attention to the social, political, economic, epidemiological and pathophysiological factors influencing the production of health, "will ultimately hinder progress toward effective global TB control."[79] The argument that they present focuses on the fact that MDR-TB and indeed treatment of complicated diseases are complex projects, especially when faced with limited resources in the developing world. It is important not to forget this fact and to give weight to accessibility and social factors rather than focusing purely on the more abstract goals of maximizing efficacy and resources.

There are many interesting cultural factors associated with TB, which can have severe implications for accessibility and acceptability of treatment strategies. It also has a direct implication for the validity of any assumptions about coverage that are made in a standard cost-effectiveness analysis. It is widely stated that TB is a poverty related disease.[80] As Girard et al put it:[81]

> "…it has long been recognised that war, malnutrition, population displacement and crowded living and working conditions favour the spread of TB among humans, whereas periods of improvement in societal conditions and hygiene favour its rapid decline."

There are many stigmas associated with TB – and these are exacerbated by any differentials that exist within the disease across many factors including gender and country of origin. Hudelson (1996) investigated the exposure to TB and concluded that socio-economic and cultural factors may play a strong role in determining gender differences in rates of infection through exposure to the disease, particularly in developing countries.[82] Further differences may arise when considering treatment of TB and the treatment outcome – even where there are no gender differentials in the disease burden, different barriers to care may exist. These barriers can exist well beyond seeking treatment of care. A study in India in 2005 illustrated the extent to which social stigmas can affect women, concluding that each year more than 100,000 women are rejected by

[78] Floyd K "Costs and effectiveness – the impact of economic studies on TB control" *Tuberculosis* (2003) 83: 187-200.
[79] Kim JY, A Shakow, K Mate, C Vanderwarker, R Gupta and P Farmer "Limited good and limited vision: multidrug-resistant tuberculosis and global health policy" *Social Science and Medicine* (2005), 847-859
[80] WHO Factsheet, April 2008 http://www.who.int/tb/publications/2008/factsheet_april08.pdf.
[81] Girard M P, U Frith and M Kieny "A review of vaccine research and development: Tuberculosis" *Vaccine* (2005) 23, 5725-5731.
[82] Hudelson P "Gender differentials in tuberculosis: the role of socio-economic and cultural factors" *Tubercle and Lung Disease* (1996) 77, 391-400

their families on account of TB.[83] The authors also considered the direct costs of the disease and the broader economic implications caused by the social difficulties of dealing with treatment:[84]

> "Each year, more than 300,000 children leave school permanently because of their parents' TB... TB costs India more than $300 million annually in direct costs alone, of which more than $100 million is incurred in the form of debt by patients and their families."

Poverty and socioeconomic disadvantage amongst patients can influence capability to seek further care and reliable diagnosis. Equally, the incentives at the point of care can have serious implications. A recent study across four provinces in China identified that the common delays and multiple visits for treatment for TB mainly occurred because of the "limited capacity of health providers to recognise TB, and financial disincentives to refer patients to TB dispensaries, due to the pressures of the cost recovery system."[85] However, this issue is highly related to the strength and quality of the general health service as well as those health services specific to TB control programmes

These factors are obviously different across countries but can have significant impacts on vaccination strategies. It is important to understand cultural issues, the financing, quality and management of the health services (particularly relating to decentralization) and the economic impact or costs of these social and cultural issues in order to account for them or at least incorporate them into qualitative analysis.

1.10. Summary of implications for policy making

Rates of progress towards meeting existing targets for TB control have to some extent been limited by the quality of health systems in countries.

Links between prevention and control strategies can be complicated. It is important for existing strategies not to "crowd out" new strategies for dealing with a disease. Interventions may have a common aim in dealing with tuberculosis disease, but slightly different intermediate goals or success metrics; and may be aimed at people in different demographic groups.

When assessing a new vaccine strategy, it is important to consider the interrelation with BCG and both direct and indirect effects of a new vaccine candidate.

Cost-effectiveness analysis can lead to the identification of knowledge gaps and the need for further research – particularly when setting up necessary assumptions for the full

[83] Chauhan, L and J Tonsing "Revised national TB control program in India", *Tuberculosis* (2005) 85, 271-276.
[84] Quote from Chauhan, L and J Tonsing, ibid.
[85] Yan F, R Thomon, S Tand et al "Multiple perspective on diagnosis delay for tuberculosis from key stakeholders in poor rural China: Case study in four provinces" *Health Policy* (2007) 82, 186-199.

analysis to be carried out, and when results from sensitivity analysis indicate certain variables as more or less significant than previous research might suggest.

It is important in cost-effectiveness analysis of any new vaccine to consider efficacy (and indeed coverage) across a range of parameters to account for the difficulties in making risky assumptions, which are inherent to any economic analysis where there are still uncertainties.

The indirect costs of morbidity should be included in cost-effectiveness analysis where possible. However, caution must be taken in assigning indirect costs relating to economic productivity and earnings through work. These factors may differ significantly both within and between countries.

It is important to note that sound cost-effectiveness analysis really goes hand in hand with sound epidemiological analysis/evidence.

Social stigma associated with TB, gender differentials and access to care are obviously different across countries but can have significant impacts on vaccination strategies. It is important to understand cultural issues, the financing, quality and management of the health services (particularly relating to decentralization) and the economic impact or costs of these social and cultural issues in order to account for them or at least incorporate them into qualitative analysis.

1.11. A very selective bibliography

Amongst the references cited herein, the following are recommended for both content and coverage of material:[86]

Baltussen R, K Floyd and C Dye "Cost effectiveness analysis of strategies for tuberculosis control in developing countries" British Medical Journal (2005) 331, 1364

Bishai, D. M., and Mercer, D., 'Modeling the economic benefits of better TB vaccines' (2001) Int J Tuber Lung Dis (11):984–993

Bloom DE, D Canning and M Weston "The Value of Vaccination" World Economics (2005) 6:3, 15-39

Bourdin Trunz B, Fine P E, Dye C. "Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost effectiveness" Lancet 2006; 367: 1173-1180

Dietrich J, C Vingsbo Lundberg, P Andersen "TB Vaccine Strategies – What is needed to solve a complex problem?" Tuberculosis (2006) 86, 163-168

[86] That is no judgment is being made about papers not cited, since the purpose is partly to achieve wide coverage of material as well as quality of content.

Dye C, A Bassili, AL Bierrenbach, JF Broekmans, VK Chadha, P Glaziou et al "Measuring tuberculosis burden, trends, and the impact of control programmes" *The Lancet Infectious Diseases* (2008) 8(4): 233-243

Dye C, "The global epidemiology of tuberculosis" Lancet (2006) 267, 938-940

Fox Rushby JA and K Hanson "Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis" Health Policy and Planning (2001) 16:3, 326-331

Floyd K "Costs and effectiveness – the impact of economic studies on TB control" Tuberculosis (2003) 83: 187-200

Frothingham R, J E stout, C D Hamilton "Current issues in global tuberculosis control" International Journal of Infectious Diseases (2005) 9, 297-311

Hussey G, T Hawkridge and W Hanekom "Childhood tuberculosis: old and new vaccines" Paediatric Respiratory Reviews (2007) 8, 148-154

Girard M, U Fruth and M-P Kieny "A review of vaccine research and development: Tuberculosis" Vaccine (2005) 23, 5725-5731

Kim JY, A Shakow, K Mate, C Vanderwarker, R Gupta and P Farmer "Limited good and limited vision: multidrug-resistant tuberculosis and global health policy" Social Science and Medicine (2005), 847-859

Nagelkerke NJD, SJ deVlas, Y Mahendradhata, THM Ottenhoff and M Borgdorff "The search for a tuberculosis vaccine: an elusive quest?" Tuberculosis (2006) 86, 41-46

Plahte J.,"Tiered pricing of vaccines: a win-win-win situation, not a Subsidy" Lancet Infect Dis (2005) 5: 58–63

Sierra VG "Is a new tuberculosis vaccine necessary and feasible? A Cuban opinion" Tuberculosis (2006) 86, 169-178

Ziv E, Daley CL, Blower S. Potential public health impact of new tuberculosis vaccines. Emerg Infect Dis 2004 Sep

2. BASIC MARKET AND REVENUE FRAMEWORKS

2.1. Some introductory thinking

A note about some key sources:

The following sources were heavily, though not exclusively, used in several of the following sections:

1) "TB Vaccine Global Market Assessment", by Applied Strategies, commissioned by Aeras Global TB Vaccine Foundation, July 2007. This was provided for the purposes of this review in the form of an extremely comprehensive set of PowerPoint slides (numbering several hundred). It is a challenge to do justice to such a large body of material given the desire not to infringe Applied Strategies and given that the purpose here is not to simply replicate past material, but to suggest a research strategy that will add value.

2) "Tuberculosis Vaccines: The Case for Investment"[87] – a report commissioned by BIO Ventures for Global Health (BVGH), with analysis performed by the Boston Consulting Group (BCG), October 2006. It also checks over previous BCG work, especially for malaria and pneumococcal vaccines.

3) "An Independent Assessment of Tuberculosis Vaccines: The Case for Investment" by A Farlow, commissioned by Aeras Global TB Vaccine Foundation, July 2007, with analysis based on BVGH/BCG figures.[88]

A note about Net Present Value, NPV:

As an organising device we will often refer to Net Present Value (NPV). Thinking about NPV should not be interpreted to mean that we are only thinking about profit and loss. Instead, NPV is a useful pedagogical device for thinking about the many factors that feed into the research, development and ultimate take-up of TB vaccines. At a very basic level, NPV is the balance between discounted expected *revenue* (in to which feeds quantities and prices of vaccines) and discounted expected *costs* from all possible sources of cost (development costs, production plant costs, cost of goods sold, etc.). It is a balancing act between several very large flows of resources, over very long periods of time.

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.[89]

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

[88] Please see original for caveats about the way analysis was done and the data limitations faced.

[89] Another measure for appraising the value of a long-term investment project is its internal rate of return, IRR. IRR is the annualized effective compounded return rate which can be earned on invested capital. It is

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:[90]

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

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[91] should invest.[92]

The dangers of NPV:
The principle danger of using NPV is that sophisticated-looking treatments can generate precise-looking numbers even if the underlying inputs are weak. There is no such thing as *the NPV* of an investment in something as complicated as TB vaccines with so many degrees of uncertainty; there are only hypothesized values of NPV based on more, or less, reasonable assumptions. In essense, working out how to make more realistic assumptions is what this scoping report is all about. Stress testing outcomes by allowing underlying inputs to be very different is a useful part of the exercise.

Portfolio thinking:
We will find along the way that thinking about portfolios is also important. It is possible to work out NPVs of particular outcomes, but to work out the overall value of the TB vaccine problem, requires us to work out the value of a *portfolio of possible outcomes* (which could number thousands of potential outcomes) under some assumption about probabilities of those outcomes occuring. The Applied Strategies approach certainly has a good go at this much more elaborate approach (several thousand vaccine combinations). However, Applied Strategies was tasked with working out results for the Aeras portfolio, rather than the global portfolio. And nobody has analysed optimality of the global TB vaccine portfolio.[93]

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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 can be thought of as 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. Applied Strategies does not report IRR, and Farlow also kept to NPV because of unresolved issues with some of the data. When discussing current potential sponsor funding, NPV gives a dollar measure of the investment problem faced roughly contemporaneously with the sponsor decision being made. For example, in the summer of 2007, BMGF was in negotiations with Aeras on a $200m grant renewal. This can easily be compared with an NPV calculation.

[90] This is the methodology used for the base case by BCG.

[91] Perhaps because they can diversify such as to be in effect risk-neutral on this investment.

[92] 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.

[93] Intuitively, if the NPV comes out very large, on the one hand this may be suggesting a very profitable investment opportunity, but, given that we are dealing with a social problem on a huge scale, it could

2.2. Comparing market and revenue frameworks

The different analyses do a range of scenarios regarding the demand for new TB vaccines, based on:

i) Country markets:
   a. BSG and AF base analysis on markets for high-risk individuals in high-income countries; public-sector markets in low- and middle-income countries; private-sector markets in low- and middle-income countries; China; India.
   b. ASC divides countries into high income countries, middle income countries without China, China, low income countries without India, India. Each of these categories is subdivided in to public and private sectors (with an assumption over distribution across public and private sectors according to income status of country, with this distribution very simple and global). The ASC base incorporates current BCG vaccine users;
   c. High Risk Adult Populations in High and Middle Income Countries are not included in the market segmentation for ASC in their base case. They get included in their global XDR case. BCG included these high risk groups, and AF does some reanalysis of the BCG figures on the basis of a wider range of assumptions than BCG about this rich segment.
   d. In the AS approach, it takes a 'Global XDR' scenario to pull in additional middle income and high income countries, but once they are pulled in, very much higher potential NPVs are achieved. These higher NPVs are partly driven by a small increase in quantities of vaccine sold, but mostly driven by the fact that these quantities are in high-price paying markets, all vaccine sales are based on a high price formula and there is quicker vaccine take-up.
   e. BSG does not consider the case of a 'global XDR' scenario. An external observer might observe that the fact that two analysis can take such a radically different approach when dealing with XDR, suggests that we are still at a relatively early days in achieving a common agreed formula for working out the shape of the market for TB vaccines.

ii) Product profiles:
   a. BVGH/BCG defines 'efficacy' as 70% for replacement/prime, 70% for Booster, and 80% for Prime-Boost.
   b. ASC defines both replacement vaccine and boost vaccine (infant and adolescent treated the same) product profiles in Base Case and Global XDR scenarios as 60%>BCG. The low efficacy scenario is for 40%>BCG. Prime + Boost efficacy is 100% > BCG under Base Case and Global XDR scenarios, and 60% > BCG in the low efficacy scenario.
   c. In the all cases other than the low-efficacy efficacy case, vaccine efficacy in the ASC scenarios is lower than BCG (60% versus 70%) but the prime and boost combined efficacy is much higher (100% compared to 80%). Like BCG, because coverage is Infant DTP3 and Adolescent TT2, there is

equally be suggesting that the portfolio is way too small (i.e. the portfolio should be bigger, driving down measures of NPV).

an opportunity to explore market thinking about how to improve performance on this.

d. ASC pulls all scenarios together to give the results for the Aeras portfolio.

iii) Assumptions about prices and willingness to pay:
These are based on product profile (and will be discussed in more detail below). It is not clear how these were determined in each case and how closely they are to what is probable.

iv) Time to adoption (see below).

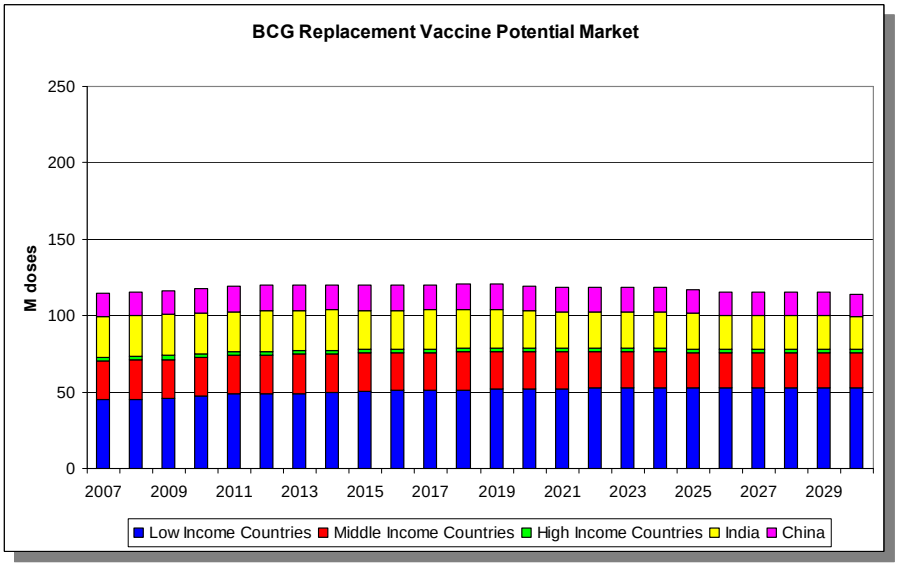
2.3. Replacement vaccine

Typical ASC demand analysis: replacement vaccine base case

To save repeating all the slides of ASC (and because that would also be unfair on ASC), for illustrative purposes we detail just one case – that of replacement vaccine in the base case (non-XDR) scenario – as an example of how the analysis is done. Essentially, the steps of analysis performed in this case is repeated for all cases, and all of the outcomes are then pooled according to probabilities of each case so as to get an overall result. The result can be read in terms of quantities or NPV.

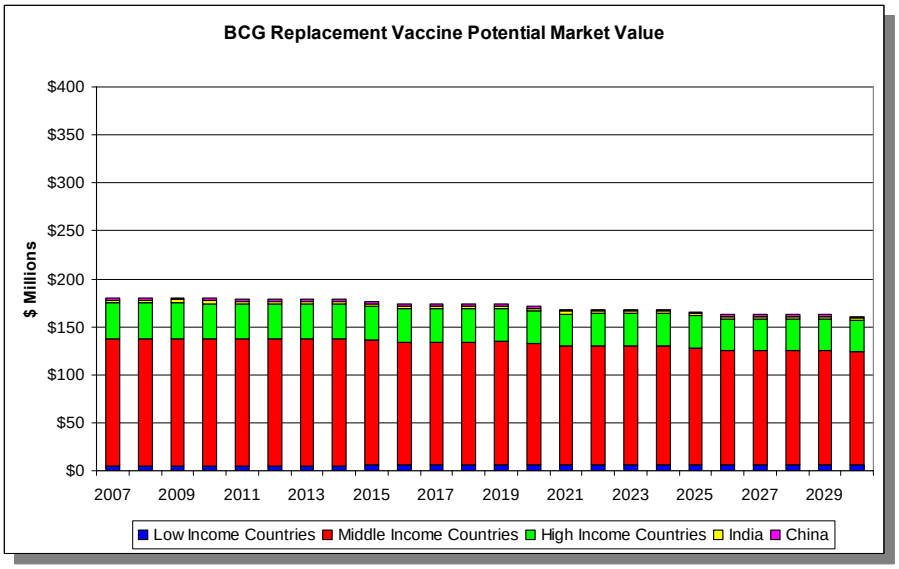
The replacement vaccine case is relatively straightforward since the vaccine possibilities of the current Aeras portfolio are limited. Once one expands the portfolio, one naturally gets huge numbers of slides to fill out all the cases, but the principles are relatively straightforward.

Step 1: BCG Replacement Vaccine – Base Case Scenario. Potential[94] Market Size (doses)

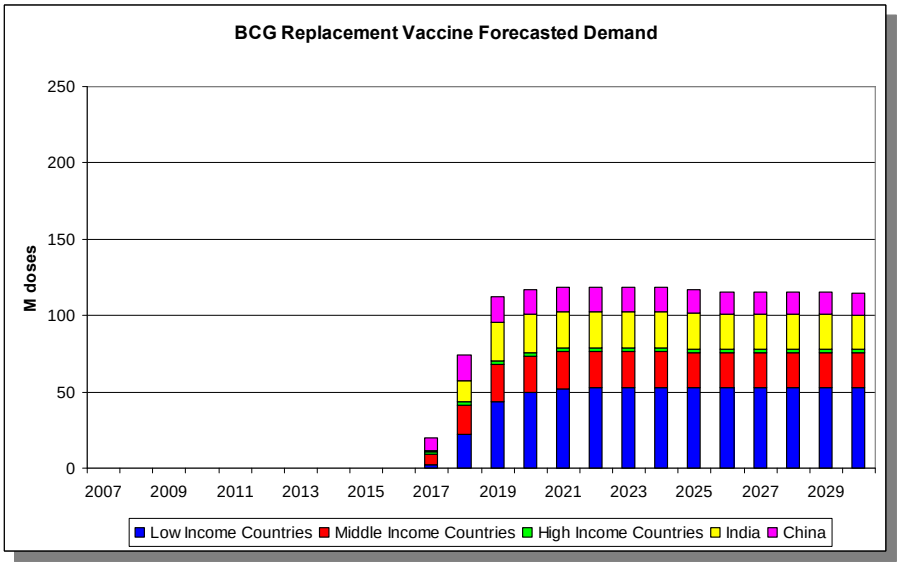


[94] Potential market given that all target populations adopt an available vaccine and implement to their full overage rates.

Step 2: BCG Replacement Vaccine – Base Case Scenario, Potential[95] Market Value ($)

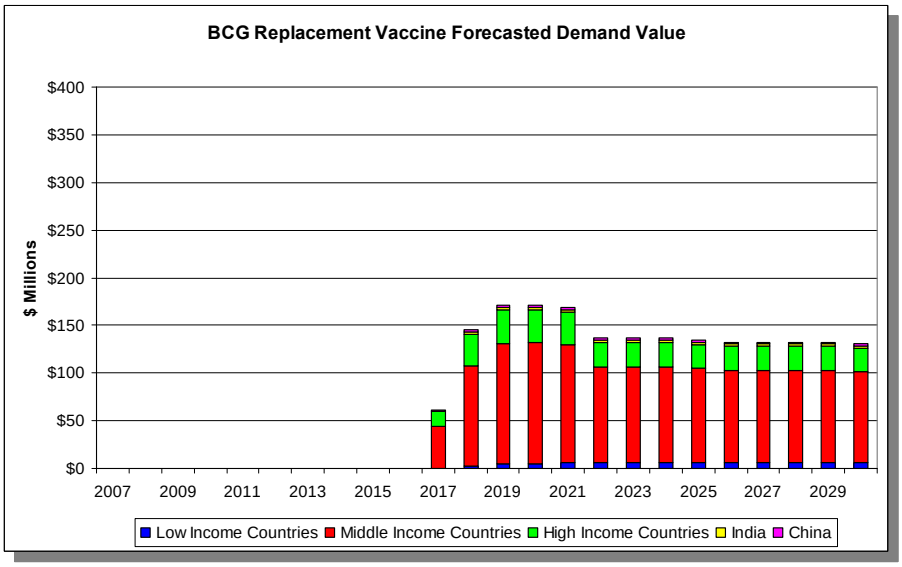


Step 3: BCG Replacement Vaccine – Base Case Scenario, Forecast Demand (in doses)

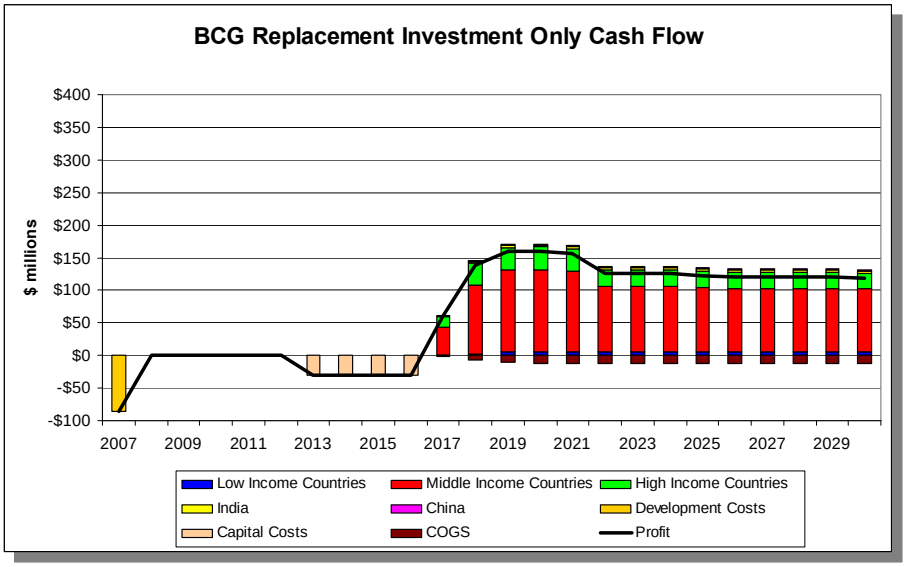


[95] Potential market given that all target populations adopt an available vaccine and implement to their full coverage rates.

Step 4: BCG Replacement Vaccine – Base Case Scenario Forecast Demand (revenue in dollars)



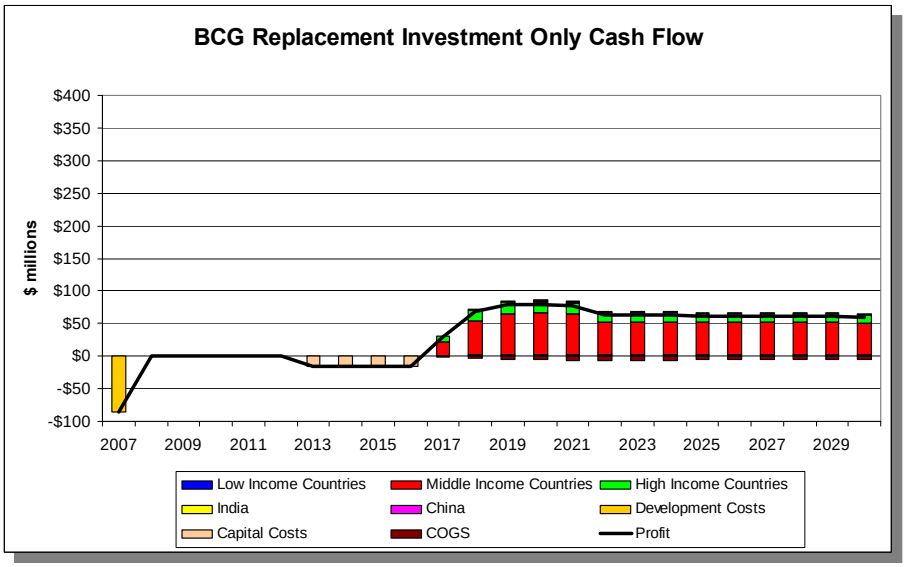
Step 5: BCG Replacement Vaccine – Base Case Scenario, showing cash flow (revenue and costs) when AERAS takes all the market[96]



Given development success of the Aeras candidate (rBCG Aeras 403) the NPV of this case is $250m given a 10% discount rate.

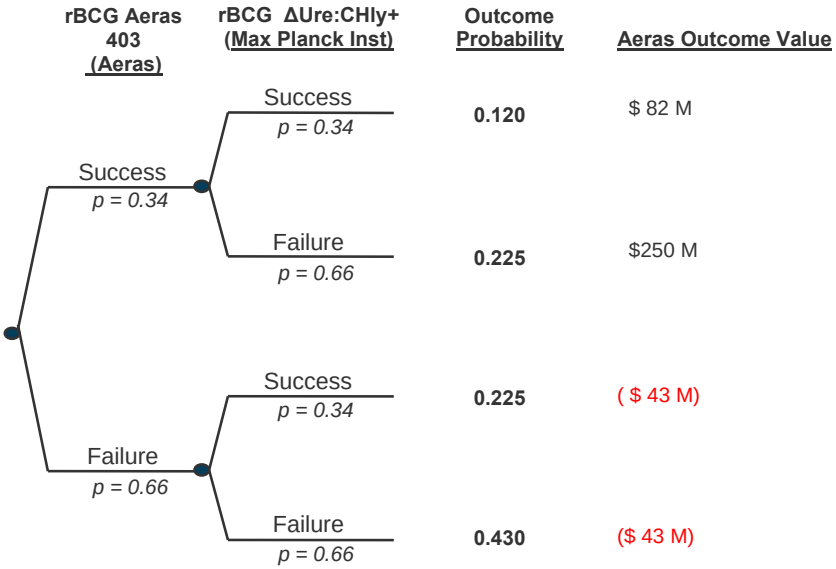
[96] Supply built to anticipated market share. Note how the expectation over the capacity of the other producer is correct so that capital costs can be suitably scaled.

Step 6: BCG Replacement Vaccine – Base Case Scenario, showing cash flow (revenue and costs) when AERAS takes half the market[97]



Given development success of the Aeras candidate (rBCG Aeras 403) the NPV of this case is $82m given a 10% discount rate.

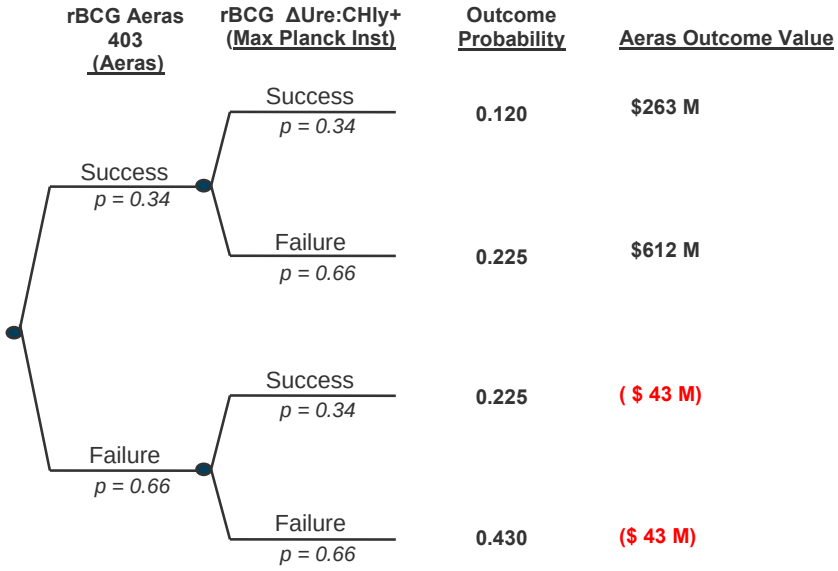
Step 7: Work out the overall outcome: All of the above diagrams are based on the Aeras candidate being successful. To work out the overall outcome, one needs to incorporate what happens if the Aeras candidate fails and the competitor is successful (the ASC analysis includes only clinical candidates, which explains why the diagram describing the replacement scenario is so simple):



This yields an overall Expected NPV to Aeras of $ 38m, given a 10% discount rate.

[97] Supply built to anticipated market share. Note how the expectation over the capacity of the other producer is correct so that capital costs can be suitably scaled.

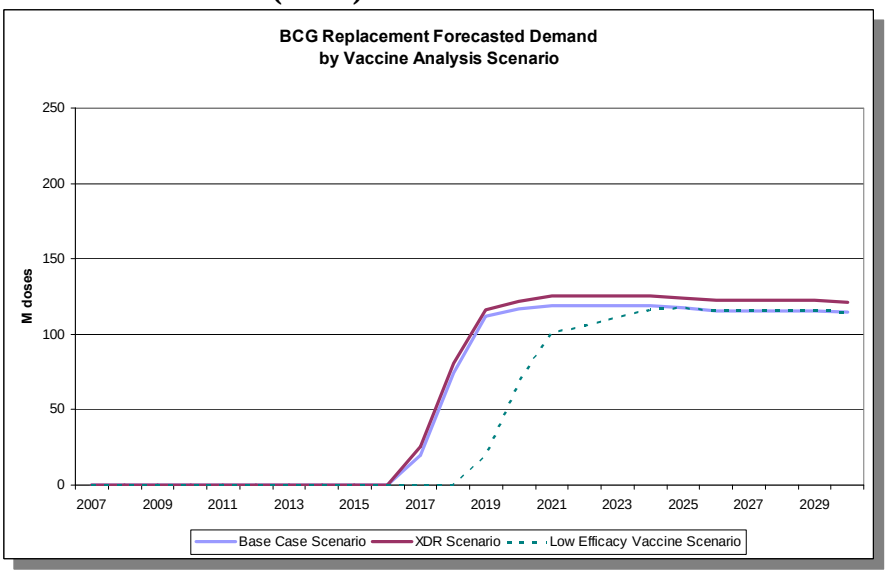
Step 8 repeated: A similar analysis can be done *for the **BCG Replacement Vaccine*** in the case of a **Global XDR Scenario:**[98,99]



This yields an overall Expected NPV to Aeras of $141m, given a 10% discount rate.

Step 9: As a side step (since this is not needed to work out the value of the portfolio) compare Base Case BCG replacement vaccine versus BCG Replacement vaccine under Global XDR:

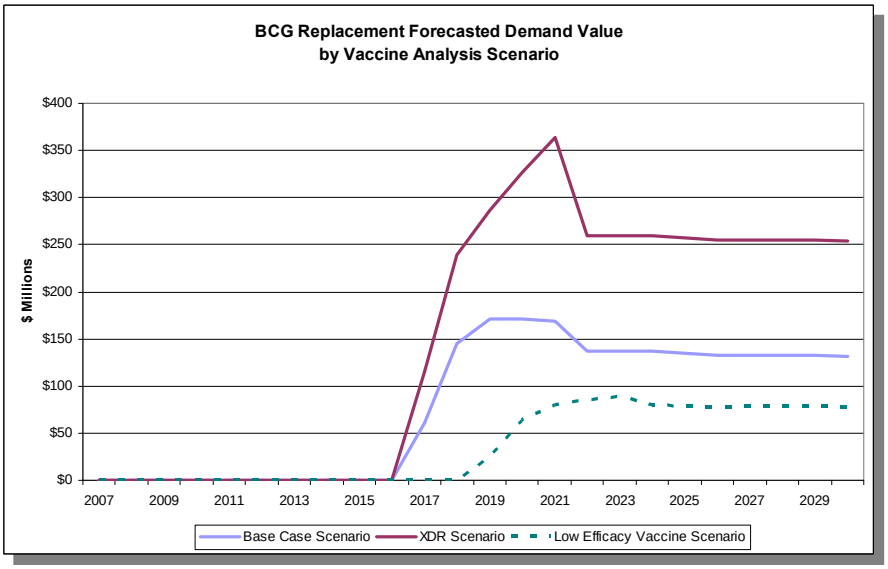
Forecasted Demand (doses)



[98] I.e. again partialing out any boost scenarios.

[99] We don't repeat here all the intervening cashflow diagrams. No analysis is done for the Low Efficacy vaccine scenario since no such vaccine is presumed in the Aeras portfolio.

Forecasted Demand (in dollars)



Step 10: Repeat for boost vaccines.

Step 11: Pull replace and boost vaccine scenarios together under assumed portfolios of all vaccines in pipeline.

Step 12: Stress test. The results are only as good as the accuracy of the inputs. Stress testing the results is useful but is always relative to a base case. The stress-testing can be thought of as either checking what happens if a variable changes compared to what was expected, or checking what happens if a mistake was made in initial assumptions.

Commentary: Comparison of replacement vaccine scenarios (non-XDR versus global XDR)

1) The value of the market as measured by NPV is low whether there is global XDR or not;
2) The difference in NPV is only just over $100m, which might be thought low for such a long-term and expensive investment. The analysis suggests that global-XDR is low 'value' in terms of any positive impact on NPV of replacement vaccines;
3) The ASC comparison is for the purpose of analyzing the differential impact on the Aeras portfolio (it is not an analysis of a global portfolio or of an 'optimal' portfolio);
4) The differences are almost entirely driven by prices since quantities hardly change, yet we also saw that the prices were essentially presumed based on 'best guesstimates';
5) The only competition is with one other BCG replacement vaccine. What is the story regarding what happens if more vaccine candidate go into clinical trials (for

example in response to high expected NPV on account of global XDR), and what about if there is competition with a range of non-TB vaccines?;
6) There is a much greater front-loaded impact on revenues, and hence on NPV, under the Global XDR scenario;
7) Little impact is picked up from variance in R&D costs;
8) Little impact is picked up from variance in COGs;
9) An extra reason for low impact caused by variance in some of these factors may follow from the fact that the base case is being held fixed in every other dimension when sensitivity is being judged (for example, uptake is not linked to COG, so the two are not correlated);
10) There is a big impact of competition;
11) No sensitivity is measured to variance of speed of uptake, although Global XDR is presumed to involve higher speed of uptake;

2.4. Boost vaccine

Both BVGH/BCG and ASC create scenarios for boost vaccine demand. ASC separate out infant and adolescent boost vaccine markets and then pull them together to give an overall boost vaccine market under base case and global XDR scenarios.[100]

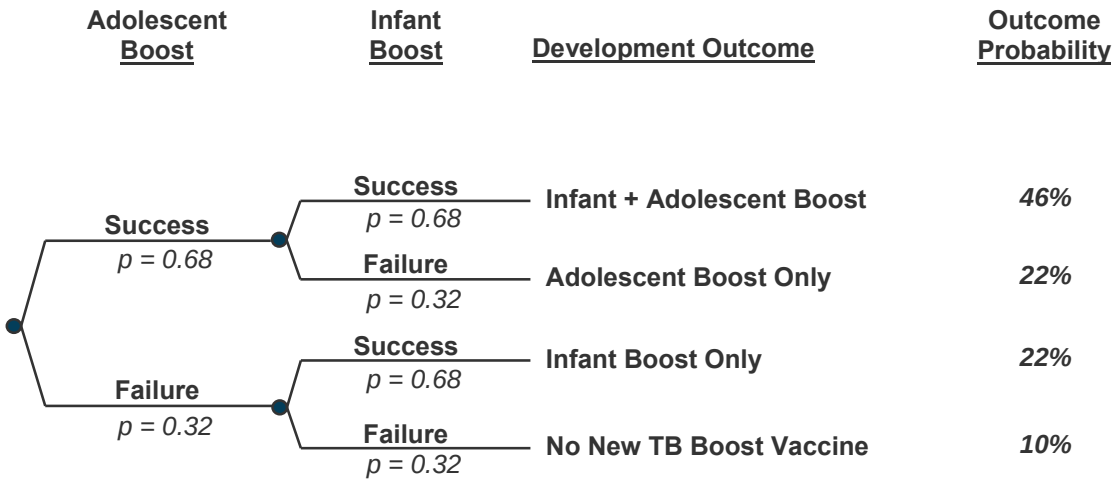
ASC Boost Vaccines

	Probability of Aeras Vaccine Development Outcomes					
	No success	**1 success**	**2 successes**	**3 successes**	**4 successes**	**5 successes**
Infant Boost	32%	42%	21%	5%	0.5%	0%
Adolescent Boost	32%	42%	21%	5%	0.5%	0%

According to these ASC figures, the most likely outcome is one vaccine, but the distribution is important. Under the assumed probabilities there is about 1/3 chance of no infant boost and 1/3 chance of no adolescent boost. These figures are of course extremely dependent on assumed probabilities of success, to which we return later.

ASC has many more boost scenarios:[101]

[100] And a low efficacy scenario that is not performed since it is presumed that Aeras do not have a low efficacy vaccine.
[101] A similar analysis is done to work out probabilities of competition.

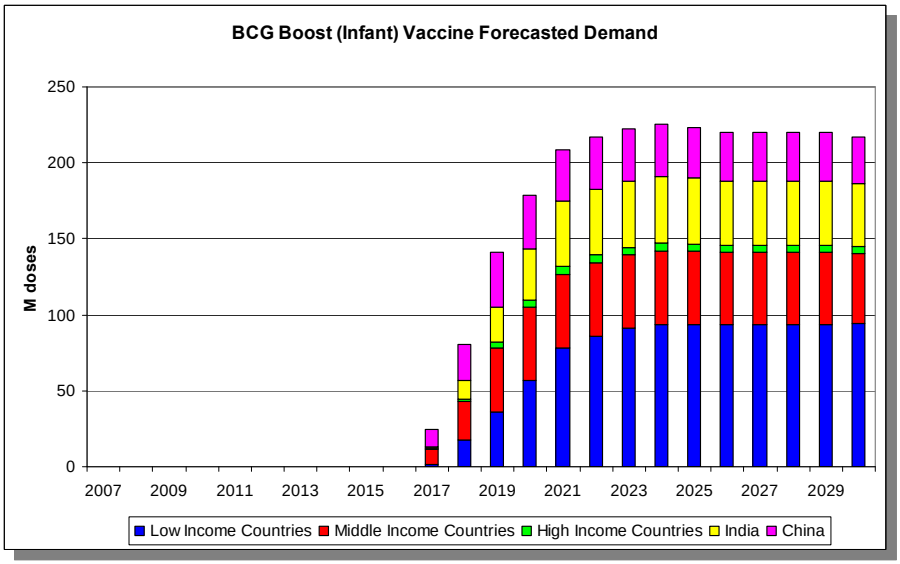


Aeras boost vaccine base case (i.e. no global XDR)

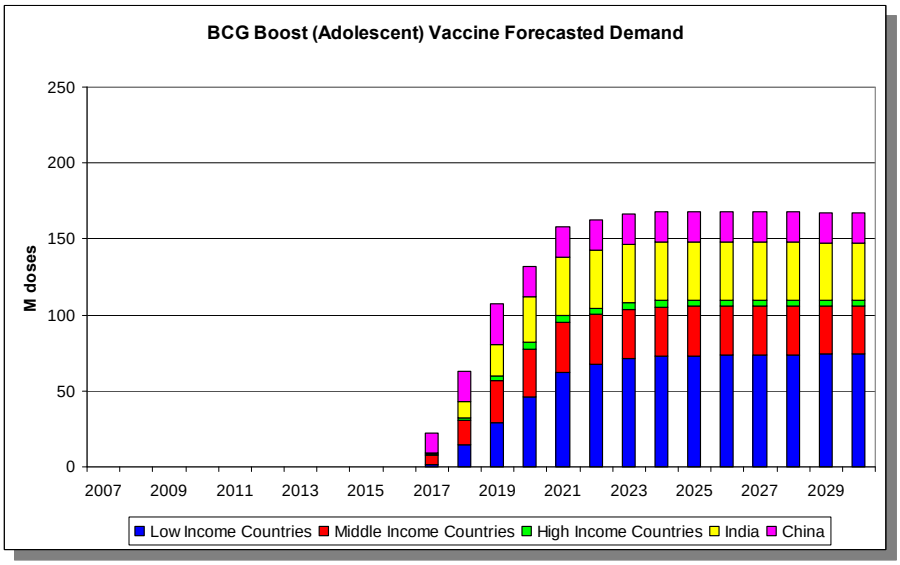
	Probability	NPV value in $ No competition	NPV value in $ Adolescent boost competition (25%)
BCG boost (infant and adolescent)	46%	2,126	1,366
BCG Boost (Adolescent only)	22%	1,115	355
BCG Boost (Infant only)	22%	606	606
No new Aeras TB boost vaccine	10%	(317)	(317)

Expected boost vaccine market NPV: $937m
Underlying the figures are the presumed following demand figures for infant and adolescent markets:

Base case infant boost vaccine demand forecast, millions of doses:



Base case adolescent boost vaccine demand forecast in millions of doses:



Commentary: ASC base case boost scenarios

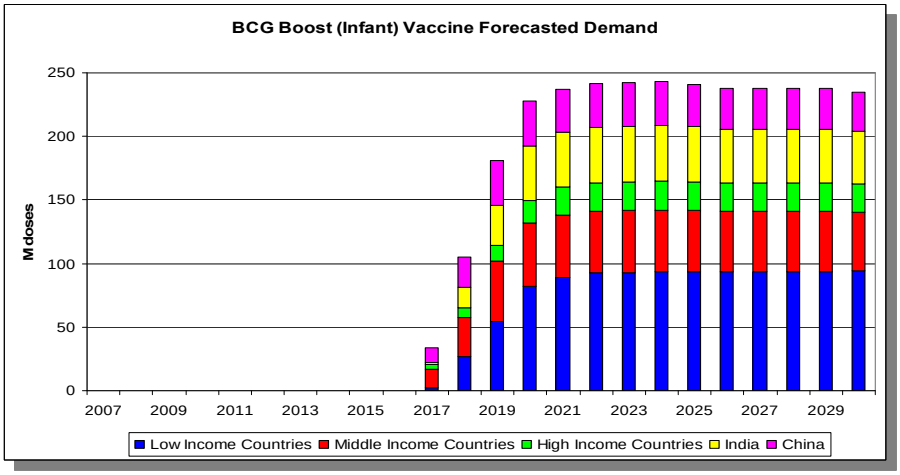
1) Comparison is for Aeras portfolio only;
2) The biggest sensitivity is on account of prices. Low prices are the only way to drive NPV into negative territory;
3) There is little impact of variance in development costs on NPV;
4) There is no epidemiological model underlying this;
5) Here, compared to the replacement vaccine base case, there is a much greater impact on account of variance in COGs;
6) Competition has impact, but it is smaller than COGS variance, and it has an asymmetric impact;
7) Front loading is already presumed in the revenues streams (see original ASC material). This probably explains the lower impact of competition (since early revenue streams are very high);
8) No sensitivity analysis is performed on speed of uptake;
9) Observe that differential pricing is taking as read in these figures. Rich markets pay much more per dose than poor markets.

Aeras boost vaccine market analysis under Global XDR

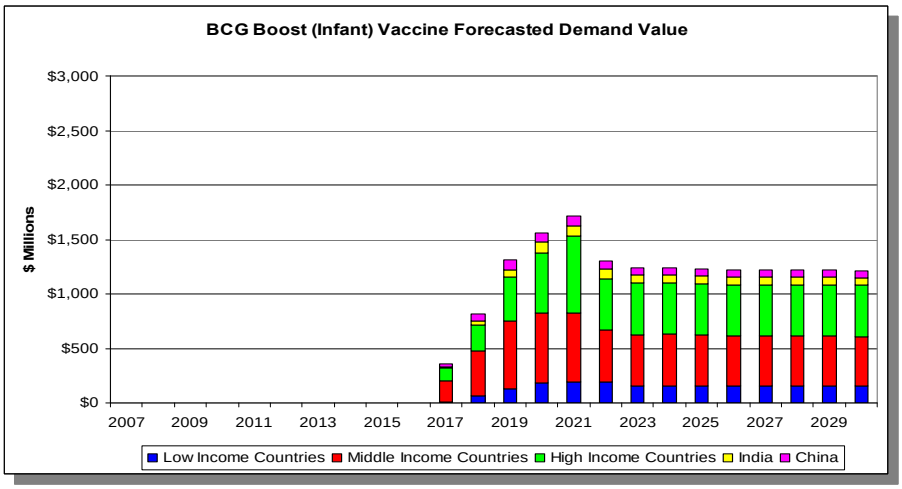
Potential Outcome of Aeras Boost vaccine investment (if Global XDR) in $million:

	Probability	NPV value in $ No competition	NPV value in $ Adolescent boost competition (25%)
BCG boost (infant and adolescent)	46%	$6,210	$4,173
BCG Boost (Adolescent only)	22%	$3,669	$1,632
BCG Boost (Infant only)	22%	$2,136	$2,136
No new TB vaccine from Aeras	10%	($317)	($317)
EXPECTED NPV: $3,036			

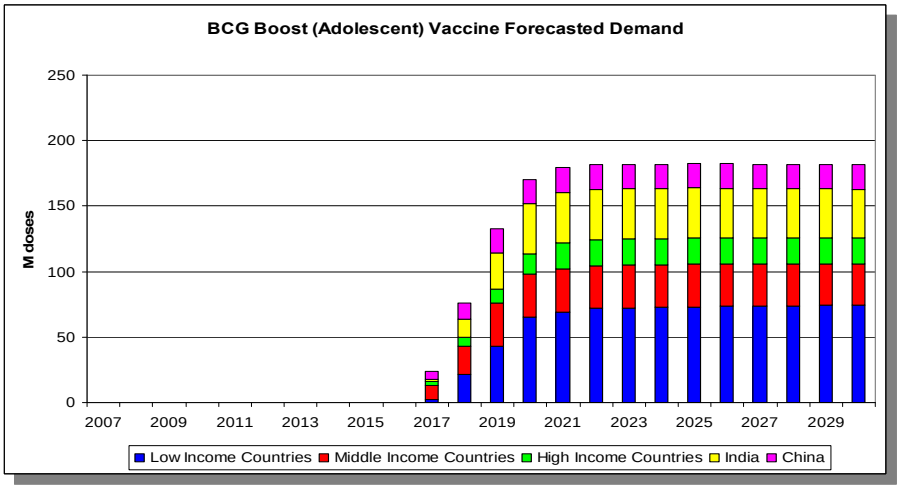
Global XDR infant boost vaccine demand forecast, millions of doses:



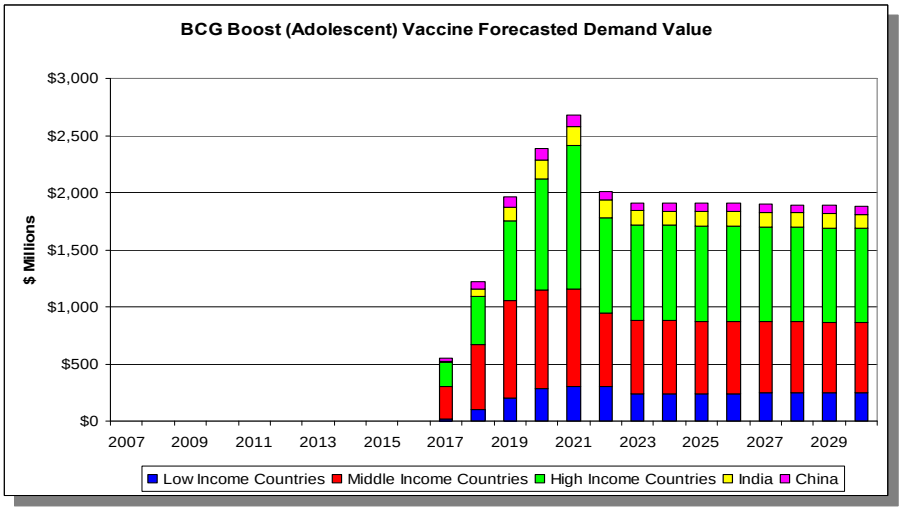
Global XDR infant boost vaccine demand forecast, in dollars:



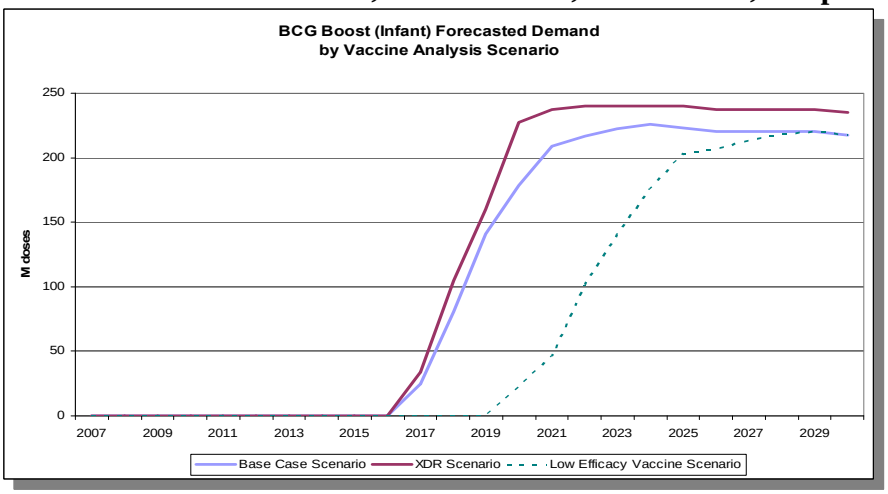
Global XDR adolescent boost vaccine demand forecast, millions of doses:



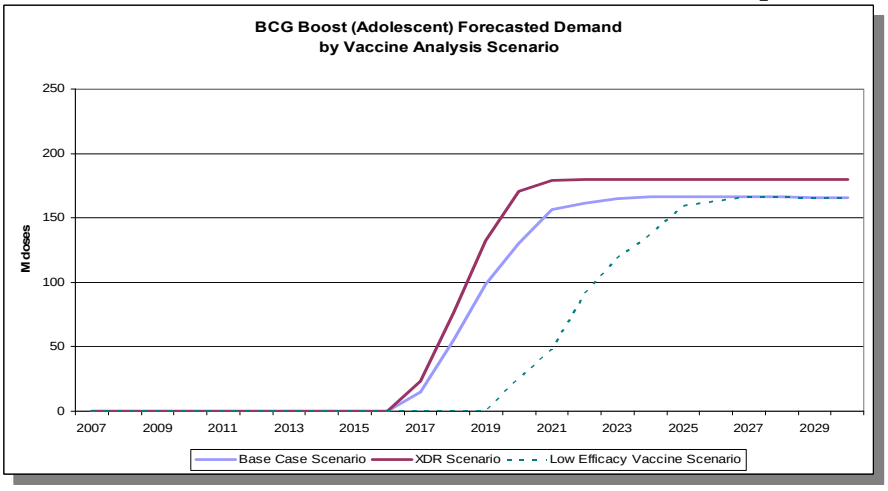
Global XDR adolescent boost vaccine demand forecast, in dollars:



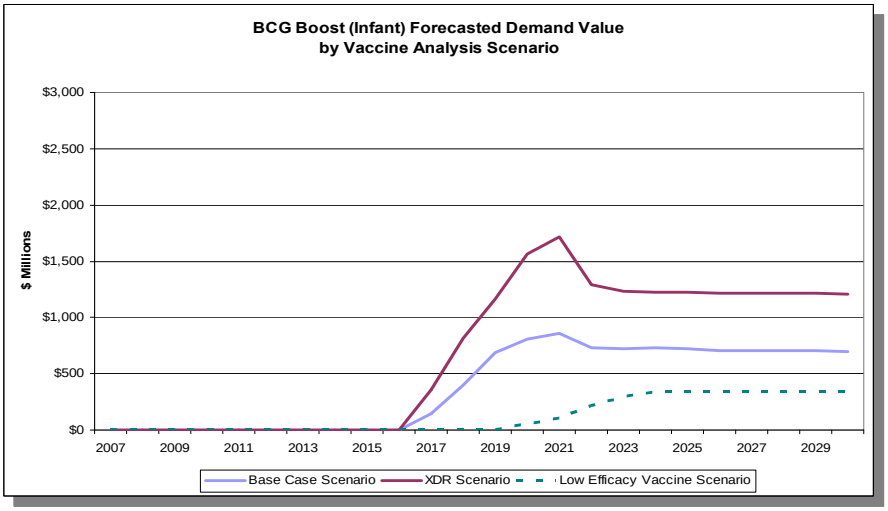
Forecasted demand in doses, infant market, all countries, compared:



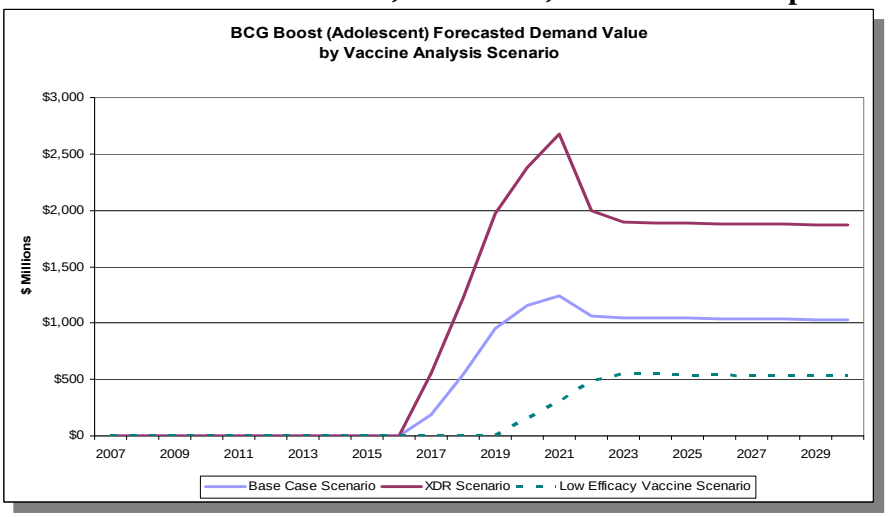
Forecasted demand in doses adolescent, all countries compared:



Forecasted demand in dollars, infant, all countries, compared:



Forecasted demand in dollars, adolescent, all countries compared:



Commentary: Aeras boost vaccine scenario comparison

1) The value of the market for boost vaccines is found under this analysis to be higher than for replacement vaccine;
2) As before, the result is mostly driven by the front-loading of pricing times quantity – so this is mostly a pricing affect – and by the strong assumption about uptake of booster vaccines;
3) There is no epidemiological framework underlying this analysis;
4) As above, percent chance of competition is not grounded in any 'fact'. No sensitivity analysis is done according to the probability of competition;
5) As before, this does not analyze the global portfolio figure, only the Aeras portfolio;
6) There is no sensitivity analysis according to speed of uptake;

7) One might wonder why, if NPV is so high for boost vaccines, the NPV is not driven down by a greater number of potential vaccine candidates (and hence higher expected development costs);
8) Indeed, depending on the probability of XDR, the *minimal* Aeras NPV in this analysis is $937m, rising to over $3000m in the case of global XDR. What does the relative lack of vaccine candidates in the face of this potentially high NPV tell us? It is at least possible that the level of NPV is coming out too high either because of an exaggerated notion of the size and value of the market, or because of an exaggerated notion of probabilities of success of candidates. If investors are not investing more in the face of such high NPVs, this is one of the more reasonable explanations;
9) The differential pricing is even more clear in these diagrams.

BVGH/BCG booster vaccine analysis

Similar to the BVGH/BCG replacement data, there were discrepancies in the number of booster doses accounted for in private market sales, and middle income sales were also off by a tiny amount. Farlow adjusts the figures to be consistent with the data provided by BVGH/BCG resulting in the following boost NPV:

'Correct figures' for BVGH/BCG boost sales:

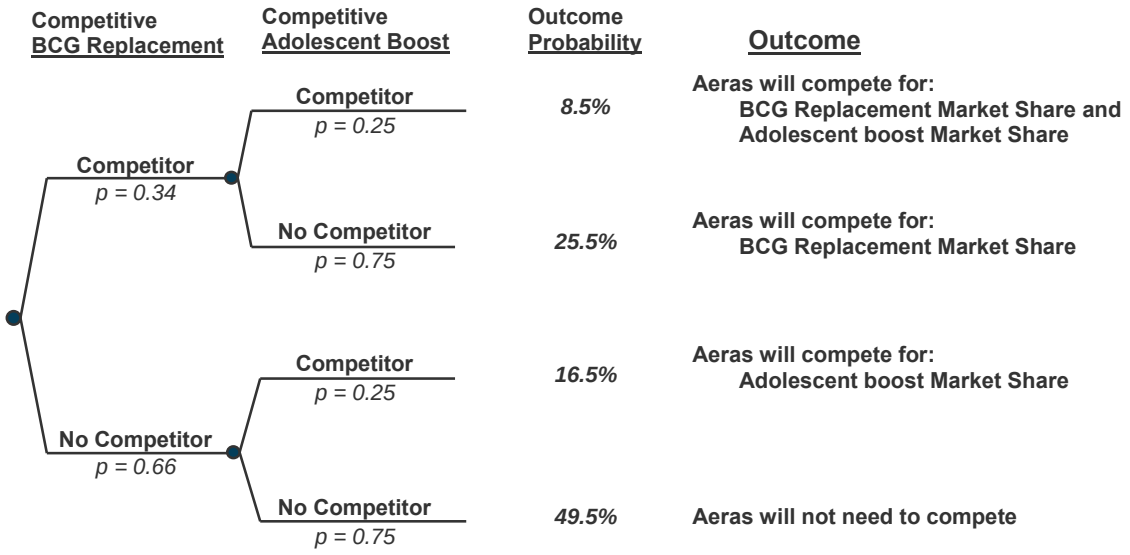
NPV at end 2012 at 20%	$1,280
Discounted to 2005 at 20%	$269
NPV at end 2012 at 15%	$2,134
Discounted to 2005 at 15%	$684
NPV at end 2012 at 10%	$3,569
Discounted to 2005 at 10%	$1,707

These booster NPV figures are much higher than those reported in the BVGH/BCG report, on account of the value of private booster vaccine markets being higher than reported and more in line with the figures of ASC.

2.5 Total portfolios

ASC: Total portfolio results

To work out the NPV of total Aeras portfolios combining both replacement and boost vaccines, a probability of competition is first needed. It is done in a very simple way – and hence is totally dependent on an assumed probability distribution of competitor entry or non-entry – as follows:



Aeras Base-case total portfolio (case of no XDR)

14 cash flow analyses generate the following NPV results for the ASC base case (non-XDR):

Potential Outcomes of Aeras' TB Vaccine Development Portfolio	Likelihood of Outcome	BCG Replacement & Adolescent Boost Competition (8.5%)	BCG Replacement Competition (25.5%)	Adolescent Boost Competition (16.5%)	No Competition (49.5%)
BCG Replacement + Adolescent Boost + Infant Boost	16%	$ 1,448 M	$ 2,208 M	$ 1,616 M	$ 2,376 M
BCG Replacement + Adolescent Boost	7%	$ 438 M	$ 1,198 M	$ 606 M	$ 1,366 M
BCG Replacement + Infant Boost	7%	$ 688 M	$ 688 M	$ 856 M	$ 856 M
BCG Replacement only	4%	($ 236 M)	($ 236 M)	($ 67 M)	($ 67 M)
Adolescent Boost + Infant Boost	31%	$ 1,324 M	$ 2,084 M	$ 1,324 M	$ 2,084 M
Adolescent Boost only	14%	$ 314 M	$ 1,074 M	$ 314 M	$ 1,074 M
Infant Boost only	14%	$ 564 M	$ 564 M	$ 564 M	$ 564 M
No New TB Vaccine	7%	($ 359 M)	($ 359 M)	($ 359 M)	($ 359 M)

Expected NPV of Aeras Vaccine Base Case Portfolio, given competition = $1,235m
Expected NPV of Aeras Vaccine Base Case Portfolio given NO competition = $1,383m

Aeras total portfolio in case of global XDR

A similar number of cash flow analyses generate the following expected returns on the Aeras portfolio in the global XDR scenario:

Potential Outcomes of Aeras' TB Vaccine Development Portfolio	Likelihood of Outcome	BCG Replacement & Adolescent Boost Competition (8.5%)	BCG Replacement Competition (25.5%)	Adolescent Boost Competition (16.5%)	No Competition (49.5%)
BCG Replacement + Adolescent Boost + Infant Boost	16%	$ 4,436 M	$ 6,473 M	$ 4,785 M	$ 6,822 M
BCG Replacement + Adolescent Boost	7%	$ 1,895 M	$ 3,932 M	$ 2,244 M	$ 4,281 M
BCG Replacement + Infant Boost	7%	$ 2,399 M	$ 2,399 M	$ 2,748 M	$ 2,748 M
BCG Replacement only	4%	($ 54 M)	($ 54 M)	$ 295 M	$ 295 M
Adolescent Boost + Infant Boost	31%	$ 4,131 M	$ 6,168 M	$ 4,131 M	$ 6,168 M
Adolescent Boost Only	14%	$1,591M	$ 3,628 M	$ 1,591 M	$ 3,628 M
Infant Boost Only	14%	$ 2,094 M	$ 2,094 M	$ 2,094 M	$ 2,094 M
No New TB Vaccine	7%	($ 359 M)	($ 359 M)	($ 359 M)	($ 359 M)

Expected NPV of Aeras Vaccine Portfolio in Global XDR case = $3,897m. **This is treble the non-XDR case making global XDR probably the most important factor in determining a large NPV according to this analysis.**

Expected NPV of Aeras vaccine portfolio in Global XDR case given NO competition = $4,283m. **This is also approximately treble the non-XDR no-competition case. Again, global XDR probably is the important factor in determining a large NPV according to this analysis.** In both cases, this is in spite of relatively little epidemiological analysis of global XDR.

3. RATE OF ADOPTION AND MECHANISMS OF UPTAKE

3.1. Introduction

In the investment cases so far performed, an important underlying set of forces generating higher or lower market revenues, and hence NPVs, comes through pattern and speed of uptake of new vaccines. The wider the coverage and the quicker the uptake, the greater the number of doses of vaccine used and the higher the revenues and the greater the chance of covering R&D costs (and, given the high rates of discounting, the higher the NPV)

BVGH/BCG

In the BVGH/BCG report, the revenue figures going into the NPV calculations are based on the following assumed coverage rates "necessary to accrue full benefits":[102]
BCG replacement: 85%
Booster (where booster used): 66%

Taking a closer look at BVGH/BCG data on dose sales (the same pattern for replacement and booster sales since, as Farlow shows, in the BVGH/BCG analysis booster sales are scaled up replacement sales figures (scaled by constant ratios that differ by country but are constant over long stretches of time), we can see certain features to the pattern:

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 India 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 jump following the competitive event.

The sort of questions one might want to ask:

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

ASC:

ASC base case **replacement vaccine** scenario:

[102] Though it is not clear whether rates build to these levels, thus *eventually* accruing full benefits, so that 85% is the long-term *steady state*. Or are these rates assumed at the start?

- All countries currently using BCG vaccine as an infant prime will switch to the more efficacious BCG vaccine replacement
- All countries currently using BCG vaccine as a boost will begin using the BCG vaccine replacement at birth
- All Low or Middle Income Countries using BCG vaccine in High Risk Populations will begin using BCG vaccine replacement at birth[103]

ASC base case **boost vaccine** scenario:

- All countries currently using BCG vaccine as infant prime will add the Boost vaccine given their high disease burden status
- All countries currently using BCG vaccine as a boost will switch to the new Boost vaccine
- All Low and Middle Income Countries using BCG vaccine in High Risk Populations will switch to the boost vaccine

Note: In the ASC case there is no presumed take-up in the base-case by High Income High Risk groups of either product if not already using the product. So this rules out the US. BVGH/BCG treats High Income country as taking up in only High Risk groups, including in the US where BCG is currently not used. BVGH/BCG presume boost sales do not take place in poor countries in their base case, while ASC do. See tables.

	Base Case Scenario Assumptions								
	Low Income			Middle Income			High Income		
	Current BCG Usage	BCG Replace Usage	Boost Usage	Current BCG Usage	BCG Replace Usage	Boost Usage	Current BCG Usage	BCG Replace Usage	Boost Usage
Prime Only	67	✓	✓	50	✓	✓	13	✓	✓
Prime & Boost	4	✓	✓	15	✓	✓	0	--	--
Prime & High Risk	0	--	--	0	--	--	1	✓	✓
Boost Only	1	✓	✓	3	✓	✓	4	✓	✓
High Risk Only	0	--	--	1	✓	✓	4	--	--
Do Not Use	0	--	--	3	--	--	14	--	--
Countries Excluded*	0	--	--	6	--	--	10	--	--
Total	72	72	72	78	69	69	46	18	18

Table 3.1: ASC adoption assumptions, base case assumptions
** Required data not available*

[103] Note that this only involved one, middle income, country.

	Global XDR Scenario Assumptions								
	Low Income			Middle Income			High Income		
	Current BCG Usage	BCG Replace Usage	Boost Usage	Current BCG Usage	BCG Replace Usage	Boost Usage	Current BCG Usage	BCG Replace Usage	Boost Usage
Prime Only	67	✓	✓	50	✓	✓	13	✓	✓
Prime & Boost	4	✓	✓	15	✓	✓	0	--	--
Prime & High Risk	0	--	--	0	--	--	1	✓	✓
Boost Only	1	✓	✓	3	✓	✓	4	✓	✓
High Risk Only	0	--	--	1	✓	✓	4	✓	✓
Do Not Use	0	--	--	3	✓	✓	14	✓	✓
Countries Excluded*	0	--	--	6	--	--	10	--	--
Total	72	72	72	78	72	72	46	36	36

Table 3.2: ASC adoption assumptions, Global XDR assumptions
** Required data not available*

3.2. Hep B as a model for adoption?

ASC has three scenarios for adoption based on their base case, global-XDR and low efficacy vaccine. See ASC for particulars.

The BVGH/BCG backup material says that the adoption curve presumed was "patterned on *average*[104] *Hepatitis B adoption curve* (Source: WHO tracking 2005)." The Hep B adoption curve in terms of millions covered is impressive:

[104] A clarification would be useful as to what averaging means, for example if there is weighting for country size.

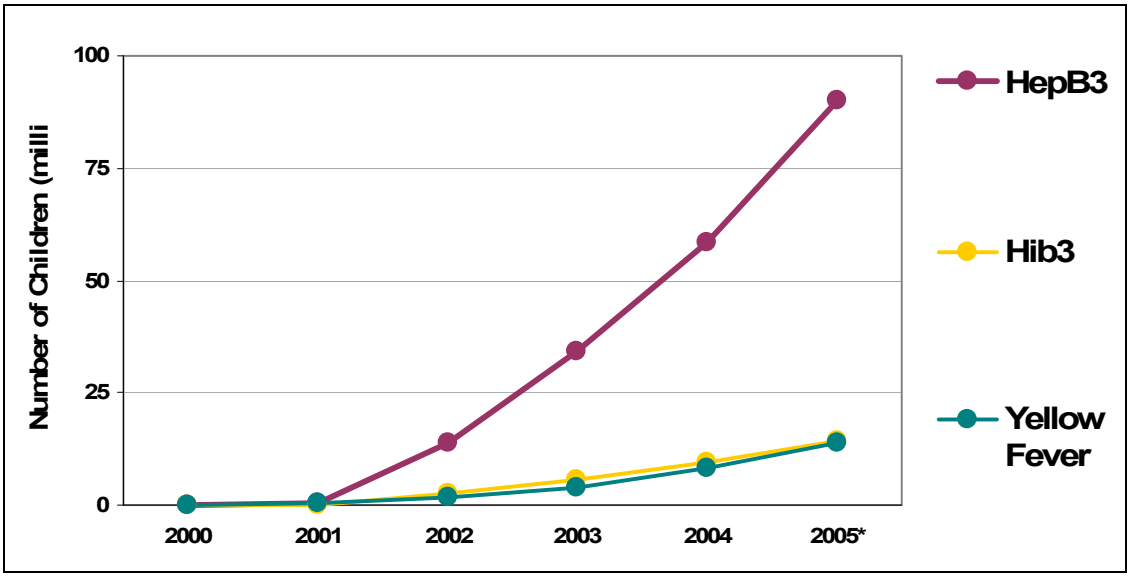


Figure 3.1: Cumulative Number of Children Reached in GAVI-Supported Countries *projected Source: WHO/UNICEF

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

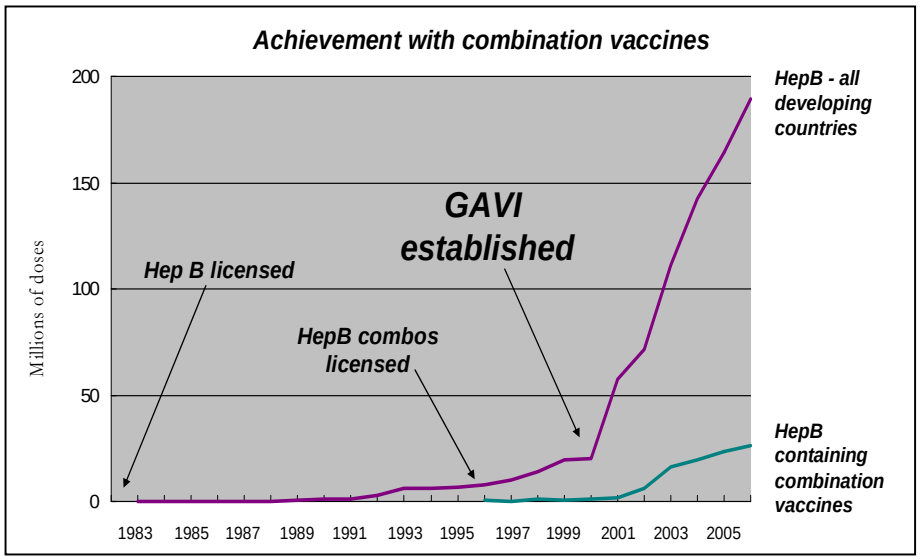


Figure 3.2: Hep B and establishment of GAVI

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%.[105] Conversely, one has to be careful reading causation into the GAVI/Hep B story (there

[105] WHO/UNICEF coverage estimates 1980-2005 as of august 2006. Furthermore, it is not clear in the BVGH/BCG analysis if the rate of *increase* is based on the *rate of increase* of HepB or relates to the levels of uptake in some other way.

were other issues going on like technology transfer and production cost issues, and a range of intensive support activities).

3.3. EPI levels

Many of the countries experiencing the highest impact from TB (and hence key for successful impact of a new vaccine or vaccines) face much lower rates of EPI coverage than 85% (though some key markets for TB vaccines do reach 85% plus).

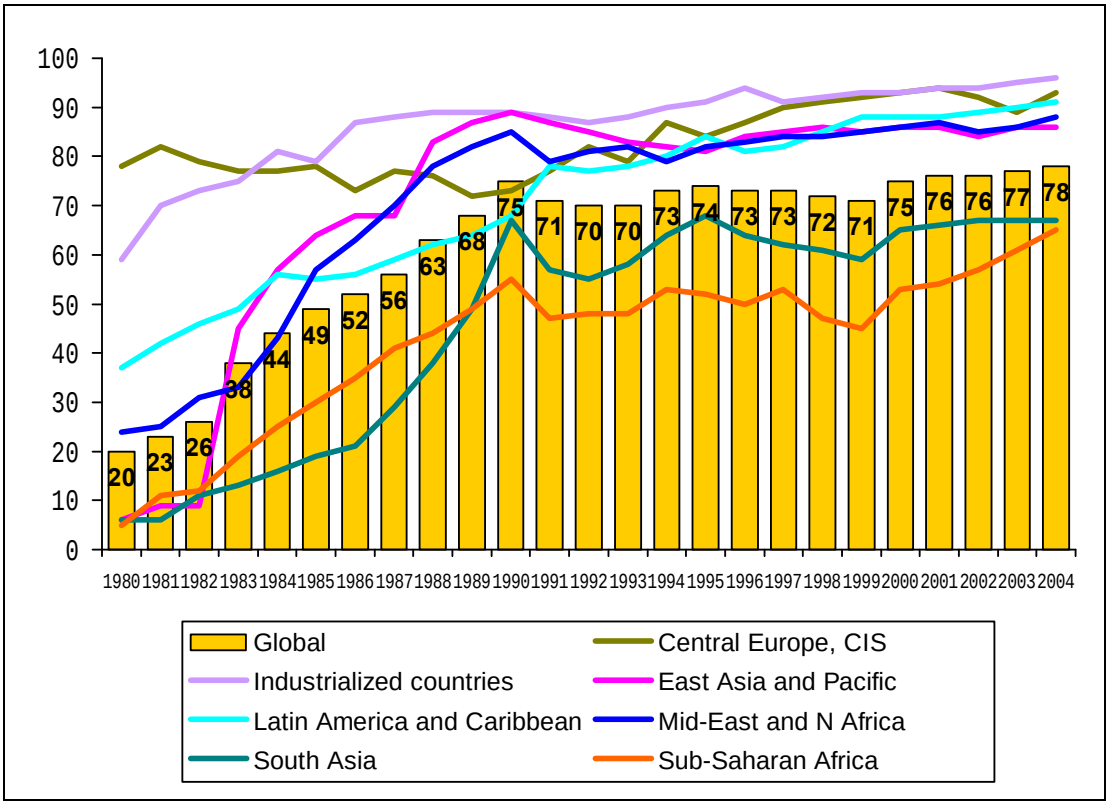


Figure 3.3: Global and regional EPI coverage. Source: WHO, 2005

The issue here would be how realistic it might be to achieve similar 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.

3.4. Efficacy and coverage

BVGH/BCG defines efficacy as 70% for replacement/prime, 70% for Booster, and 80% for Prime-Boost.

ASC defines both replacement vaccine and boost vaccine (infant and adolescent treated the same) product profiles in Base Case and Global XDR scenarios as 60%>BCG. The low efficacy scenario is for 40%>BCG. Prime + Boost efficacy is 100% > BCG under Base

Case and Global XDR scenarios, and 60% > BCG in the low efficacy scenario. In the all cases other than the low-efficacy efficacy case, vaccine efficacy in the ASC scenarios is lower than BCG (60% versus 70%) but the prime and boost combined efficacy is much higher (100% compared to 80%).

The BVGH/BCG report has pretty much no analysis of the role of the relationship between 'target' product profile, coverage/market penetration, and price, since only one profile per vaccine type was speculated by BVGH/BCG. The BVGH/BCG report says that to work out "the potential return on industry investment, the target product profiles needed to capture those market opportunities" still need to be derived (p 7). It is difficult to use the BVGH/BCG 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 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 is that there is a continuous uptake-probability distribution over efficacy with no such discontinuity.

Similarly, in such analysis it is hard to model a big upside if efficacy is higher. It would also be interesting to see more exploration in such analyses surrounding the issues that arise for different degree of immunological memory achieved. What would the impact on NPV be of different possible cases? 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.

4. PRICING STRUCTURES, TIERED PRICING, WILLINGNESS TO PAY

4.1. The principles of tiered/Ramsey vaccine pricing

> "I cannot believe that anyone seriously believes that America should manufacture vaccines for the world, sell them cheaper in foreign countries, and immunise fewer kids as a percentage of the population than any nation in this hemisphere but Bolivia and Haiti."

The argument for tiered pricing (price discrimination) in the vaccine sector is that the cost and demand structures mean that all parties – producers, consumers in rich and poor markets – can benefit, somewhat in defiance of the last quote.[106,107,108]

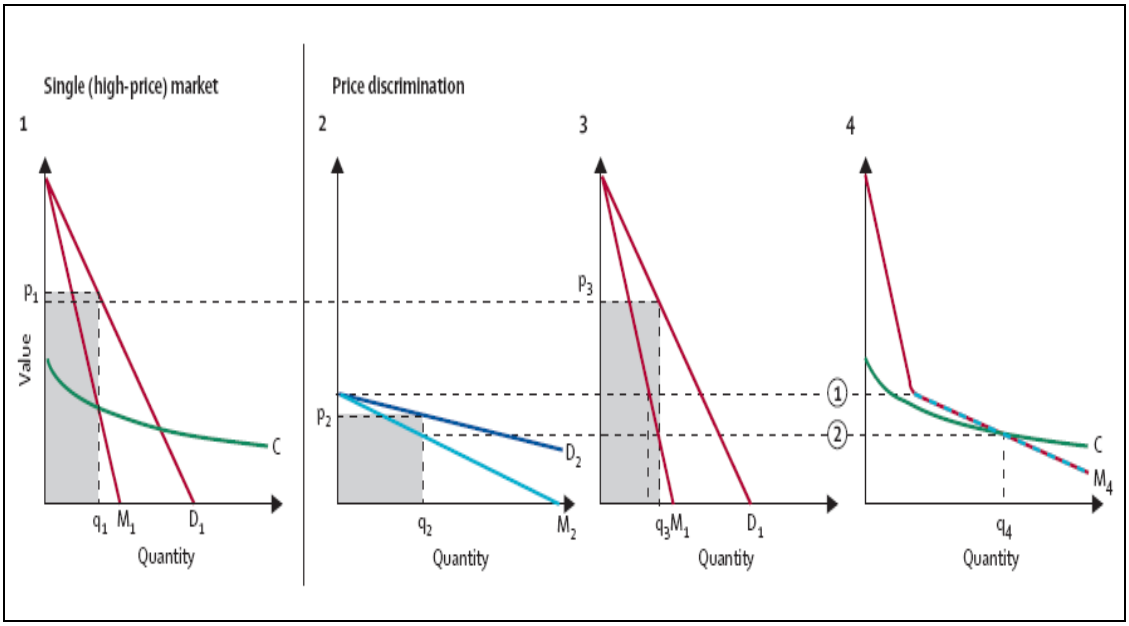


Figure 4.1: The principles of tiered pricing.

[106] The wording of the boxed explanation below is taken from Plahte, J. 'Tiered pricing of vaccines: a win-win-win situation, not a subsidy' *Lancet Infect Dis* 2005; 5: 58–63.
[107] With apologies to Bill Clinton. This is an oft-cited quote of in the vaccine literature, taken from a press conference on the Childhood Immunisation Initiative in 1993. Public papers of the president of the United States. William J Clinton. Book I. January 20 to July 31, 1993. Washington, DC: Office of the Federal Register, National Archives and Records Administration, 1994. These days the Clinton Foundation plays its part in getting product prices down for the developing world, usually well below rich-world prices.
[108] Batson A. "Win-win interactions between the public and private sectors", Nat Med 1998; 4 (5 Suppl): 487–491.

Figure 4.1: *Comparing a producer's output, price, and total revenue when serving a high-price market only (graph 1) with the situation when serving two markets under tiered prices (graphs 2–4).*

Graph 1 shows the situation of a monopolist serving a high-price market only. The producer seeks to adjust total output so that the cost of producing one additional dose (C) would equal the additional revenue gained by selling one additional dose (M_1). Or in more precise terms, optimum profits are attained when marginal cost (C) equals marginal revenue (M_1). This quantity sold (q_1) is obtained by setting the price at p1 according to the demand curve D_1, which shows the expected responses of the consumers' purchases to price changes. Consumers in the high-price market purchase a relatively limited volume at the price p_1, and even dramatic price reductions will only lead to a small increase in sales. Graph 1 shows, more or less, today's situation of US vaccine manufacturers.

Graph 2 shows demand in the low-price market and graph 3 shows demand in the high price market under price discrimination (tiered pricing). Note the diverging demand structures in the two markets. (The high-price market demand curve D_1 is, of course, identical in graphs 1 and 3.) The low-price market demand curve D_2 shows that these consumers will buy nothing when the price exceeds the level of the broken horizontal line 1, but, contrary to the high-price market, sales increase dramatically at even modest price reductions. It follows from graph 2 that the price p_1, which is optimal when serving the high-price market only, would lead to no sales at all if set in the low-price market.

Graph 4 shows the situation of the producer when using price discrimination. Just as in a single market, the producer seeks to adjust production so that the cost of producing one additional dose (C) equals the additional revenue gained by selling one additional dose (M_4). This optimum quantity q_4 is at the intersection of the C and M_4 curves. In terms of economics optimum total output is reached when compound marginal revenue M_4 (the sum of M_2 and M_3) equals marginal cost (C). The producer then seeks to distribute the sales of this output in the two markets so as to maximise profits.

The optimum distribution is reached when the revenue lost of diverting one additional dose from one market is equal to the revenue gained by selling it in the other market. In other words, profits are highest when M_1 and M_2 have the same values, which is on the level of broken horizontal line 2. To achieve these sales volumes, prices have to be aligned with the demand curves in the two markets (D_1 and D_2 respectively), resulting in sales volume q_2 at the price p_2 in the low-price market, and the volume q_3 at the price p_3 in the high-price market.

Graphs 2–4 show the approximate situation of non-US developed-country vaccine manufacturers. Total revenue from the two markets for these producers (the two shaded areas in graphs 2 and 3 taken together) is larger than the revenue of the single high-price market producer (the shaded area in graph 1).

The ability to do tiered pricing is a function of the degree to which a product has sales in richer markets, to which we turn in a moment.

As Plahte puts it:[109]

> "Use of the term subsidy suggests that vaccine prices in the developed countries are higher than they would have been in the absence of low-price sales to the developing countries. This assumption, however, is not correct. Using the term subsidy to describe the tiered prices on the international vaccine market is not only unhelpful, it is also evident from the above that it can mislead politicians and decision makers into discouraging the use of a mechanism that is beneficial to all parties involved."

And as Bishai and Mercer put it:[110]

> "Current world financial systems do not direct TB control resources to areas with the greatest epidemiological need… but to areas with the greatest financial need…Financial criteria alone would allocate a vaccine based on ability to pay, just like any other commodity. Unless world leaders agree to policies that support public and private cooperation to correct inequity, a new TB vaccine is likely to be allocated as unequally as any other scarce commodity…….More attention to measures such as tiered pricing regimes could offer a 'winwin' solution to the tension between public health goals and the participation of private firms in vaccine development."

4.2. Consultancy model pricing structures

We can see some of these tiered pricing principles at work in the consultancy model pricing structures, although the microfoundations of the pricing structures proposed are not spelled out. BCG and AS split markets and use pricing rules different from each other.

BCG Pricing structure:
BCG has a relatively simple pricing structure:

Initial price → post-competitive event price

	BCG Replacement:	**Booster:**	**Prime-Boost:**
High Income:	$75→$20	$75→$49	Prime follows BCG
Private:	$26→$4	$29→$22	replacement price-drop
Middle Income:	$14→$1.25	$15→$6.13	Boost follows BCG
India/China:	$1→$1	No uptake	boost price-drop
Low income:	$3→$1.25	No uptake	

[109] Plahte, J. ibid.
[110] Bishai, D. M., and Mercer, D., 'Modeling the economic benefits of better TB vaccines' (2001) Int J Tuber Lung Dis (11):984–993.

ASC Pricing structure

ASC has a relatively more complex pricing structure:

Countries are grouped as Low Income, Middle Income, High Income (and India and China get LI prices). Within this, there is a public-private market segmentation across all country group cases as follows[111]

Country classification:	***% Public Sector***	***% Private Sector***
Low Income/India/China	90%	10%
Middle Income	70%	30%
High Income	50%	50%

Pricing scenarios are split according to three groups of scenarios: base price, high price and low price.

ASC therefore has 18 potential period 1 prices for replacement vaccine and 18 each for infant boost and adolescent boost under three pricing scenarios. The cases are spread over the next few pages (to avoid squeezing two diagrams to a page and making them too small to read).

ASC Base case prices:

Base

	BCG Replacement Vaccine[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$10.0	$7.5	$20.0	$15.0
MI	$4.0	$3.2	$8.0	$6.5
LI	$0.1	$0.1	$0.2	$0.2

High

	BCG Replacement Vaccine[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$15.0	$10.0	$30.0	$20.0
MI	$5.0	$3.7	$10.0	$7.5
LI	$0.1	$0.1	$0.2	$0.2

Low

	BCG Replacement Vaccine[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$5.0	$4.5	$10.0	$9.0
MI	$2.0	$1.7	$4.0	$3.5
LI	$0.1	$0.1	$0.2	$0.2

Base

	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$20.0	$15.0	$25.0	$18.7
MI	$7.5	$6.0	$15.0	$12.0
LI	$1.5	$1.3	$3.0	$2.7

High

	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$28.0	$18.7	$35.0	$23.5
MI	$10.0	$7.5	$20.0	$15.0
LI	$2.0	$1.5	$4.0	$3.0

Low

	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$8.0	$7.2	$10.0	$9.0
MI	$3.0	$2.7	$6.0	$5.5
LI	$0.7	$0.7	$1.5	$1.4

Base

	Adolescent Boost to BCG[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$40.0	$30.0	$50.0	$37.5
MI	$15.0	$12.0	$30.0	$24.0
LI	$3.0	$2.7	$6.0	$5.5

High

	Adolescent Boost to BCG[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$56.0	$37.5	$70.0	$47.0
MI	$20.0	$15.0	$40.0	$30.0
LI	$4.0	$3.0	$8.0	$6.0

Low

	Adolescent Boost to BCG[3]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI	$16.0	$14.5	$20.0	$18.0
MI	$6.0	$5.5	$12.0	$11.0
LI	$1.5	$1.4	$3.0	$2.8

[111] Public and Private market segmentation assumptions for LI & MI from PneumoADIP, 2006 analysis (ASC comment that there is "no credible segmentation data available"). HI assumptions from Aeras/ASC discussions, May, 2007.

ASC global XDR prices:

Base Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$15.00	$10.00	$30.00	$20.00
MI Countries	$5.00	$3.75	$10.00	$7.50
LI Countries	$0.10	$0.10	$0.20	$0.20

High Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$22.50	$15.00	$45.00	$30.00
MI Countries	$7.50	$5.60	$15.00	$11.30
LI Countries	$0.10	$0.10	$0.20	$0.20

Low Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$7.50	$5.00	$15.00	$10.00
MI Countries	$2.50	$1.90	$5.00	$3.80
LI Countries	$0.10	$0.10	$0.20	$0.20

Base Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$28.00	$18.75	$35.00	$23.50
MI Countries	$10.00	$7.50	$20.00	$15.00
LI Countries	$2.00	$1.50	$4.00	$3.00

High Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$42.00	$28.10	$52.50	$35.30
MI Countries	$15.00	$11.30	$30.00	$22.50
LI Countries	$3.00	$2.30	$6.00	$4.50

Low Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$14.00	$9.40	$17.50	$11.80
MI Countries	$5.00	$3.80	$10.00	$7.50
LI Countries	$1.00	$0.80	$2.00	$1.50

Base Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$56.00	$37.50	$70.00	$47.00
MI Countries	$20.00	$15.00	$40.00	$30.00
LI Countries	$4.00	$3.00	$8.00	$6.00

High Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$84.00	$56.30	$105.00	$70.50
MI Countries	$30.00	$22.50	$60.00	$45.00
LI Countries	$6.00	$4.50	$12.00	$9.00

Low Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$28.00	$18.80	$35.00	$23.50
MI Countries	$10.00	$7.50	$20.00	$15.00
LI Countries	$2.00	$1.50	$4.00	$3.00

Commentary on consultancy firm pricing structures

Looking at the ASC pricing structure the following thoughts come to mind:

1) These prices do not appear to be based on market research on the ground related to TB per se, or on comparative (with other vaccines) market analysis. This is not a criticism per se; if one is asked to generate revenues and NPV, some prices are needed. If there are none, one comes up with plausible-sounding prices. We should treat them with a great deal of provisionality until proven otherwise.
2) Low Income public sector market prices are low.
3) Private market prices in Low Income countries are presumed to be low too. They may be twice the public sector price, but the public sector price is an already low price. In China, families were prepared to pay $3 a dose for Hep B when they could not get it in the public sector, and this is well above the 20 cents presumed here.
4) There is a huge amount of tiered pricing nevertheless presumed across countries; the rich markets pay for a very small number of doses at up to 100 times the

prices paid in poor countries. The biggest case of tiered pricing takes place when there is global XDR replacement.

5) If China and India are given LI prices, this will underestimate the size of contribution from China and India.
6) 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? Is ten years long enough (in light of some of the discussion in Section 1 above)
7) Although scenarios were done across pricing, the implications of different pricing outcomes were relatively lightly stress-tested in the ASC case.
8) Given the quantities involved, the ability to price discriminate within Low Income and Middle Income countries across the public and private sectors may be an important way to sustain access to the poorest segments of society. The framework here is not testing sufficiently for this.
9) It would be useful to do some comparative analysis of other vaccine markets.

ASC low efficacy prices:

Base Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$5.00	$4.50	$10.00	$9.00
MI Countries	$2.00	$1.75	$4.00	$3.50
LI Countries	$0.10	$0.10	$0.20	$0.20

High Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$7.50	$6.80	$15.00	$13.50
MI Countries	$3.00	$2.60	$6.00	$5.30
LI Countries	$0.10	$0.10	$0.20	$0.20

Low Pricing	BCG Replacement Vaccine[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$2.50	$2.30	$5.00	$4.50
MI Countries	$1.00	$0.90	$2.00	$1.80
LI Countries	$0.10	$0.10	$0.20	$0.20

Base Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$8.00	$7.25	$10.00	$9.00
MI Countries	$3.00	$2.75	$6.00	$5.50
LI Countries	$0.75	$0.70	$1.50	$1.40

High Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$12.00	$10.90	$15.00	$13.50
MI Countries	$4.50	$4.10	$9.00	$8.30
LI Countries	$1.10	$1.05	$2.30	$2.10

Low Pricing	Infant Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$4.00	$3.60	$5.00	$4.50
MI Countries	$1.50	$1.40	$3.00	$2.80
LI Countries	$0.40	$0.35	$0.80	$0.70

Base Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$16.00	$14.50	$20.00	$18.00
MI Countries	$6.00	$5.50	$12.00	$11.00
LI Countries	$1.50	$1.40	$3.00	$2.80

High Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$24.00	$21.80	$30.00	$27.00
MI Countries	$9.00	$8.20	$18.00	$16.60
LI Countries	$2.20	$2.10	$4.60	$4.20

Low Pricing	Adolescent Boost to BCG[1]			
	Public Markets[2]		Private Markets	
	t = 0	t = 5	t = 0	t = 5
HI Countries	$8.00	$7.20	$10.00	$9.00
MI Countries	$3.00	$2.80	$6.00	$5.60
LI Countries	$0.80	$0.70	$1.60	$1.40

4.3 Incentives for rich market and 'high risk' market uptake, and implications for tiered pricing strategies

Rich market sales are potentially key ability to price discriminate and to creating positive NPV (though this depends on what closer analysis shows is possible in terms of middle income and private markets and pricing power in poorer countries. And this does not rule out the option of heavily subsidizing the R&D of new vaccines and using a heavy dose of price discrimination even at low or negative NPV).

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.

In the biggest high-income market of all, the US, vaccination with BCG is not recommended because it has unproved efficacy in the U.S. population,[112,113] it confounds the results of tuberculin skin testing,[114] and other measures have proved to be more effective in reducing incidence of TB. A previous episode of TB resurgence, including multidrug-resistant TB, encouraged recommendation of use of BCG for infants and children with exposure to *M. tuberculosis* in settings in which other protective measures were either inaccessible or proven ineffective and HCWs when likelihood of exposure to multidrug-resistant TB was high and control measures have not been successful.[115] However, once TB control improved and there was a decline of multidrug-resistant TB, use of BCG declined.[116] Unless multidrug-resistant TB breaks out again, US interest is mostly in a vaccine that protects adults with LTBI against acquiring TB disease.[117]

The BVGH/BCG report observes that "Epidemics of similar impact [to poor countries, and especially those being ravaged by HIV][118] 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.

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[112] Comstock GW, Woolpert SF, Livesay VT. Tuberculosis studies in Muscogee County, Georgia. Twenty-year evaluation of a community trial of BCG vaccination. Public Health Rep 1976;91:276--80.
[113] Comstock GW, Livesay VT, Woolpert SF. Evaluation of BCG vaccination among Puerto Rican children. Am J Public Health 1974;64:283--91.
[114] Menzies D. What does tuberculin reactivity after bacille Calmette-Guerin vaccination tell us? Clin Infect Dis 2000;31 Suppl 3:S71-4.
[115] CDC. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. MMWR 1996;45 (No. RR-4):1-18.
[116] More of the history of this at 'Controlling Tuberculosis in the United States Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America' http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5412a1.htm.
[117] CDC. Development of new vaccines for tuberculosis: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET). MMWR 1998;47 (No. RR-13):1-6.
[118] Comment not in original.

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.[119]

To motivate an argument that there would be incentives to adopt a new TB vaccine, the BVGH/BCG 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 in that analysis to back a $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 and how different product profiles would affect this decision:

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 means, 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 by rigorous monitoring and antibiotics. We need to 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? There must be point when use of a vaccine is triggered, and one imagines reaction is very discontinuous around this point (that is there is not a smooth function of take-up as efficacy rises – it discontinuously jumps once a critical threshold is reached).

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

iii) This increases the chances of any new vaccine not being adopted in rich markets and it therefore being difficult to price discriminate. Note, however, that there is an expected and an actual outcome in the price discrimination 'game' once R&D and uncertainty are properly factored in. In the expected outcome – before we know what sort of vaccine we get (to the extent that a universally applicable vaccine is targeted) – a successful product may lead to R&D costs recouped across all markets with price discrimination and positive NPV. In the actual outcome, the ex post state of the world may dictate a vaccine that can only be used in developing countries (insufficient efficacy) at prices that still reflect this ex ante reality even if NPV is negative; from investors' perspectives it is the ex ante 'gamble' that matters.

In the key US market, on which the BVGH/BCG 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 VGH/BCG 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, something that is quite difficult to imagine.

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? None of the market and investment case analyses really grapple with the degree to which rich and poor countries might have different incentives to adopt solutions. In fact neither contains 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. Relying 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) may not be the most obvious; 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?

Is there an overly optimistic view being taken also of the speed of response of organizations to change their practice. Certainly, given the required size of the rich market and the requirement that it be activated soon after licensure in order to make the

market quantities and NPV analysis favorable in some of the analysis (because of the high rates of discount), it would be extremely valuable to have some more in-depth analysis of the decision mechanisms for achieving quick uptake in such markets for, say, a 70% replacement efficacious replacement product.

In conducting this portion of the work, 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 of a replacement vaccine of, say, 70% efficacy as presumed in the BVGH/BCG analysis, was not at all a given. Similarly for booster vaccines; 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 issues here have yet to be explored. It would be useful to see further analysis of the costs of reaching some of these groups (LTC, homeless), 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.

As a case in point, successful TB control in the US relies on strategies to control immigrant TB in the US and support by the US in TB control in the countries of origin. One consequence is that number of cases in foreign-born persons in the US has remained constant over the last 15 years, and the number of cases in US-born persons has actually fallen over time.

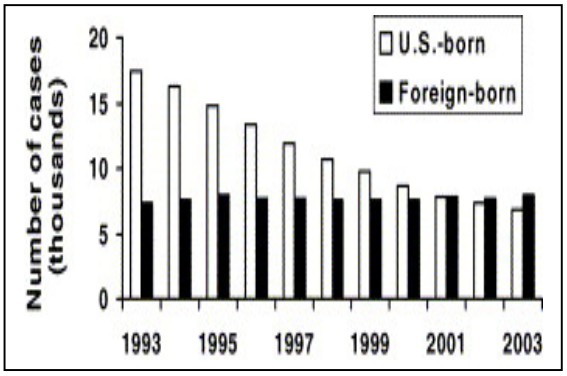

Figure 4.2: Number of US TB cases in US-born and foreign-born persons, 1993–2003. Data from the Centers for Disease Control and Prevention (CDC).[120]

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/BVGH report comes from richer markets, and, indeed, from high-risk groups in these markets, especially in the richest market of all – the US.

[120] Taken from Frothingham R, J E stout, C D Hamilton "Current issues in global tuberculosis control" *International Journal of Infectious Diseases* (2005) 9, 297-311.

The following table shows some additional NPV calculations performed by BCG for BVGH allowing for some changes in rich market high-risk groups compared to that in the original report:[121]

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**

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 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? Here are some more figures to peruse:[122]

[121] 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.

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

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

Further rich market scenarios based on BVGH Figures

Clearly, we need to explore further how useful rich-world markets will be in helping to cover R&D costs and enabling price discrimination. To help illustrate the possibilities, Farlow does a range of further calculations.[123]

As an extreme case, Farlow removes the rich market high-risk sales from the original BVGH/BCG base case replacement figures,[124] keeping the BVGH/BCG assumptions about other costs (R&D and manufacturing) and probabilities of success.

SCENARIO: No high income market compared to BVGH/BCG

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)

[123] 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 BVGH/BCG. Further scenarios involving different cost assumptions are presented in Section 6 further down.

[124] Requiring also removal of revenues and COGS.

All NPV are heavily negative. If costs of development are higher than BVGH/BCG presume (see below), these figures become even more negative (see below). *Clearly, sales in these rich market high-risk markets are key to the BVGH/BCG finding of positive NPV in the case of replacement vaccines.* To assess the harm of presuming lower – though still positive – high-income markets, Farlow does two more scenarios on the BVGH/BCG figures:[125]

SCENARIO: 50% less high income market compared to BVGH/BCG report[126]

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

Rich-world per dose price, replacement vaccine

The BVGH/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 impacts all countries including rich countries. Farlow does a number of rich market scenarios based on less generous pricing.[127]

SCENARIO: High income pays $50 till competitive event in 2022[128]

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

SCENARIO:

50% less high income market. $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

[125] With appropriate adjustment to COGS in light of change in quantities.
[126] Based on original BVGH/BCG figures Throughout, the comparison, unless otherwise specified, is with respect to the report, which itself is not 100%. We drop this henceforth from scenario descriptors.
[127] Presuming the quantities are the same. Based on the same R&D costs and success probabilities as BVGH, with COGS adjusted.
[128] 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 original BVGH/BCG report – that sales stay the same in rich markets. Based on BVGH/BCG original figures.

SCENARIO:
20% less high income market. $50 in high-income market till competitive event, 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 all market analyses there is a presumed competitive event that reduces prices greatly in rich markets. Indeed, the absolute level of decline is huge compared to poor markets. It is not clear why this should necessarily hold. If prices in richer market persisted at higher levels for longer, more ability to price discriminate would be possible. What if licensing and other agreements can stipulate higher prices post-2022 in these richer markets?

Rich market scenarios: Booster vaccine

The spreadsheet of data provided by BVGH/BCG comes from their base case scenario for booster vaccines.[129] Given important caveats, the following were done:[130,131]

SCENARIO:
No high income market for booster vaccine at all[132]

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 booster market[133]

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

[129] 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.
[130] There were problems making the private market booster figures add up. In the following calculations this tends to pull NPV down compared to what it would be. For details, see the original Farlow report.
[131] 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.
[132] Based on original BVGH/BCG figures.
[133] Based on original BVGH/BCG figures.

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.)

The BVGH/BCG figures re-analyzed.

The problem is that the original BVGH/BCG figures underestimate the private sector revenue figures (and BVGH/BCG agreed that this was the case). With the figures adjusted, matters look a bit rosier:

Scenario: With no high income markets at all, booster vaccine NPV is as follows:[134]

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

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:

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

Clearly, it needs to be clarified exactly what is going on in the figures supplied by BVGH/BCG, since a straight removal of high income markets under the revenue figures given in the BVGH/BCG report yields much worse figures than these.

On the positive side, at least the recalculations illustrate the power of private market sales. It also suggests that under the NPV figures based on the revenue figures provided by BVGH/BCG, the power to use tiered pricing in the case of booster vaccines is very weak, while under the corrected figures the power to use tiered pricing is much greater. 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.

[134] 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.

BVGH/BCG Prime-boost figures

Farlow reports problems with the BVGH/BCG prime-boost data. The main problem seems to be under-reporting of prime-boost revenue figures because high income replacement vaccine is excluded in the spreadsheet provided by BVGH, and the private market figures used in the spreadsheet calculations seem to have been too low by quite some margin. Doing the needed adjustments and using the BVGH/BCG pricing rules, we get much higher NPV in the prime-boost scenario. With these adjustments, NPV rises (details in the Farlow report) and is more in line with the calculations of ASC.

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

Using these 'corrected' figures, we can do the following calculations.

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

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

All these figures are much better than the original report. The bottom line is that one needs to be extremely cautious in interpretation of the base case prime-boost financial returns in Table 2 of the BVGH/BCG report, if based on the spreadsheet figures given to Farlow.[135] Together the different analyses point to the importance of high value prime boost sales in NPV.

Clearly the 'rich market' issue needs to be more rigorously thought through and settled.

4.4. Scenarios for non-rich markets and implications for tiered pricing strategies

Meanwhile, price discrimination need not be just about rich markets. It can involve intermediate-income markets and the private as well as the public sector in middle- and low-income markets. Based on the BVGH/BCG data, Farlow does a number of scenarios of replacement vaccine for non-rich markets regarding coverage and speed of uptake (holding the rich market the same and presuming costs are the same[136]) and comes up with plenty of interesting findings. None of these can be said to be anything other than experiments.[137] It

[135] Along the way, Farlow also discovered that the boost demand figures (in spite of relevant epidemiological thinking) are simply scaled up versions of the replace demand figures, and not independently driven.
[136] As always too, that this is the base case needs to be factored into discussion of the results.
[137] In order to do this analysis, 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. No adjustment is made for R&D, facilities and maintenance One might imagine that the latter two might be scaled, but it is not obvious. 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.

should be pointed out there were a series of issues regarding the data in the BVGH/BCG report (in particular India/China replacement data, and the overall private sector replacement figures), and hence caveats to bear in mind when reading the following scenarios.[138]

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).[139]

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.

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.[140]

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

Here we add a lower COGS (a cut of just 50 cents on the original COGS of $1) to the above poorer market 'early' scenario. The impact is large because though the sales are at a much lower prices than in 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).[141] Lower manufacturing costs to $0.5. China pays $1. Add India at same doses as China.

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[138] See original Farlow report for the data issues. For example: 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.

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

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

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

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

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

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.[142] If price pressure on COGS is weakened, so is the value of the pull instrument. The key to large NPV here is to boost the uptake of poorer markets earlier. A $1 or $2 mark-up adds greatly to NPV if the quantities are big enough and early enough. The reader may note that a different mechanism is at work to that of a large prize-like mechanism to 'repay R&D costs'. Here the incentive is from generating higher NPV via large purchases early at low COGS in poorer markets, on top of any tiered pricing going on.

4.5. Vaccine catch-up

BVGH/BCG rich market figures do not seem to contain a catch-up phase (that would show up in a bulge of vaccine doses while catch-up was being attempted). Rich market replacement 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 key upshot of this in terms of NPV is that it is not front-loading payments as much as would be the case if there was a stronger catch-up element.

[142] 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).

Aeras gave Farlow some alternative figures[143] that have a large rich-market catch-up component, but are much more pessimistic about long-run rich-market steady state sales (1.4m doses per year, or about half the BVGH/BCG figure).[144] In both the original BVGH/BCG and these alternative figures a huge proportion of the value of sales comes from the US high-risk market.[145]

SCENARIO:
Replace BVGH/BCG with the rich-market catch-up figures provided by Aeras.[146]

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:

SCENARIO:
Replace with catch-up figures
2016 all adjusted to new steady state volumes
No competitive event affecting US market

NPV at end 2012 at 20%	$89.34
Discounted to 2005 t 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:
Replace with catch-up figures
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

[143] Provided by Sanyour.
[144] As well as being very negative about poor markets. This is ignored in the next section so as to concentrate on what happens to the BVGH/BCG figures if only adjusting rich market figures.
[145] See the original Farlow report for the caveats about these figures, in particular that they may undervalue rich-world high-risk markets.
[146] Note that this excludes Finland, Greece, Ireland and Portugal purchasers of current BCG vaccine. IN all calculations appropriate COG adjustments are made. 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

Thus, the catch-up period was beneficial to NPV since early sales are less heavily discounting in calculating NPV. In contrast, as the first set of figures in this section show, the lower long-run equilibrium value of sales pulls NPV down compared to the BVGH/BCG figures.

Observer that this treatment continues to adopt the BVGH/BCG perhaps generous notion of what the price of vaccine of 70% efficacy will be in rich markets

4.6. 'Willingness to pay'

In order to work out 'willingness to pay', BVGH/BCG used a questionnaire.[147] Willingness to pay is always relative to expectations of product impact, efficacy, immunological memory, costs, etc. The sort of issues we might be interested in are:

1) Does questionnaire protocol w.r.t. explanation of efficacy discuss impact on lives saved of different vaccines and vaccine combinations? For example, BCGH/BCG describe 70% as the "minimal target threshold for vaccine efficacy" (BCGH/BCG p11) but is also described as "observed efficacy" (BCGH/BCG Table 1);
2) The BCGH analysis seems to suggest that efficacy and lives saved are very non-linearly related, as evidenced in Figure 6 of the BVGH/BCG report. We know this is also the case from epidemiological reasoning. For example, in the BVGH?BCG report 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 same assumptions regarding duration of immunological memory). How is this (and the limitations of this) communicated in a questionnaire protocol? How does the response to this affect the figures claimed for willingness to pay in different settings?
3) In terms of 'lives saved', the BVGH/BCG report suggests *high value to booster technology*. THE BVGH/BCG 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. The booster vaccine saves a further 400,000 more *per year* at the 2030 horizon when combined with the BCG replacement vaccine. Compared to the costs of development this is high value. It would be nice if some of this value could show up in some way in the investment case analysis.
4) At the 2030 horizon, the BCG replacement strategy saves 300,000 lives per year, 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). The value of the booster seems very high, and may have been poorly communicated in questionnaires based simply on efficacy, where respondents are expected to respond to the difference between 70% and 80% efficacy rates (we presume they understand the implications given boost vaccine, and the extremely high value of this 'extra' efficacy).

[147] The author is not clear what ASC did.

5) If questions are framed in terms of lives saved, does this change the claimed willingness to pay for different vaccines?
6) There seems some confusion regarding what various consumers are willing to pay. On the one hand, BVGH/BCG report 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 $1 maximum threshold. It is very difficult to do controlled experiments in this area, but should claimed limits to be taken as seriously as findings based on actual choices? The BVGH/BCG analysis used 1$ per dose across the analysis of low-income sections of the market.

5. POLICY PROCESS METHODOLOGY TO IMPROVE ACCURACY OF PRICING AND DEMAND FIGURES AND SPEED OF VACCINE UPTAKE

5.1. Introduction

This section explores a possible approach to constructing a framework to improve the demand figures underlying the investment case analyses for TB vaccines. It also starts the process of thinking through ways to use policy processes to improve speed of vaccine uptake, and to take us away from an exclusive focus on figures to the detriment of strategies. At the moment this is mostly a literature review. The comparative work on other vaccines described a separate sections adds to this attempt at a paradigm shift.

It is relatively more obvious how replacement vaccines, if manufactured cheaply, might simply replace current BCG vaccines, but it is not necessarily straightforward. If the costs of manufacturing booster vaccines can be lowered, at some critical point it will become necessary to have a good grasp of how to stimulate their uptake too. For example, a key problem in a country like India is working out how policymakers navigate a space full of new vaccines and not just TB vaccines, each of which makes a potential call on limited resources. Finally, another key interest seems to be how to speed up policy decision-making processes in all cases. Whether one thinks through the investment case lens or the social welfare lens, speed of uptake adds NPV and social value.

This section begins by discussing how analysis of the decision-making process can be used to inform market-building and procurement strategies. The latter is not the focus of this section. This section also does not consider the calculation aspect of any model necessary to convert a decision on vaccine adoption and target demographic into a numerical market size. The literature review focus was on decision-making processes as a key under-exploited lever. This can be seen as a complement to the TB investment case analysis.

The document considers components of the Boston Consulting Group's and Applied Strategies' models which apply to decision making processes, and concludes that, whilst these may have useful elements which should be extracted, these components lack a convincing underlying analytical structure. These parts of their frameworks are largely there because they have proved a convenience for the purposes of projecting results. They have not actually been stress-tested in practice – we have not had a malaria or TB vaccine launch, and the pneumococcal 'launch' is limited – so the reliability of this part of those frameworks has not be tested.

This section then outlines a very brief survey of vaccination and health policy literature. It concludes that some approaches may be worth further exploration, but that others fail to provide an analytical method which could be used to generate anything like the predictions we seek.

This section then sets out some frameworks from the political science and public policy literature. These are argued to provide an analytical structure which is both more convincing (partly because more well-established) and more likely to generate outputs which could be used for prediction, and so should be further explored.

This section then suggests that we progress from this point to map out previous vaccine adoption stories for selected study countries using these frameworks as a rough guide, returning to both the political science literature and vaccination policy literature as appropriate to refine the developing models. These country-specific models would then suggest a research agenda for TB vaccine adoption, especially booster vaccine adoption.

Some of the market assessments presume that booster vaccines are not used in resource-poor settings even though they also suggest that such vaccines hugely amplify the lives saved with vaccines (Figure 5.1: taken from BVGH/BCG TB market assessment without raising any of the obvious caveats about how it was derived):

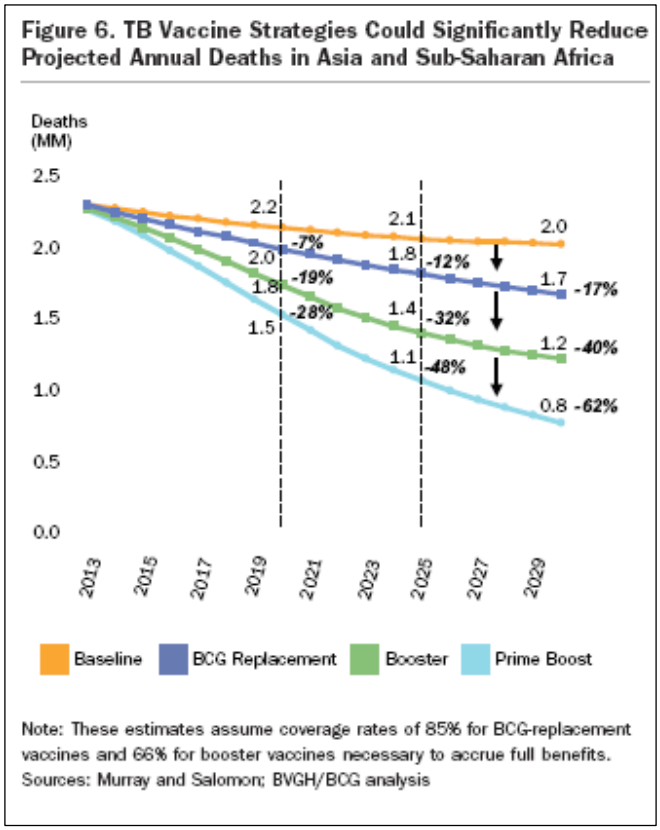

Figure 5.1: Reduction in projected annual deaths in Asia and Sub-Saharan Africa, BVGH/BCG analysis

5.2. Aim

The ultimate purpose of a set of market estimates is presumably to inform the development of appropriate market-building and procurement strategies for TB vaccines. A 'number' would therefore not seem to be of great interest; what is really important is the effect of a particular strategy on country demand and on vaccine product profile via pharmaceutical companies, and so the relationship between different market stimulation scenarios and the respective market sizes associated with them, and that between different product profiles and market sizes.

In trying to influence country demand, we will be trying to affect countries' decisions about vaccine adoption and vaccination strategy: whether to adopt the vaccine, when to adopt the vaccine and how widely to vaccinate.[148,149] Any model or framework we design should therefore include an appropriate analysis of these decision-making processes.

We can think of such a framework as including a machine for each country which models the decision-making process, with a final component converting decisions into numbers (of people vaccinated, of doses purchased). The final outputs are the market sizes on a global, regional, and national basis; whilst the inputs are different market stimulation scenarios or strategies, and the vaccine product profile.

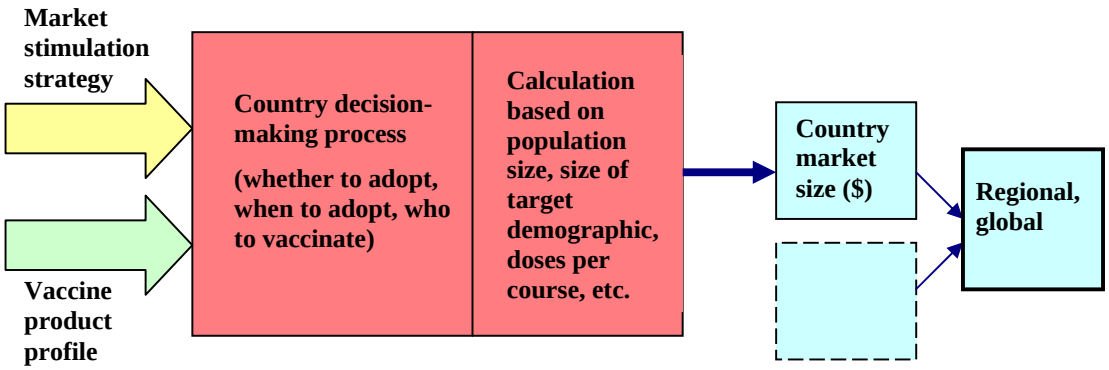

Figure 5.2: The links

5.3. Consultancy models

Two types of model have been surveyed: those designed by the Boston Consulting Group (BCG, used in the BVGH investment case) and by Applied Strategies.

[148] The aim with regard to the last would ideally be chosen in line with a public health objective function, but would not necessarily involve, say, universal vaccination.
[149] Other variables do of course affect market size, but we will not be trying to increase country populations or the severity of dengue epidemics.

The BCG/BVGH model used for its assessment of markets for vaccines[150] what it calls the "Demand Leakage Framework". The important criticism here is of the design of the framework:

- The four stages of the framework do not seem analytically distinct. Funding appears as a determinant in both the Access and Attitude stages. Reaction to product profile seems intuitively an issue of decision-makers' attitudes, but is given its own stage (Product).
- It is not clear that such a progressive 'leakage' process from Need to Product to Access to Attitude reflects the decision-making process, and what the rationale is for use of this approach is apart from a vague plausibility and neatness. Do "decision-makers" (who are they, anyway?) all sit down together and work out who needs the vaccine, then cut down their purchase order by thinking about product profile, then further by thinking about who will be able to access the vaccine, and then (rather conflicting with the first stage) who they *want* to vaccinate? The plausibility does not run very deep.

The Applied Strategies models used for the rotavirus[151] and pneumococcal[152] vaccine investment cases are slightly different to each other. Due to constraints, Applied Strategies work on TB builds off a framework already there.[153] These models are described in rather less detail than is presented in BCG's malaria vaccine work. The rotavirus model classifies countries into tiers. "Early adopters" meet four criteria:

- Relatively high DPT3 coverage
- Hepatitis B and/or Hib vaccines have been introduced
- Significant disease burden
- Country expressed an interest in the vaccine.

The next tier meets most of these criteria but not all, and so on, leaving 8 countries which are not likely to ever adopt (because of reasons such as political instability or poor adoption history for previous vaccines).

The pneumococcal model works out the "earliest time to adoption" (ETA), the minimum number of years for a country to adopt the vaccine given their willingness and ability to adopt. Willingness is assessed by four criteria:

- Burden of child pneumonia deaths
- Ability to measure pneumococcal disease (e.g. the existence of surveillance)
- Presence or absence of other diseases competing for attention
- History of adopting new vaccines

For each of these criteria a country is allocated to a segment. Ability to adopt is assessed by three criteria:

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[150] For purposes of argument, we concentrate on Boston Consulting Group "Market Assessment for Malaria Vaccines" (January 2005) http://malariavaccine.org/files/Market-Assessment-18Jan05-LB-BOS.pdf and a range of PowerPoints issued by BCG.

[151] Rotavirus Vaccine Program "Accelerating the Introduction of Rotavirus Vaccines in GAVI-Eligible Countries" (October 2006).

[152] PneumoADIP "GAVI Alliance Investment Case: Accelerating the Introduction of Pneumococcal Vaccines into GAVI-Eligible Countries" (October 2006).

[153] TB Vaccine Global Market Assessment, July 2007.

- Vaccination infrastructure (using DPT3 coverage as a proxy)
- Economic strength and political stability (using GNI/capita for economic strength)
- Ability to sustain vaccination after donor funding ends

Again, countries are allocated to segments. This process generates three overall segments (early, mid and late) for assigning ETA. These results were then checked by consulting WHO regional offices and other international experts from organisations such as GAVI, USAID and UNICEF.

Without considering these methodologies in detail,[154] some general comments can be made:[155]

- The sets of criteria both models lay out include elements which are quite plausible indicators of the timing of a country's vaccine adoption.
- Without knowing Applied Strategies' rationale for choosing these criteria, we cannot immediately tell if anything important is missing. (This is not necessarily a criticism, but means we could not immediately apply them without answering this question ourselves.)
- Without knowing Applied Strategies' method for combining these criteria, we cannot immediately tell how to weight these criteria and convert them into predictions about timelines. (Again, this is not necessarily a criticism of what Applied Strategies actually did.)
- The pneumococcal model especially has an analytical structure (willingness and ability as determinants of demand) which is relatively convincing.
- Without knowing Applied Strategies' rationale for choosing this structure, we cannot tell immediately whether such a model structure generates demand predictions which are accurate.

This last point is the important one. A list of elements which seem relevant to the timing of vaccine adoption is all well and good, but to what extent should it have credibility as a means of making accurate predictions? Are such models tested to check if they predict past vaccine adoptions accurately? Are such models constructed by using past vaccine adoptions as a guide? Are such models constructed by thinking logically and in detail about the vaccine adoption decision-making process – trying to make sure that they have what economists and other social scientists refer to as good 'microfoundations' which justify it?

Ultimately, given resource constraints, we may have to construct a model or mechanism similar to that used by consultancies such as BCG and Applied Strategies, allocating countries in a relatively crude manner to tiers, and consequently, to years of adoption, so that we can produce a quantitative result for 'market size'. Nevertheless, any such model will have some 'theory' guiding its design, even if that theory is not fully thought through and is based on 'common sense', or on what 'seems plausible', or on 'what people we've interviewed mention as relevant'. The Demand Leakage Framework is based on a theory

[154] The respective reports do not in any case provide as much detail as BCG's malaria vaccine presentation.
[155] It should also be noted that both these models are concerned with GAVI-supported countries, and so are not strictly transferable to our work as they stand.

– it is just not a very good one. The pneumococcal ETA model is slightly better because it at least brings in some basic economic ideas about demand.

Arguably, therefore, we should try to ensure as best we can that any model is underpinned by a solid theory of decision-making, which justifies any predictions made about vaccine adoption more rigorously. There are, roughly two sources of literature which could provide such theory: recent literature on vaccination and health policy (by both practitioners and academics), and disciplines of political science and public policy. The former source seems to try to draw on the latter.

5.4. Vaccination and health policy literature

The literature review has been quite limited in time and scope and this section is not intended to give a comprehensive overview. Rather, this section presents and discusses some ideas and concepts which might be worth employing and pursuing further for the development of an improved demand side of TB vaccine (and drug and diagnostic?) analysis. For future reference, a list of further literature which has been noted but not surveyed is given in section 5.7.

Munira and Fritzen (2007) on government adoption of vaccines in developing countries[156]

The authors criticise the vaccination literature for undertheorising the role of the policy process in adoption. They put forward a framework with three elements:

- Vaccine value characteristics (including target disease burden, safety, effectiveness, efficacy, cost-effectiveness)
- Health system characteristics (including programmatic feasibility of vaccination, vaccine price)
- Policy process and context (including actor interests and interactions, decision-making process and context)

They then continue by describing the hepatitis B adoption stories in Taiwan and Thailand fairly clearly though without really using the framework, and conclude by arguing for the incorporation of policy analysis perspectives into the vaccination literature.

The framework is more a list of relevant elements than a way of thinking about vaccine adoption in a structured way. It is also analytically quite confused: the third element surely encompasses the first two, as policy actors and processes include the consideration of vaccine value and capacity for adoption. In fairness it should be noted that the authors outline interesting policy analysis frameworks and argue convincingly for their use in considering vaccination. We will return to these later.

Gauri and Khaleghian (2002) on political and organisational determinants of immunisation[157]

[156] Munira S L and S A Fritzen "What influences government adoption of vaccines in developing countries? A policy process analysis" *Social Science and Medicine* (2007) 65: 1751-1764.

The authors do a statistical study of coverage rates but also include vaccine adoption, looking at political and institutional variables measuring democracy, regime durability, characteristics of the head of government, extent of decentralisation, and 'institutional quality'. They found that contact with donor agencies was negatively correlated with adoption of new vaccines (the other findings were with regard to coverage rates).

This statistical approach is recognised as a possibility by Munira and Fritzen, although they do not believe it will cast much light on the detail of the adoption process. Although this study is limited in its consideration, such an approach might allow more substantive input into predictions about adoption and the relative importance of different determinants. A similar study was conducted by Miller and Flanders (2000) on the epidemiological and economic determinants of hepatitis B and Hib vaccine adoption,[158] which may be worth exploring.

Much of the more vaccine-specific literature is not so relevant to this question – as Munira and Fritzen point out, it tends to be focused more narrowly on technical questions. It might be useful at some stage though to review this again quickly to incorporate any material. Some specific articles look more promising and might be worth prioritising – these have been highlighted in Section 5.7.

The general tendency though of the more policy-process-specific literature recently surveyed is to draw on political science frameworks and apply to health policy, or even simply to make an argument that this should be done. The logic therefore seems to be that we should go straight to the political science literature and pull out the frameworks which seem most applicable to our question.

Where the vaccination literature will be most relevant is where it describes the vaccination policy process, and it is for this description that we should return to it. Based on this brief survey (and with the caveat that it has been very brief), it is unlikely that this literature analyses that policy process in a structured enough way to yield the type of predictions needed for a quantitative demand estimate.

Walt and Gilson (1994) on using policy analysis for considering health sector reform[159]

The authors here put forward a 'simple analytical model': actors, context and process. The article is mostly an explanation of policy analysis, including a literature review, some elements of which may be worth pursuing further. There is then a section reviewing the literature that exists applying policy analysis to health, including Leichter's (1979) comparative framework for health policy using four contextual categories (situational,

[157] Gauri V and P Khaleghian "Immunization in Developing Countries: Its Political and Organizational Determinants" *World Development* (2002) 30(12): 2109-2132.
[158] Miller M A and W D Flanders "A model to estimate the probability of hepatitis B and *Haemophilus influenzae* type B-vaccine uptake into national vaccination programs" *Vaccine* (2000) 18:2223-2230.
[159] Walt G and L Gilson "Reforming the health sector in developing countries: the central role of policy analysis" *Health Policy and Planning* (1994) 9(4): 353-370.

structural, cultural, environmental) [160] and Reich's (1995) political mapping framework.[161]

The authors' focus is major health sector reform and so some features of the discussion are not so relevant to us. The 'model' itself which they put forward is more a guideline to how one should think about policy, and is not very applicable.

5.5. Political science and public policy literature

In this section are described two frameworks referred to in the health policy literature; other literature noted but not yet surveyed is listed in Section 5.8. for future reference; and there is a substantial political science literature more generally.

Kingdon (2003) on agenda setting and alternative specification[162]

Kingdon focuses on one stage of the policy process, the selection of agenda items for addressing and alternative policy proposals for addressing them, and does not consider the policy selection stage. His framework is based on a detailed empirical study of health and transport policy in the US – care must therefore be taken in transferring the framework to developing countries, but alterations could conceivably be made whilst holding to the logic of the original analysis.

Kingdon sets out two categories of factors: participants and processes. He finds in practice that participants divide into two types: *visible* participants who have considerable press and public attention (such as senior politicians and their high-level appointees, the media, and election-related actors), and *hidden* participants (academic specialists, career bureaucrats and legislative staff). Visible participants are more relevant to the setting of agenda items for consideration, whilst hidden participants are more influential to the specification of alternatives for addressing these items.

Processes divide into three separate streams, which are distinct, although the same participants may be active in different streams. The *problems* stream is where conditions are brought to attention, and where they are defined as 'problems'. The determinants of this process are systematic indicators, focusing events (such as crises), and feedback from current government programmes. The *policies* stream is where proposals are generated – interestingly, *independently of problems*. This process is driven by a sort of natural selection, where successful proposals 'survive' if they meet several criteria: technical feasibility, fit with dominant values and national mood, budgetary constraints, and potential political attitudes. Finally, the *political* stream consists of national mood, interest group activity and legislative and executive orientation, and is driven by the respective political processes relevant to these (e.g. elections).

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[160] Leichter H M, *A comparative approach to policy analysis: health care policy in four nations.* Cambridge: Cambridge University Press, 1979.

[161] Reich M R "The politics of health sector reform in developing countries: three cases of pharmaceutical policy" *Health Policy* (1995) 32:47-77.

[162] Kingdon J W, *Agendas, Alternatives and Public Policies.* New York: Longman, 2003.

Kingdon draws on the 'garbage-can model' developed by Cohen, March and Olsen (1972)[163] which describes 'organized anarchies' (taking academia as their model) where separate streams exist and need to be 'coupled' for action to be taken. Kingdon sees the policy process as a similarly fluid 'organisation'. 'Coupling' is undertaken by *policy entrepreneurs*, people willing to invest resources to push their pet proposals (or problems), and take advantage of a *policy window* to couple proposals to problems, problems to politics, or better still all three, thus successfully setting the policy agenda.

The framework provides a structured way of looking at agenda setting, in contrast to some of the vaccination articles which tend to list elements without relating them to each other. There is logical underpinning to the model and it is borne out by empirical evidence. It is also a way of thinking comprehensively about the policy space, in contrast to the consultancy models – because it is systematically thought through we can be more certain that we are covering all relevant elements of the process.

It also seems to have resonance of what a realistic picture of TB vaccine adoption might look like. There are a range of different actors who will be relevant to adoption (this is of course referred to in the health policy literature, but not so much in the consultancy models which seem to posit a single set of 'stakeholders' who will all think alike). The problem and policy streams may have overlapping participants but are distinct: in each country, TB may or may not be pushing up the agenda as a problem, whilst TB vaccine proponents (Aeras, the pharma companies, country supporters) are pushing the vaccine itself in the field of ideas (including against other TB interventions). Meanwhile the political situation will have to be conducive to the launch of a new vaccination programme if it is to get on the agenda. Kingdon's model is a way of mapping out a complex policy space.

Sabatier and Jenkins-Smith (1999) on the advocacy coalition framework[164]

The authors set out a framework to think about policy debate within a policy 'subsystem', a system within the overall policy system, about the role of policy learning and the formation of policy coalitions. Briefly, policy players have a range of beliefs of varying importance to them, and it is the intermediate category, the *policy core* which holds coalitions together. Actors will abandon their *secondary* beliefs about the detail of policy before the policy core which includes both normative commitments and empirical beliefs about the underlying structure of the problem and the fundamental features of how it should be solved. Cognitive bias plays an important role in both maintaining conflict and maintaining coalitions. The framework generates a number of hypotheses about coalition survival and positions, the drivers of policy change and policy learning.

The framework was cited by Munira and Fritzen (as was Kingdon's) and might be interesting to come back to. At this stage however, it is not clear that it is very relevant to vaccination, because of its overwhelming emphasis on policy conflict. Although there

[163] Cohen M, J March and J Olsen "A Garbage Can Model of Organizational Choice" *Administrative Science Quarterly* (1972) 17:1-25.
[164] Sabatier P A and H C Jenkins-Smith, "The Advocacy Coalition Framework: An Assessment", in P A Sabatier (ed.) *Theories of the Policy Process.* Boulder, Colorado: Westview Press, 1999

may be conflict over TB vaccination, it will more likely be driven by competition between different interventions (for TB or for different diseases), whilst the framework seems more orientated to more politically heated issues such as environmental protection versus economic growth. For instance, the framework refers to a phenomenon called 'devil shift', where opponents see each other as more powerful and more threatening than they actually are, which drives coalition dynamics.

Tsebelis (2002) on veto players[165]

Tsebelis' framework links the ease of policy change to the number of 'veto players' in a particular policy space, i.e. the number of actors who have the power to prevent change. Each actor will have a 'winset' of new policy positions which they prefer to the status quo. With an increase in actor, the policy area corresponding to the overlap of winsets becomes smaller, meaning that the number of new policy positions which are possible decreases.

This has influence much recent political science research. It would be interesting to map out the veto players in the vaccine adoption policy space for each country, which would give some indication of the ease and hence time needed to gain acceptance of new TB vaccine introduction from all critical actors.

5.6. Next steps

It would be valuable to conduct much more review of the literature, both on the vaccination/health policy side and on the political science side, to develop a framework for looking at vaccine adoption.

It therefore might be best at this stage to start looking at vaccine adoption in probable key study countries, to prompt thinking about how knowledge of the detail of these processes can be combined with models from the political science literature (and maybe with a consultancy-type categorisation method) to yield some sort of framework which gives predictions. This could be done alongside coming back to the literature to pull out relevant models as they seem appropriate. For instance, if it appears that in Thailand the bureaucracy plays a major role in vaccine adoption whilst politicians do not, it will be more worthwhile drawing on this literature, whilst leaving aside theories of legislative action or legislative-executive interaction. The theories however, with their pedigree of logical development over decades and empirical testing, will add more 'bite' and structure compared to simply looking at a few Thai vaccine adoption stories and trying to draw conclusions from 'what seems to be the case'.[166]

In this way vaccine adoption stories could be mapped for each country (similarly to Munira and Fritzen), only including those recent enough to be relevant to current processes, using the existing literature review as an initial guide and supplementing it as

[165] Tsebelis G, *Veto Players: How Political Institutions Work.* Princeton: Princeton University Press, 2002.
[166] As noted earlier, it is not clear that the consultancies necessarily do this anyway, so even this review of 'stories' could add to existing practice.

necessary. If this works, and once there is some kind of 'model' with some quantitative aspect to it, the next step would be to identify the necessary predictive elements for the case of TB (perhaps booster vaccines in particular): these might be e.g. the existence of policy entrepreneurs, policy and problem streams where the TB vaccine and TB disease burden respectively are 'making progress', a dominant pro-vaccination advocacy coalition, etc.

This could then guide any interview questions in a later stage of demand analysis, i.e. rather than asking general questions ("Do you think TB is a problem?", "What are the most important features of a TB vaccine?"), there could be enquiries which might be suspected would elicit more revealing information about how the policy process will actually play out ("What individuals or organisations are currently pushing for TB vaccination? How much access do they have to government officials?" and so on).

5.7. Vaccination and health policy literature for future review

As noted above, some literature has been reviewed much earlier in the project, but may be of value to this component. Articles/books of particular interest are highlighted.

Batson A "The problems and promise of vaccine markets in developing countries" *Health Affairs* (2005) 24(3):690-694

Catford J "Creating political will: Moving from the science to the art of health promotion" *Health Promotion International* (2006) 21(1):1-4

Clemens J D "Thinking downstream to accelerate the introduction of new vaccines for developing countries" *Vaccine* (2003) 21:S2/114-S2/115

Cutts F and P Smith (eds), *Vaccination and world health.* London: John Wiley, 1994.

Dasgupta R and R Priya "The sustainability of Hepatitis B immunization within the universal immunization programme in India" *Health Policy and Planning* (2002) 17(1):99-105

DeRoeck D, J D Clemens, A Nyamete and R T Mahoney "Policymakers' views regarding the introduction of new generation vaccines against typhoid fever, shigellosis and cholera in Asia" *Vaccine* (2005) 23:2762-2774

Doyal L and I Pennel, *The political economy of health.* London: Pluto Press, 1979

Duma R "Establishing a national universal immunization programme" *Vaccine* (1995) 13(S1):S58-S60

Griffiths U K, G Hutton and E D Pascoel "The cost-effectiveness of introducing Hepatitis B vaccine into infant immunization services in Mozambique" *Health Policy and Planning* (2005) 20(1):50-59

Hausdorff W P "Prospects for the use of new vaccines in developing countries: cost is not the only impediment" ***Vaccine*** **(1996) 14:1179-1186**

Justice J (2000) ***Study of factors influencing the introduction of new and underutilized in Philippines*** **[and ...*in Uganda*]. Papers commissioned by Children's Vaccine Initiative**

Leichter H M, *A comparative approach to policy analysis: health care policy in four nations.* Cambridge: Cambridge University Press, 1979

Levine M M and O S Levine "Influence of disease burden, public perception, and other factors on new vaccine development, implementation, and continued use" *Lancet* (1997) 350:1386-1392

Madrid M Y (1998) ***The introduction and use of new vaccines in the public and private sectors, Country Reports: Morocco, Thailand, Zimbabwe*** **Global Programme on Vaccines, Immunization, Vaccine Supply and Quality Unit, WHO**

Mahoney R T and J E Maynard "The introduction of new vaccines into developing countries" *Vaccine* (1999) 17:646-652

Miller M A and W D Flanders "A model to estimate the probability of hepatitis B and ***Haemophilus influenzae*** **type B-vaccine uptake into national vaccination programs"** ***Vaccine*** **(2000) 18:2223-2230**

Milstien J, S L Munira and S L McKinney "Issues in the selection of DTwP-based combination vaccines" *Vaccine* (2003) 21:1658-1664

Muraskin W "Origins of the Children's Vaccine Initiative: The political foundations" *Social Science and Medicine* (1996) 42(12):1721-1734

Muraskin W, ***The war against Hepatitis B: a history of the International Task Force on Hepatitis B immunization.*** **Philadelphia: University of Pennsylvania Press, 1995.**

Reich M R, "The political economy of health transitions in the Third World" in L C Chen and A Kleinman (eds.), *Health and social change in international perspective.* Cambridge: Harvard University Press, 1994

Ugalde A "Health decision-making in developing nations: a comparative analysis of Colombia and Iran" *Social Science and Medicine* (1978) 12:1-7

Vryheid R E, M A Kane, N Muller, G C Schatz and S Bezabeh "Infant and adolescent hepatitis B immunization up to 1999: a global overview" *Vaccine* 19:1026-1037

Walt G, *Health policy: an introduction to process and power.* London: Zed Books, 1994

Walt G and J Cliff "The dynamics of health policies in Mozambique 1975-1985" *Health Policy and Planning* (1986) 1(2):148-157

Wenger J D, J L Fabio, J M Landaverde, O S Levine and T Gaafar "Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries" *Vaccine* (2000) 18:736-742

Widdus R "Introduction of vaccines into the Third World" ***Comptes Rendus de L'Académie des Sciences*** **(1999) 322:909-1016**

Woodle D "Vaccine procurement and self-sufficiency in developing countries" *Health Policy and Planning* (2000) 15(2):121-129

5.8. Political science and public policy literature for future review

As noted above, the main source for the political science literature might be DPIR suggestions according to which kind of frameworks we felt we needed. Noted below are other literature noted from reviewing the vaccination and health policy literature.

Brinkerhoff D W and B L Crosby, *Managing policy reform: Concepts and tools for decision-makers in developing and transition countries.* Bloomfield: Kumarian Press, 2002.

Grindle M and J Thomas, ***Public choices and policy change: The political economy of reform in developing countries.*** **Baltimore: Johns Hopkins University Press, 1991.**

Gulhati R "Who makes economic policy in Africa and how?" *World Development* (1990) 18:1147-1161

Lindblom C "The science of muddling through" *Public Administration Review* (1959) 39:517-526

Rose R, ***Lesson drawing in public policy: Learning across time and space.*** **New Jersey: Chatham House, 1993**

6. COST ISSUES

6.1. Cost to develop a new vaccine

The market and investment case analyses come to significant differences of opinion on expected R&D costs (that appear as a negative stream to the left in typical cash-flow NPV diagrams, either spread over time or amortized to a point in time). Attrition rates are key to this – though not the only factor – since they affect the expected size of costs and the timing of any vaccine arrival and the number of vaccines that arrive.

Applied Strategies runs a range of portfolios, although the main interest is in working out the value of the Aeras portfolio. BVGH/BCG does not appear to run a proper portfolio analysis and does relatively much less analysis of cost issues. None of the investment cases stress test attrition rates – beyond each presuming a particular set of rates – and hence they do not stress test R&D cost structures and vaccine arrival times.

According to BVGH/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. 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."[167,168] This reviewer is of the opinion that, even given all the limitations of the data, BVGH/BCG did not work out the expected R&D costs rigorously.

The BVGH/BCG 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. This would not appear to be using a portfolio approach.

BVGH/BCG figures:

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

[167] P12, italics added.

[168] 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).

ASC calculates a much lower base cost of product development for a single *replacement* vaccine:[169,170]

	rBCG-Aeras 403 (Aeras)
Phase 1	$15M
Phase 2	$13M
Phase 3	$42M
Licensure	$1M
Manufacturing	$15M
Total	$86M

ASC calculates a lower base cost of development for a single *booster* vaccine:[171]

	All boost vaccines	
	Infants	Adolescents
Phase 1	$15M	
Phase 2	$13M	
Phase 3	$42M	75M
Licensure	$1M	
Manufacturing	$15M	
Total	$161M	

Therefore, Applied Strategies is coming out with much lower figures, based on portfolio analysis. rBCG is about a third of the base cost presumed by Boston Consulting Group for a replacement vaccine product. With overall success of rBCG-Aeras 403 assumed to be about 34%, this gives an attrition adjusted R&D cost of about $253 for a successful product of this type worked out by similar reasoning to BCG (which, of course, is not how one should work it out).

The lack of a portfolio approach in BVGH/BCG can be seen in the lack of independence between the three Financial Returns scenarios listed in the BVGH/BCG report (Table 2, replacement, boost, prime-boost), when a portfolio approach would have seen them dependent on each other.[172]

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[169] Source: Aeras, July 2007. All costs in 2007 dollars. Phase I – includes $5M for age de-escalation studies and $10M for special population studies (e.g., + HIV). Phase II – 2,900 infants (efficacy in 1,400 and safety in an additional 1,500 infants at $4,500 each). Phase III – 14,000 infants at $3,000 each. Manufacturing costs include process development, formulation development, scale up, ICH stability & clinical supplies.

[170] I.e. this is the cost if a product goes all the way through to development. To work out the expected costs of development, we need to work at the portfolio level.

[171] Source: Aeras, July 2007. All costs in 2007 dollars. Phase I - includes $5M for age de-escalation studies and $10M for special population studies (e.g., $\pm$ HIV); Phase II – 2,900 infants (efficacy in 1,400 and safety in an additional 1,500 infants at $4,500 each); Phase III – 14,000 infants and 25,000 adolescents at $3,000 each; Manufacturing costs include process development, formulation development, scale up, ICH stability & clinical supplies.

[172] See Farlow 2007 for details. Essentially, 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 BVGH/BCG Table, lower than just looking at the payoffs scenarios for each approach treated separately. For example, the negative NPV

At this stage in time, it is clear that we do not have a good handle on likely R&D costs for any level of future probable provision of TB vaccines.[173]

6.2. Attrition rates / probabilities of success

Part of the difference in the R&D cost figure comes from the way it is calculated for any given success probabilities. Partly, the difference comes from those success probabilities themselves. In an ideal world we would use success probabilities 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.

The only source quoted for attrition/success rates in the BVGH/BCG report 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.

BVGH/BCG success probabilities

In the backup material to the BVGH/BCG report,[174] three cases of probabilities of success are reported:

FIRST CASE:

Pharma vaccine[175]	
Discovery/Preclinical	57%
Phase 1	72%
Phase 2	79%
Phase 3	71%
Licensure	96%

---

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. Indeed if the target is '95% chance of at least one success', this will raise the chances of this joint outcome, at the same time as inflicting much heavier R&D costs (offsetting this, scaling to hit the 95% target may increase revenues if the average expected efficacy is therefore also higher, though the average number of products may reduce the average revenues per product for any given level of efficacy). The better our endeavors, perversely the lower the financial value of some of our investments. Clearly, another layer of portfolio analysis is needed to do these calculations.

[173] Another area of uncertainty is appropriate costs of capital. This is discussed in more length in the prior Farlow report. The cost of capital used in the BCG's analysis for pharmaceutical firms is 10-15% for pharmaceutical companies and 20-25% for typical bio-tech firms. Using estimates of cost of capital of companies, which may be benefiting from their diversified portfolio, may not reflect well the systematic risk of a TB Vaccine. The cost of capital estimates may be adjusted to reflect the risk of the project and not of the whole company. One method would be to study a number of investments that were made for developing vaccines in the past, and to note the variance in their operating profits/sales revenue along with variance of profits/sales of the firms above, to make adjustments to the cost of capital of the whole firm. This analysis must be undertaken with caution however.

[174] Background material "TB Vaccine Development Ranges to Test," p4.

[175] Top pharma company from BCG interviews. It seems singular.

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

SECOND CASE:

'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

THIRD CASE:

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 these figures are used to calculated R&D cost figures.

Are these success probabilities plausible? Is it obvious that 'current industry benchmarks' apply to the case of TB vaccines?

Applied Strategies success probabilities

Replacement vaccine success probabilities (same probabilities presumed for Aeras as well as Max Planck Inst.):[176]

Discovery/Preclinical	Not analyzed
Phase 1	80%
Phase 2	60%
Phase 3	75%
Major NRA Approval & WHO Prequalification	95%
Overall PTRS[177]	34%

Boost vaccine success probabilities:

	Phase I	Phase II	Phase III[178],[179]	Major NRA Approval & WHO Prequalification[180]	Overall PTRS[181]
MVA85A (Oxford, Wellcome Trust)	-	60%	75%	95%	43%
Mtb72F + AS01 or AS02 (GSK, Aeras)	95%[182]	60%	75%	95%	41%
Hybrid-1 (Ag85B-ESAT6) + IC31 or LTK63 (SSI, Novartis)	95%[183]	55%[184]	50%	95%	25%
Aeras 402 (Ad35.TB-S) (Aeras, Crucell)	95%[185]	60%	75%	95%	41%

[176] rBCG-Aeras 403 (Aeras); rBCGΔUre:CHly+ (Max Planck Inst.). Not that this also means that the probabilities of mistakes in these probabilities are not independent.
[177] PTRS=Probability of Technical and Regulatory Success.
[178] Increased probability due to ≥4200 subjects in Phase II.
[179] Represents the likelihood of either an infant or adolescent boost, or both, except for Hybrid-1 and HyVac-4 which are adolescent boosts only.
[180] High probability that WHO will prequalify products with major market licensure.
[181] Probability of Technical and Regulatory Success of either the adolescent, the infant or both TB vaccines developed independently from phase II.
[182] No safety issues observed in adults & adolescents, assume high probability of obtaining infant safety.
[183] No safety issues observed in adults & adolescents, assume high probability of obtaining infant safety.
[184] Novel vaccine platform or adjuvant.
[185] No safety issues observed in adults & adolescents, assume high probability of obtaining infant safety.

HyVac-4 (Ag85B–TB10.4) + IC31 (SSI, Aeras)	80%[186]	55%[187]	50%	95%	21%
dsRNA capsids (Aeras)	50%[188]	60%	75%	95%	22%

All these figures agree on probability of licensure, and pretty closely agree on probabilities at Phase 3 (with some low boost probabilities making an exception). The differences of opinion are more prominent at Phases 1 and 2.

6.3. Portfolio reasoning of 'at least one' success

The cost in terms of lives lost of getting no vaccine is high. The 'no vaccine' outcome is a 'high risk' outcome. If policy makers/sponsors are very risk averse, they might rather be interested in the expected costs of generating "95% chance of getting at least one vaccine" to market (controlling for vaccine characteristics), tolerating only a 5% chance of getting no vaccine at all.

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 costs. This latter interpretation has several 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 very expensive, since at that 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. Once we know the expected costs of bringing '*at least* one single, successful product' to market, we will know the *average number* of successful products, and the average cost per successful product, for any given probability of at least one product. For example, in the case of TB drug development (an issue with which the author is familiar[189]), given assumed attrition rates, achieving 95% probability of at least one success generates nearly three products on average. While this

[186] Based on four Phase I successes (MVA85A, Mtb72F, Aeras 402 & Hybrid-1 and one Phase I failure (rBCG30).
[187] Novel vaccine platform or adjuvant.
[188] Novel vaccine platform.
[189] http://www.economics.ox.ac.uk/members/andrew.farlow/FarlowTBPortfolio.pdf

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 portion of the overall cost of achieving this that is not paid for by sponsors still has to be recouped from the overall market for *all* of these products, with some of these products having little market in order to generate the few products that do have a sizeable market. Hence, if this 95% thinking generates a cost much greater than that calculated by the various market and investment analyses, this may swamp market figures these analyses generate.

3) Getting a better fix on early success probabilities will have a big impact on the R&D cost figures. If there is need for many more early phase trials than the scientific understanding in market and investment analyses presume, this will have to be compounded into a much larger measured R&D cost in the year of licensure. If the analyses have been overly optimistic about the success probabilities, 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 also be useful to see the impact on costs of shorter phase II trials (on account of biomarkers). Intuitively, one would imagine a potentially big impact.

6.4. Applied Strategies portfolio analysis

To work out possible costs and development timelines, ASC does portfolio analysis over the Aeras part of the global portfolio, allowing scenarios that involve competition.[190] ASC work through the options – replacement, boost, Aeras portfolio on its own facing no competitor, Aeras portfolio facing competitor – with these done under scenarios – of base case, global XDR, and low efficacy – before being pulled together to generate an overall figure.

Compared to BVGH/BCS, ASC has the first vaccines arriving three years later than BVGH/BCG.

[190] Of course, this means they are dealing with a sub-portfolio of a global portfolio and reasoning should also be based in part on the global portfolio.

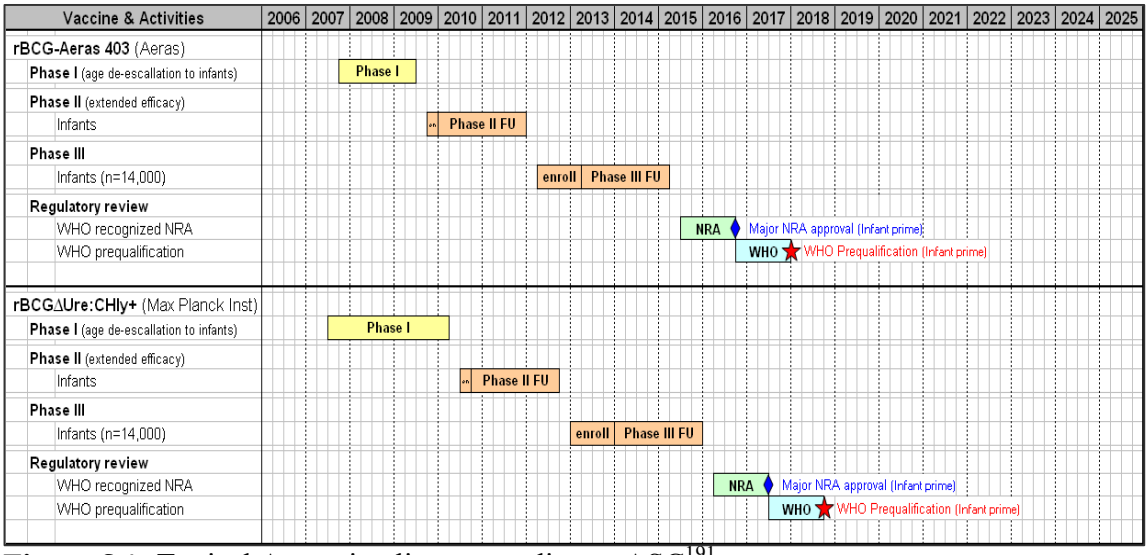
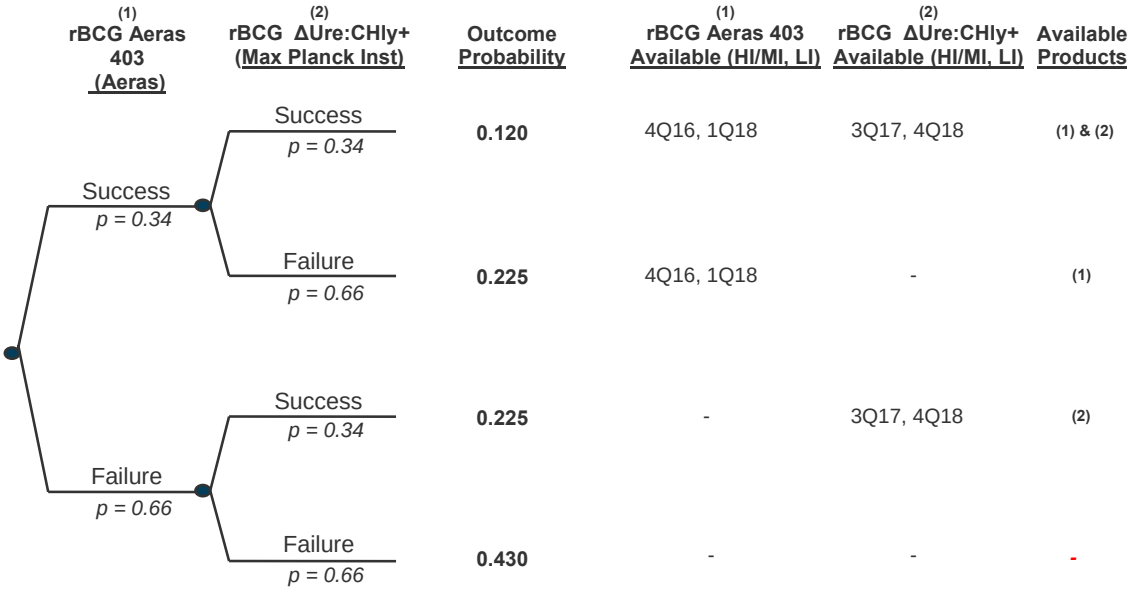


Figure 6.1: Typical Aeras timelines according to ASC[191]

ASC Replacement portfolio:

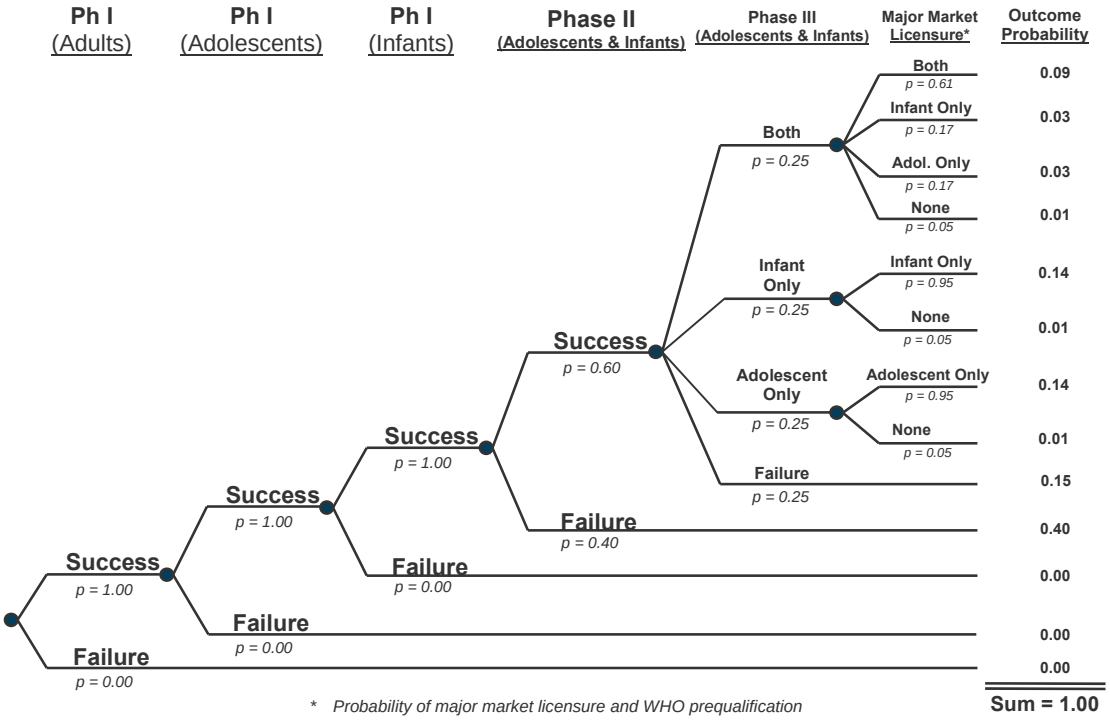
Using the success probabilities that ASC assume for the case of a replacement vaccine, yields the following replacement vaccine portfolio results:



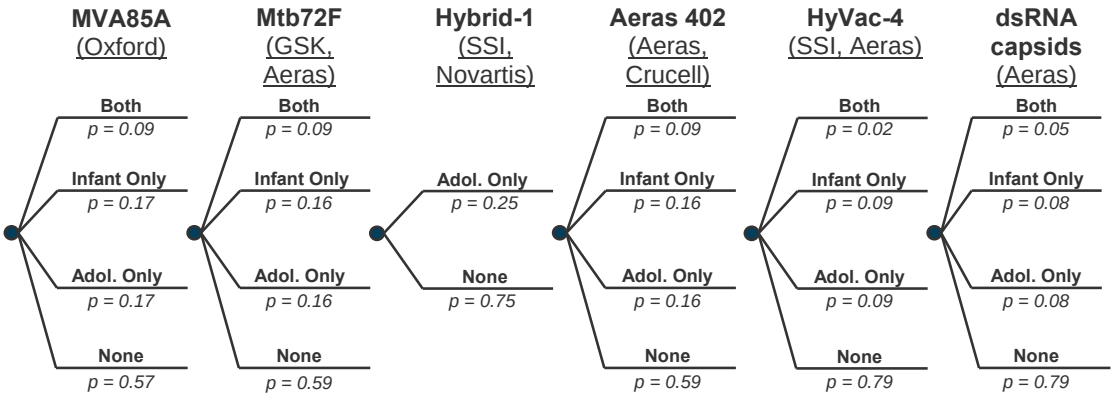
Probability of:	
One product	45%
Two available products	12%
No available product	43%

[191] Adults = >18 yo; Adolescents = 12-17 yo; Children = 1-11 yo; Infants = <1 yo.

ASC Boost vaccine:
Just looking at one of the candidates listed in the table (the 'MVA85A opportunity') yields the following result (described as 'illustrative' by ASC):



Looking at *all* of the candidates generates 2048 different boost outcome combinations ranging from all boosts successful to no boosts successful:



* *Includes MVA85A as part of the Aeras portfolio.*

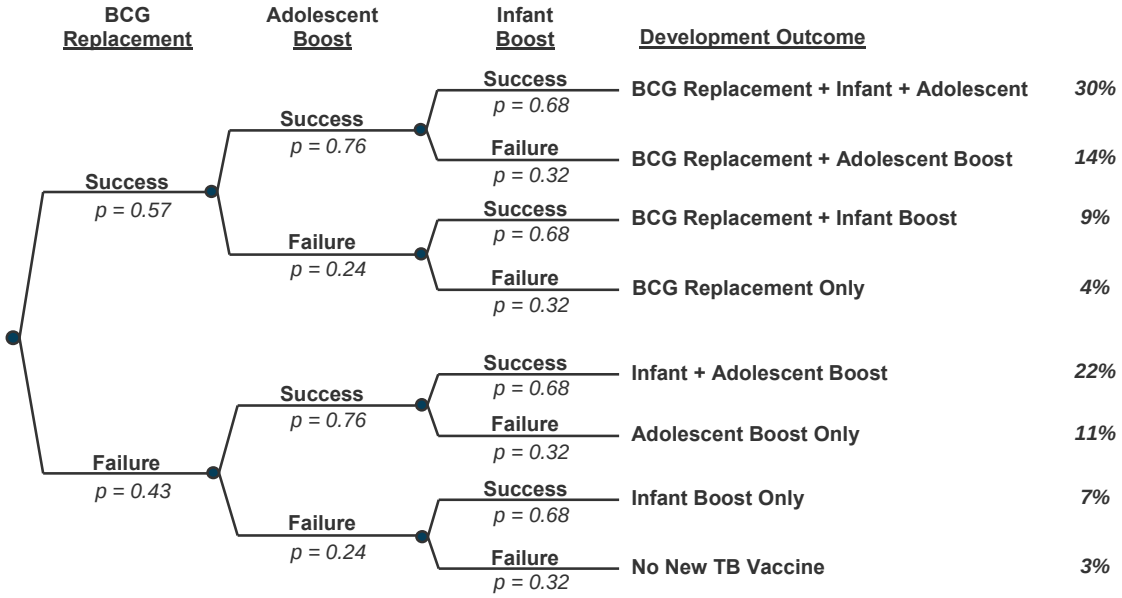
Given trial independence, these 2048 outcomes generate the following probability of a boost vaccine

No vaccine	9%
1 vaccine	28%
2 vaccines	34%
3 vaccines	21%
4 vaccines	7%
5 vaccines	1%
Probability of one or more vaccines	91%
Probability of only 1 vaccine[192]	28%

And the following probabilities over types of vaccine:

Chance of at least one boost vaccine	91%
Chance of adolescent boost vaccine	76%
Chance of infant boost vaccine	68%
Chance of one or more Aeras boost vaccine	87%
Chance Aeras has the only successful boost vaccine	66%

Potential development outcome scenarios:
Putting all of this together yields the following:



6.5. Commentary: Attrition rates and costs of development

Clearly the ASC work is the most sophisticated in terms of actually running through a portfolio analysis over all extant candidates.

[192] This could be either an Adolescent boost, an Infant boost, or both from 1 product.

Several observations can be made and several things need to be further done:

1) The sophistication can hide the fact that the results are completely dependent on a still hotly debated set of underlying probabilities. A huge number of combinations can easily be generated based on no more than 8 success probabilities, simply because of the number of candidates and basic mathematical logic (and note how adding candidates has an exponential affect on the number of possible boost outcomes). So, the analysis is both sophisticated and not sophisticated at the same time.
2) This is only one set of possible probabilities. Results need to be stress-tested much more for more pessimistic as well as more optimistic success probabilities. Quite likely, the more important stress-test is for pessimistic.
3) We do not know what the efficacy of any of these candidates will be, though we have clues about some (such as significant antibody and T-cell responses seen in the case of Mtb72F, GSK, Aeras). We know the thresholds we need in each scenario performed, but we don't have a particularly good grasp of whether any of this portfolio will make those thresholds.
4) We can't therefore know the value of the portfolio in terms of probable impact.
5) These analyses are of the extant portfolio. None of the analysis explores what the 'optimal portfolio' might look like. For example, holding efficacies constant, adding more candidates changes the probability distribution over outcomes. It also increases the cost of running the portfolio. Intuitively, adding one more candidate to a small portfolio has a different marginal impact to adding one more candidate to a large portfolio in terms of raising probabilities of at least one success. On top of this one needs to layer the efficacy issue.
6) This is a social welfare problem not a maximization of profit problem. If one sees a very high NPV value under some scenarios (some of the boost scenarios generate large NPVs) this almost certainly is telling us that the portfolio is too small from a social welfare perspective. Intuitively, more boost candidates should be included to get the NPV down. But how far should it fall? Indeed, the optimal portfolio could have negative NPV.
7) Different players do not go the 'whole way', but account for different parts of the R&D chain. We ideally need a measure of NPV going forward at each point in time over a combination of public/sponsor funded entities and biotechs and big pharma under realistic scenarios of their involvement along the R&D 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.
8) In particular, even if the overall size of NPV is negative, it would be interesting to know the NPV when having several candidates reaching phase III. 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. 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.

To illustrate sensitivity of analysis over attrition rates, Farlow does the next best thing that avoids portfolio analysis,[193] and simply explores what happens if R&D costs are higher and this is applied to the BVGH/BCG figures.[194] That analysis shows 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 BVGH/BCG report. 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.

6.6. Other cost of development issues including biomarkers, trial site limitations, time to licensure

1) If one were to run a portfolio model to help sponsors guide in resources and set the terms of additional incentive devices (market guaranties, prizes and so forth) for potential sponsors, it would be extremely useful to break down the expected total cost figure to get a vaccine into the expected costs needed to get to each stage of development, and hence the expected 'remaining costs', and expectations to get to a product starting from each point in the chain of product development, and NPV from that moment onwards. This should be relatively doable from current portfolio models.
2) We need a better calculation of the cost of 95% of "at least one success".
3) We need 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 vaccine or booster vaccine), and hence what cost/capacity issues will have to be tackled first. The current analysis does not tackle this timing issue. Intuitively, the 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 given the many other booster vaccine candidates in the pipeline?
5) The BVGH/BCG report acknowledges serious bottlenecks in trial sites (p19). On p11 of the BVGH/BCG report 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.

[193] Since he is working on a tiny proportion of the resources of the other two groups and has none of their proprietary models at hand.
[194] Note, as elsewhere, this all needs checking after clarifying how the 2013 figures were worked out by BCG, since this takes these as read.

6) The lack of surrogate markers means that trial sizes need to be large and long. The creation of predictive biomarkers 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 in to the development of biomarkers (incidentally, this is another case where 'risk' and 'cost' seem to be mixed up in the wording of the BVGH/BCG report, see p6).
7) We need to know more about how lack of clinical biomarkers relates 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, and this pushes costs down. This can have a 'price' put on it.
8) Can the value of some of these options be transferred into reduced risk and 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 heavily and hence NPV up. What is the marginal return to investment in this new biomarker technology given this externality effect? This should have a big payoff in terms of NPV.
9) The value of reducing delays in use of trial sites could be big. The value of individual $10m investments in trial sites and cross country regulation (RHS of BVGH/BCG p 20) are not calculated but would be worth doing since this is an alternative way to spend funds.
10) Diagnostic allows better targeting of booster vaccines (it enables targeting of those who have not been infected with TB already). What is the impact of diagnostics on improving cost-effectiveness of booster vaccine?
11) It would be good to put possible interventions side by side to work out marginal effectiveness. 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. How does this compare to spending the same level of money on, say, an AMC-style subsidy (also when factoring in price pressures)?
12) It is not clear exactly how sponsor funding is treated in the R&D cost figures in the BVGH/BCG 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 BVGH/BCG 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 BVGH/BCG 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 of the BVGH/BCG report, 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 BVGH/BCG analysis.

13) 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?
14) All the BVGH/BCG figures are based on licensure *by 2013*. The BVGH/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 BVGH/BCG show that even a one or two year delay to licensure significantly harms NPV (both from the cost and revenue sides). Similar logic would seem to apply to slow achievement of market penetration, and slow provision for new fully burdened costs.

6.7. COGS and LDC sales brought forward

The BVGH/BCG report presumes low take-up of booster vaccines, entirely because of the cost of goods sold, COGS, of such vaccines, and not because of the R&D costs of developing such vaccines.

The BVGH/BCG spreadsheet presumes $1 COGS for replacement vaccines.[195] Therefore, Farlow does several scenarios using the BVGH/BCG figures on the notion of $2 and $0.5 COGS, and on the basis that nothing else is changed. 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 vaccine, 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

[195] 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.

SCENARIO:
$2 production costs, replacement vaccine, 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

Given the impact on the BVGH/BCG base case, this suggests exploring what might happen if sales in less developed countries are brought forward under COGS of $2 and $0.5. The results are as follows.[196]

SCENARIO:
Pull all low income, middle income, private market and China forward by three years.[197]
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.[198]
COGS raised to $2
China pays $1[199]

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

WITH INDIA:
Since the figures provided by BVGH/BCG had no demand from India (to the extent these are not covered in the private market data provided), a scenario was done with India entered paying $1 when costs are $0.5. This would positively enhance NPV. We need

[196] The following scenarios need checking, after it is clarified if there is a fault in the private market data provided.
[197] COGS pulled forward three years (adjusting for rich-world component, since the timing of that has not changed).
[198] COGS pulled forward three years (adjusting for rich-world component.
[199] So China is being subsidized, something that may be questionable given that China can afford not to be subsidized.

some India data to do the figures, since this is too rough to treat with a high degree of confidence.

SCENARIO:

$0.5 COGS, no change in quantities demanded.	
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 countries 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.

6.8. Booster COGS

Recent progress in science has enabled progress in effective subunit vaccines with several candidates under development, including fusion protein vaccines and viral vectors for key antigens. Indeed, all three vaccines described in the BVGH/BCG as being in clinical trials are these booster vaccines. Yet, we are told that these are the more expensive type of vaccine to manufacture (p6 of BVGH/BCG report: "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). The presumed high cost of booster technology means those who need booster vaccines the most do not get them under either the BVGH/BCH 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 (BVGH/BCG 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 vaccine technology, at least according to the BVGH/BCG report.

BCG for BVGH 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, BVGH/BCG expected manufacturers to reduce prices in the low and middle income markets. With this price change, the number of doses demanded rises.[200]

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 BVGH/BCG 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 these findings, 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:

1) How might lower booster manufacturing costs on their own stimulate more uptake? And how does that feed in to NPV and IRR?

[200] However, as the figures above show, the quantity responses are very insensitive in the BVGH/BCG framework 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).

2) What are the calculations underlying the increased NPV/IRR on page 17 of BVGH/BCG? 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?
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[201] (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) IN the BVGH/BCG report, 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 BVGH/BCG 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. With COGS feeding into NPV, different groups are coming to quite different conclusions about NPV.

Within the limitations of the evidence provided, Farlow did some COG-based scenarios on booster vaccines.

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

Observe that way that lower COGS make a sizeable impact, even if most of the value of sales is still driven by the high income market: It is all down to the high quantities in the low price markets.

[201] 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.

6.9. Some sensitivity analysis

Bearing in mind that these are based on base case scenarios, ASC produces a range of interesting results that are worth reviewing.

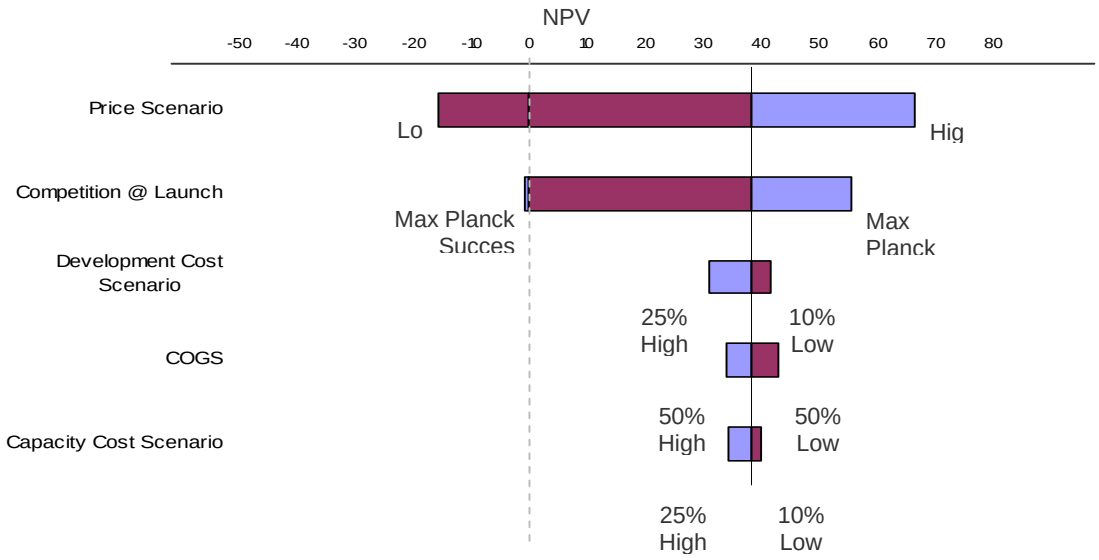
In all cases:

Scenario variable set to its "High" value
Scenario variable set to its "Low" value

Each dimension listed down the left hand side is stress-tested holding all other dimensions constant.

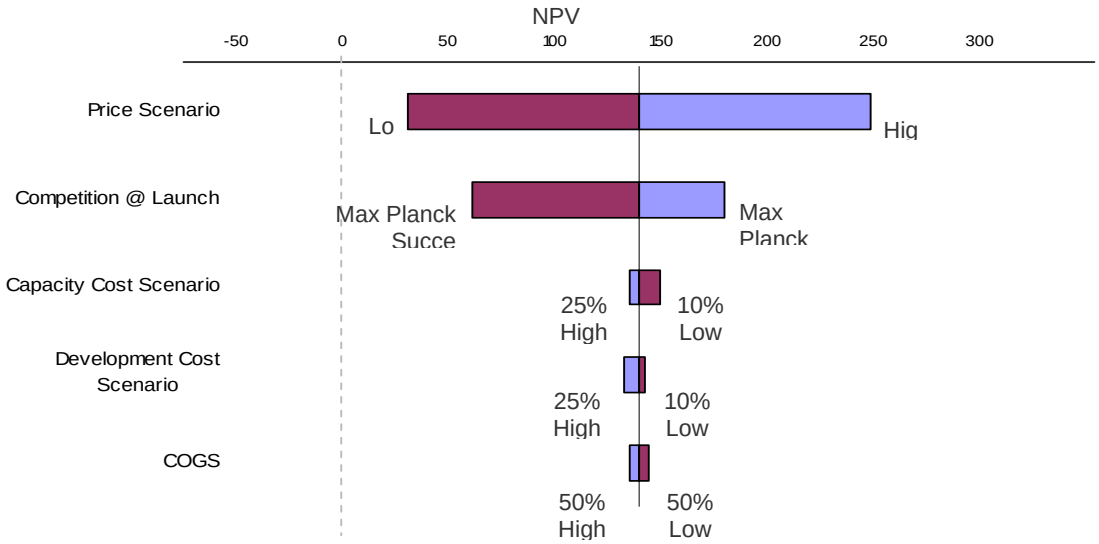
Aeras base case Replacement vaccine

Expected Return Sensitivity Analysis: BCG Replacement Base Case Scenario, Based on Expected NPV = $ 38m



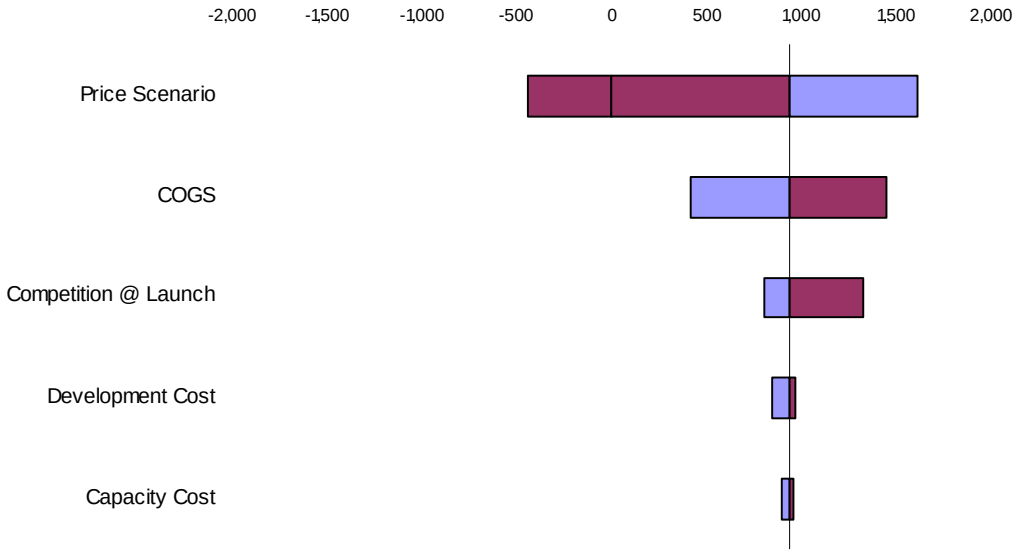
Aeras Replacement vaccine, Global XDR

Expected Return Sensitivity Analysis: BCG Replacement, Global XDR Scenario, based on Expected NPV = $141m.



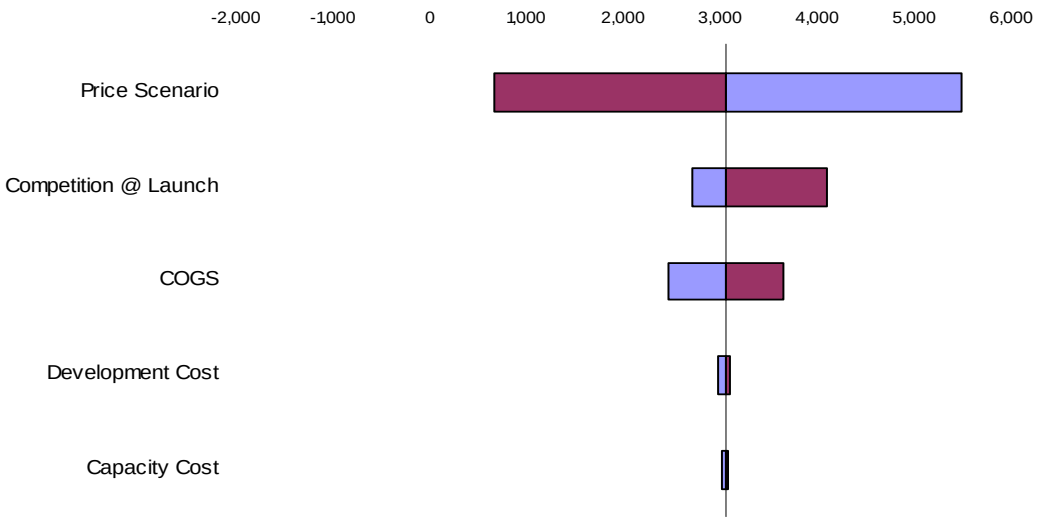
Aeras base case boost vaccine, non global XDR

Expected Return sensitivity analysis: Aeras boost vaccine base case (non-global XDR) based on Expected NPV of $937m:



Aeras boost vaccine, global XDR

Expected Return sensitivity analysis of Aereas portfolio, boost vaccine based on Global XDR with expected NPV of $3036m:

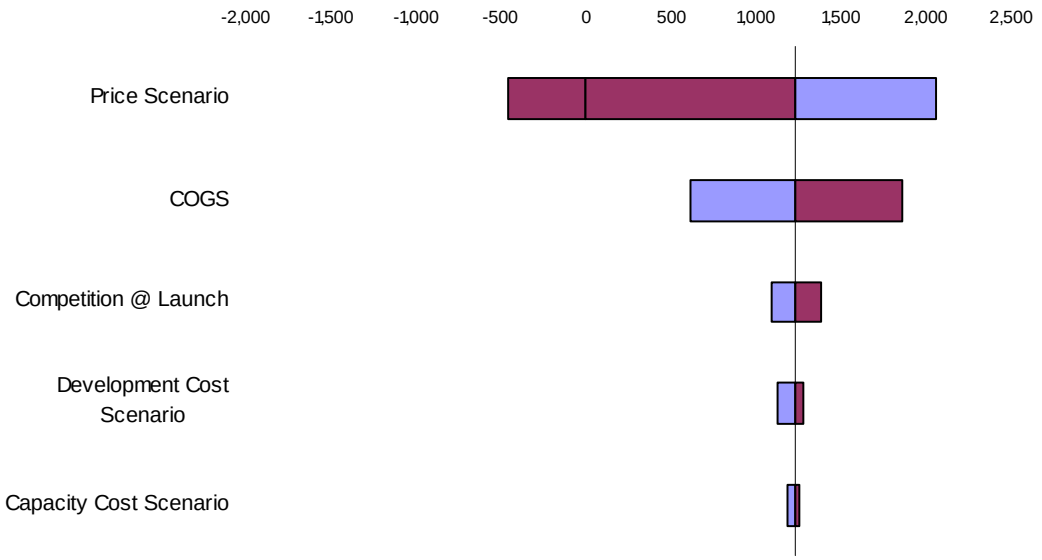


Commentary on ASC XDR boost scenario

1) Comparison is for Aeras portfolio only;
2) The biggest sensitivity is on account of prices. This time, low prices do not drive NPV into negative territory;
3) There is even less impact of variance in development costs on NPV;
4) Here, compared to the replacement vaccine base case, there is a much bigger impact on account of variance in COGs, but less than when there is no XDR (for obvious reasons);
5) Competition has impact, but it is smaller than COGS variance, and it has an asymmetric impact (greater in case of XDR than non-XDR);
6) Front loading of revenue streams keeps NPV out of negative territory;
7) No sensitivity analysis to speed of uptake.

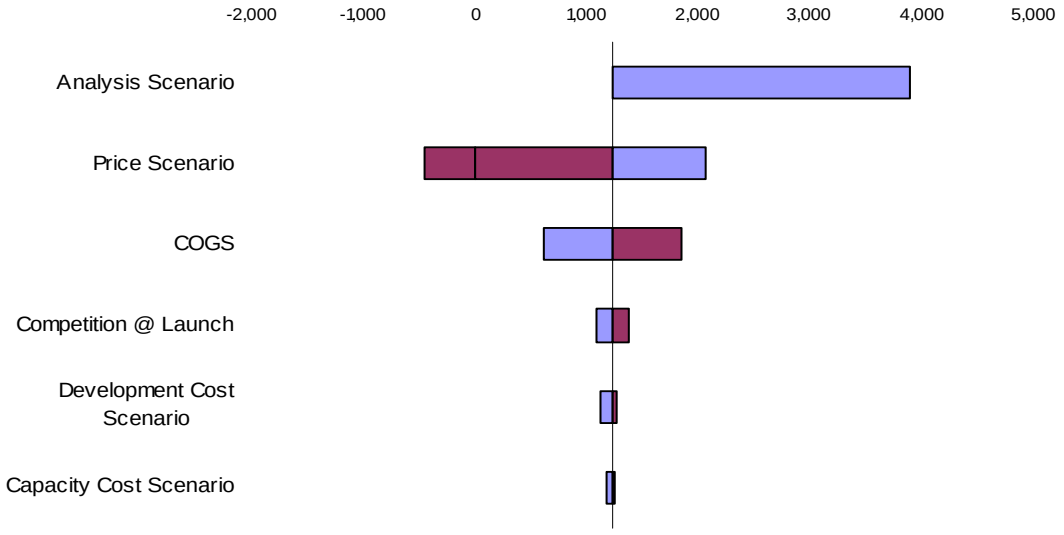
Aeras base case total portfolio sensitivity

Total Aeras portfolio with similar sensitivity analysis to that done on the subportfolios. Base case expected NPV is $1235m (given no competition):



Aeras global XDR total portfolio sensitivity

Total Aeras base-case portfolio (NPV $1235m) run with base-case global XDR scenario on top (**Expected NPV = $3,897m):**



Trying to work out the ex ante NPV of investing in vaccine R&D (that is the expectation over both non-global XDR and global XDR) would require placing a value on the probability of global-XDR. The author is not aware of any treatments of this probability.

6.10. Costs caused by plant size and capacity issues

In Table 1 of BVGH/BCG (p12, the base case assumption), production plant cost is quoted on the basis of 120 million doses. In Figure 3, p13 (presumably the base case underlying Table 2 figures) shows that 120 million is never used in a year. Indeed, booster vaccine sales are about 50 million maximum in a given year; average yearly doses sold in the base case over the period 2013-1030 are 54.3 million, 35.35 million, and 90.60 million 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 BVGH/BCG report as *peaking* at 60 million for replacement and *peaking* at 40 million for booster vaccine. It is not clear how this relates to the assumption of costs based on 120 million dose plant size. Only the prime-boost combination comes to 100 million combined doses, but the costs of capacity in that case still seem in the BVGH/BCG report to be based on two lots of 120 million.