Tuberculosis Vaccines: The Case for Investment

A Report Prepared by BIO Ventures for Global Health

October 2006

Breaking Down Barriers...Building Solutions
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Cover image photographed and processed by Dr. Volker Brinkmann, Max Planck Institute for Infection Biology. Macrophages taking in improved BCG vaccines.
About BVGH

BIO Ventures for Global Health, a non-profit organization, is harnessing the resources of the biotechnology industry to create new medicines for neglected diseases of the developing world. Our mission is to break down barriers that hinder industry involvement in global health product development and to catalyze industry investment through new market-based solutions. We are supported by the Bill and Melinda Gates Foundation, the Rockefeller Foundation, the Biotechnology Industry Organization, and leading companies in the biopharmaceutical industry.
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Preface and Acknowledgments

This report is based on a study recently undertaken by BIO Ventures for Global Health (BVGH). The analysis, which was conducted by BVGH and The Boston Consulting Group, received extensive input from product developers, public health officials in developing and developed countries, and tuberculosis vaccine experts.

BVGH would like to thank the many people who contributed time, effort, and insight to this project. This study was significantly enhanced by the involvement of a group of industry experts who contributed their time over the course of this study to advising the team and helping improve the analysis and the reliability of our results. We are very grateful to Jerry Sadoff, Lew Barker, Larry Geiter, and Bruce Kirshenbaum of the Aeras Global TB Vaccine Foundation; Alexander von Gabain of Intercell; Oscar Izeboud of Crucell; Carel Featherston of GlaxoSmithKline; and Joerg Schneider of Oxxon Therapeutics.

From The Boston Consulting Group, Michael Yeh, Rodrigo Martinez, and Jim Larson worked tirelessly on this project and retained their sense of humor even after days without sleep. Thanks also to Wendy Woods and Dave Matheson, who provided superb oversight for the project.

BVGH would also like to thank the following individuals for their helpful comments on the report: Dr. Adrian Hill and Dr. Helen McShane of Oxford University, Dr. Stefan Kaufmann of the Max Planck Institute for Infection Biology, Peter Andersen and Peter Nabben of the Statens Serum Institute, and Michel Greco and Uli Fruth of the Stop TB Partnership.

Finally, this project could not have been possible without the generous support of the Bill & Melinda Gates Foundation. In particular, we would like to thank Dr. Hannah Kettler and Dr. Peter Small. We are grateful not only for their financial support, but also for their enthusiasm and interest in the ways that BVGH can highlight the unexplored opportunities for industry and donors (governments and foundations) to work together to increase the incentives for new global health product development.
Executive Summary

BIO Ventures for Global Health (BVGH) aims to catalyze neglected disease product development by helping companies build sound business strategies that can contribute to solving global health challenges. The objective of this study is to build the case for private-sector investment in tuberculosis (TB) vaccines or—if existing markets are inadequate to support such investment—reveal gaps where donor involvement may improve the market opportunity.

BVGH developed a comprehensive model to evaluate the business and social case for investment in TB vaccines. To conduct our study, we assembled a team consisting of BVGH executives, The Boston Consulting Group, and a group of advisers that included the Aeras Global TB Vaccine Foundation and the major commercial players investing in TB vaccine development today. The advisers’ contributions provided a reality check on our assumptions and, in our view, significantly enhanced the quality of the results. We then “pressure-tested” our findings with a broader range of stakeholders, both public and private.

Disease Burden and Description

Even the most experienced healthcare experts in the developed world are frequently stunned to learn that TB has infected one-third of the world’s population. While most of these infections are latent, between 5 and 10 percent of infected individuals develop active, contagious disease and suffer significant debility or death.

The TB bacterium, Mycobacterium tuberculosis (M. tuberculosis), is extremely slow growing compared to other bacteria, and the waxy outer coating of mycolic acids of M. tuberculosis renders the bacterium resistant to many of the powerful antibiotics that are effective against other bacterial infections. Those few drugs that are effective are used in courses of combination treatment for a minimum of six months. In recent years, multi-drug-resistant TB strains (MDR-TB) have arisen that are resistant to standard treatment and require extensive and costly treatment with new cocktails of potent, toxic drugs.

Ultimately, the path to reducing the epidemic levels of TB infection, particularly in the poorest countries of the world, is through a TB vaccine. Such a vaccine—provided it is safe, effective, and affordable—would have a profound impact worldwide on death and morbidity from this widespread disease.

Fortunately, we now have a better understanding of how the organism causes disease and how the host immune system responds to M. tuberculosis infection. DNA sequencing of the M. tuberculosis genome has led to advances in vaccine development and accelerated the identification of novel antigens that are protective in animal models. As a result, there are nearly a dozen vaccine candidates in the pipeline, with several promising candidates in late stages of pre-clinical development or in human clinical trials.

Study Overview

Recognizing that demand for TB vaccines will vary across different markets, we analyzed three different market segments:

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

To gain deeper insights into what certain representative countries expect from a TB vaccine, and to assess their willingness to adopt a new product, we conducted primary research in six TB-endemic countries—India, China, South Africa, Nigeria, Russia, and Brazil—as well as in the United States.

Using information derived from interviews with a wide range of product developers, public health officials in developing and developed countries, and tuberculosis vaccine experts, we modeled three different product profiles for new TB vaccines:

- BCG-replacement vaccine (prime): administered at birth (70 percent effective for ten years);
- Booster vaccine (which boosts the existing BCG vaccine): administered to infants at 14 weeks and then one dose at ten-year intervals (70 percent effective); and
- Prime-boost strategy: a combination of the BCG-replacement vaccine administered at birth and booster vaccines administered at ten-year intervals (80 percent effective).
**Business and Social Case for Investment**

Even under pessimistic market scenarios, TB vaccines would yield significant value. For the base-case (expected) scenario, we estimated a peak annual market of $450 million for a BCG-replacement vaccine and nearly $800 million for a booster vaccine. If both a BCG-replacement vaccine and a booster vaccine were available, enabling a prime-boost strategy, the peak annual market for both vaccines combined would be about $1 billion. These markets are sufficiently high to attract industry investment, generating significant positive risk-adjusted net present values (NPV) and internal rates of return (IRR) in excess of 20 percent between 2013 and 2030.

The social case for investment is equally compelling. In Asia and Sub-Saharan Africa, two of the regions with the greatest disease burden, we found a 17 to 62 percent annual reduction in TB-related deaths and a 20 to 45 percent reduction in disability-adjusted life years (DALYs)\(^3\) at a cost of $6 to $26 per DALY, depending on the product profile.

**Challenges and Opportunities**

We believe the current global market for TB vaccines presents a viable investment opportunity for industry. The market is sufficiently attractive to compete with other opportunities, and, given the current state of the product pipeline, the time is right for developers to launch new research and development (R&D) programs. We encourage vaccine developers to review this analysis and assess the value of this opportunity for their own companies.

There are several key hurdles for TB vaccines along the vaccine development and supply chain—each of which can be overcome through targeted donor interventions. Because donor investment in TB vaccines could substantially improve global health, we strongly encourage donors to direct their investments to meeting the following challenges.

First, *the need for highly predictive biomarkers*: There are no surrogate markers for TB to predict the efficacy of a TB vaccine. Thus, we expect Phase III clinical trials to be long (at least three to four years) and require large patient populations, thereby increasing the investment risk. *Investment in new, highly predictive biomarkers to measure infection or protection from disease could eventually have a dramatic impact in reducing the length of clinical trials and the risk to developers.*

Second, *the shortage of clinical test sites*: There is currently a shortage of clinical trial sites for TB vaccines. *Investments to help establish additional trial sites are needed to support the current TB vaccine pipeline.*

Third, *public support for supplying developing countries with TB vaccines*: While the global market for TB vaccines may be sufficient to attract industry investment, estimates of the cost of certain booster vaccines suggest that current technology for producing those vaccines may be too expensive for developing countries to afford. Pressure on public resources to assist with developing country vaccine purchase will become particularly acute over the next decade as a number of new vaccines addressing other major neglected diseases are approved. *Additional public support, through mechanisms such as Advance Market Commitments, will be necessary to ensure that developing countries can access these new products quickly once they are available.*
Approach

Study Rationale and Objective
BVGH aims to catalyze neglected disease product development by helping companies build sound business strategies that can contribute to solving global health challenges. The objective of this study is to build the case for private-sector investment in TB vaccines or—if existing markets are insufficient to support such investment—reveal gaps where donor involvement may improve the market opportunity.

The purpose of BVGH business cases is to develop a deep understanding of the markets for treatments for neglected diseases. By shining a spotlight on viable markets that otherwise might not have been noticed, BVGH can illuminate the potential return on industry investment, the target product profiles needed to capture those market opportunities, and the regulatory and distribution pathways that will bring safe and effective products to the developing world. Where the markets are insufficient to attract industry investment, or where there are significant challenges and hurdles to development or market entry, BVGH aims to point to areas where public-sector intervention can improve the likelihood that industry will invest.

Business cases are used regularly by industry to support internal decision making. Companies develop detailed information on markets to assess the potential revenues of a product, understand the potential returns on their investments, and bolster decisions about whether to invest in new R&D. Such information has not been available for TB vaccines, and companies have little incentive to pursue it on their own.

Public-sector donors, including foundations and governments, also need information to support their investment decisions. Given many competing priorities for their funds, donors need to understand an intervention’s potential to significantly improve health. For later-stage products, donors also need market information to better understand the financing required to support the uptake of vaccines in low-income countries and to prepare countries for vaccine adoption.

Analysis
BVGH developed a comprehensive model to evaluate the business and social case for investment in TB vaccines. To conduct our study, we assembled a team, consisting of BVGH executives, The Boston Consulting Group, and a group of advisers that included the Aeras Global TB Vaccine Foundation and the major commercial players investing in TB vaccine development today. The advisers’ contributions provided a reality check on our assumptions and, in our view, significantly enhanced the quality of the results. We then “pressure-tested” our findings with a broader range of stakeholders, both public and private.

Our analysis was built on five key components:
- Mapping the disease burden and current R&D landscape;
- Developing a range of market scenarios based on three distinct product profiles and assumptions about price, countries’ willingness to pay, and time to adoption;
- Estimating development and supply costs;
- Evaluating the financial and social return on investment (ROI) for industry and donors respectively; and
- Identifying the key success factors for introducing a new TB vaccine into the developing world.

In conducting our analysis, we created a robust model that can readily adjust to different assumptions and yield quantitative information on both financial and social returns. See Appendix I (TB Vaccine Pipeline) for more detailed information on the model.
The Global Need for a TB Vaccine

Even the most experienced healthcare experts in the developed world are frequently stunned to learn that TB infects one-third of the world’s population. While most of these infections are latent, between 5 and 10 percent of infected individuals develop active, contagious disease and suffer significant debility or death.

The TB bacterium, \textit{M. tuberculosis}, is extremely slow-growing compared to other bacteria. As a result, \textit{M. tuberculosis} is inaccessible or resistant to many of the powerful antibiotics that are effective against other bacterial infections. Those few drugs that are effective are used in courses of combination treatment that can take more than six months. In recent years, multi-drug-resistant TB strains (MDR-TB) have arisen that are resistant to standard treatment and require extensive and costly treatment with new cocktails of potent, toxic drugs.

Even if novel, highly potent, and rapid-acting drugs were available, they still would not reduce the vast reservoir of TB-infected patients. The path to reducing the epidemic levels of TB infection, particularly in the poorest countries of the world, is through a TB vaccine. Such a vaccine—provided it is safe, effective, and affordable—would have profound impact worldwide on death and morbidity from this widespread disease.

Fortunately, we now have a better understanding of how the organism causes disease and how the host immune system responds to \textit{M. tuberculosis} infection. The sequencing of the \textit{M. tuberculosis} genome has led to real advances in vaccine development and accelerated the identification of novel antigens that are protective in animal models. As a result, there are nearly a dozen vaccine candidates in the pipeline, with several promising candidates in late stages of pre-clinical development and three in human clinical trials.

Figure 1. Global Incidence of TB

![Global Incidence of TB](image)

Source: BVGH/Boston Consulting Group analysis based on WHO data
Disease Description

While the direct effects of tuberculosis infection (illness, death, and economic loss) have been minimized in the developed world, the airborne transmission of this disease—particularly in this era of globalization and widespread travel—makes it a global threat. The infectious agent, *M. tuberculosis*, infects macrophage cells deep in the lung, where they typically establish a latent infection that is clinically dormant for years. While only a small proportion of infected individuals develop active TB, a single patient with active infection can spread the disease to 10 to 15 people per year. Infection is especially devastating in immunocompromised patients. In fact, active pulmonary TB is now the leading cause of death in HIV/AIDS patients in the developing world.

Disease Burden

Approximately 2 billion people have been infected with *M. tuberculosis*. According to the World Health Organization (WHO), TB kills over 2 million people, and approximately 8 million new cases develop each year.

While the disease is present throughout the world, the burden is concentrated in a small number of developing nations. About 80 percent of the global burden is borne by just 22 countries. (See Figure 1.) The largest number of cases and deaths occur in South Asia, with one-third of the world's cases in India and China alone. Because TB latency requires an active immune system, the extremely high prevalence of HIV/AIDS in Sub-Saharan Africa has led to an explosion of TB in those countries. As a result, the highest incidence and per-capita mortality from TB is found in Sub-Saharan Africa.

Given its long latency period, the debilitating effects of active disease often surface in the most productive years of adult life—more than 60 percent of all cases occur in individuals between 25 and 54 years old. As a result, the disease exacts a vast economic toll not only in treatment costs but also in lost productivity (around $16 billion). Epidemics of similar impact 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.

Outdated and Inadequate Tools

TB control is seriously compromised by outdated and inadequate tools.

PREVENTION. The most commonly administered vaccine in the world is a vaccine against TB. *Mycobacterium bovis* bacille Calmette Guérin (BCG) was introduced into humans in 1921 by French physicians who attenuated strains of *M. bovis* (a disease of cows related to human TB) by growing strains in culture over 13 years and monitoring their decreased virulence in animals. BCG, which is safe and inexpensive, is recommended by WHO for infants at or close to birth in high-burden countries, but it is not used in the United States and parts of Europe where TB is much less prevalent and is mainly controlled with antibiotics.

However, the vaccine has had limited effect against the TB epidemic in the developing world. While reasons for its variable efficacy are a matter of debate, there is an emerging consensus that it has been effective at reducing the rate of severe pediatric TB (such as TB meningitis), but its protection against pulmonary TB in infants is of limited duration. The vaccine given to infants does not appear to protect adolescents and adults against pulmonary TB, the most common form of active disease. In addition, because BCG is likely not effective in populations already sensitized to mycobacterial antigens (whether by prior BCG vaccines, environmental mycobacterial exposure, or latent TB infection), it is targeted at infants. 1

TREATMENT. Standard treatment for TB involves a six- to nine-month treatment regimen with a poorly tolerated cocktail of three or four antibiotic drugs. Although these drugs are reasonably effective against standard TB strains when the entire course of treatment is completed, low patient compliance has led to the emergence of multidrug-resistant TB (MDR-TB) strains. DOTS (Directly Observed Therapy—Short course)—the internationally recommended TB treatment method—is generally viewed as an effective means for control, but it is unlikely to have a significant impact on incidence. While DOTS can have a 95 percent cure rate for drug-sensitive TB, when followed, the lengthy treatment regimen requires regular observation by a health worker, which is often difficult in the developing world. It is also important to note that no new drug to fight TB has been developed in the past 40 years.
The best hope of bringing TB under control—especially in the face of HIV/TB co-infection and MDR-TB—lies in the prospect of a new vaccine regimen.

**Current Research and Development**
Renewed public interest in, and funding for, TB vaccine development, combined with a revolution in vaccine-development technology, have brought forth several new approaches to TB vaccine design over the past decade. The leading candidates fall into two categories: live mycobacterial vaccines (genetically engineered TB or BCG) and subunit vaccines (genetically engineered TB proteins combined with immunostimulants or viral vector vaccines using genes for TB antigens expressed by viral carriers).

BVGH has identified at least eight TB vaccine candidates in early stages of development, including three that have entered human clinical trials. (See Figure 2 and Appendix I.)

The pipeline includes two distinct product profiles:
- Vaccines that aim to replace the existing BCG vaccine with improved duration of immunologic memory (more than 20 years) for newborns (typically live attenuated strains); and
- Vaccines targeted toward children, adolescents, and adults as a boost to the neonatal BCG vaccination (typically subunit vaccines or viral vectored vaccines).

Both are prophylactic vaccines to be given prior to TB infection.

The live attenuated vaccine candidates intended to replace BCG include genetically modified BCG vaccines (live attenuated *M. bovis*) and live attenuated *M. tuberculosis*. These vaccines are aimed at immunologically naïve recipients. Given widespread use of BCG, a replacement vaccine would need to demonstrate superior efficacy to BCG to be seriously considered.

### Figure 2. Partial Pipeline of Current TB Vaccine Research

<table>
<thead>
<tr>
<th>Core technology</th>
<th>Development Stage</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Research &amp; Discovery</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>1. Live Recombinant + Pox virus as vector</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Recombinant protein + MPL adjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Recombinant Fusion-protein Ag85B &amp; ESAT–6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Aeras 403</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Recombinant Protein PER, C6 &amp; AdVac</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Ag85B &amp; Ag10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Attenuated live TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Live r-BCG (r-BCG ΔureC:Hly)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: BVGH
Development of effective subunit vaccines has progressed considerably with the sequencing of the *M. tuberculosis* genome. There are now several subunit vaccines under development, including fusion protein vaccines and the use of viral vectors for key antigens. These vaccines, which would be used as booster vaccines, aim to boost immunity in infants or young adults already primed by earlier vaccination with BCG as an infant. However, since not all individuals will have been vaccinated as infants, booster vaccines should be able to stimulate effective primary responses as well.⁶

Experts in tuberculosis generally agree that ultimately what is needed is a combined neo-natal and adult vaccine regimen—or "prime-boost" strategy—if TB immunity is to continue through the adult years. While not evaluated as part of this study, a therapeutic vaccine to treat individuals already infected with TB is also needed before a broad-spectrum solution will be in hand.⁶

Several promising candidates are in early stages of development, with three in human clinical trials. Oxford University’s viral vector vaccine candidate (MVA85A) is currently in Phase II trials and, if Phase II testing is successful, Oxford expects to enter Phase III trials in 2008. GlaxoSmithKline and Statens Serum Institute/Intercell have subunit vaccines under development that are expected to enter Phase III testing in 2010. Several other BCG-replacement and booster vaccines are scheduled to begin Phase I trials within 12 months. Given the range of products in development and anticipated development timelines, we expect that at least one new vaccine will successfully complete Phase III testing and be licensed by 2013-2015.

The Drivers of Demand for a New TB Vaccine

To evaluate the global market for TB vaccines, it is necessary to understand the key factors that drive demand in different markets. TB vaccines, however, are still at an early stage and the attributes of the final products are yet to be determined. To develop a realistic expectation of market demand, we consulted with a wide range of industry and public health experts, as well as officials from a range of different endemic countries. These consultations allowed us to build a realistic target product profile and generate assumptions about development costs, probability of success, timing, price, and time to adoption.

Given that demand for TB vaccines will vary across different markets, we analyzed three different market segments:

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

To gain deeper insights into what certain representative countries expect from a TB vaccine and to assess their willingness to adopt a new product, we conducted primary research in six TB-endemic countries, as well as in the United States.⁷ Not surprisingly, product profile and anticipated pricing influence demand significantly.

**Product Profiles**

Our interviews with public health officials indicated that efficacy and safety are the top priorities among product profile characteristics and will have the greatest impact on demand. Country and WHO officials agreed that 70 percent efficacy against primary infection with TB is the minimal target threshold for vaccine efficacy. They also made it clear that new TB vaccines must be at least as safe as BCG, and they must be safe to administer to HIV-positive infants, without requiring pre-vaccine testing of HIV status.
Our analysis tested three principal scenarios:

- **BCG-replacement vaccine (prime):** one dose administered at birth (70 percent effective for ten years)
- **Booster vaccine:** administered to infants at 14 weeks and at ten-year intervals (70 percent effective against primary infection with TB)
- **Prime-boost strategy:** a combination of the BCG-replacement vaccine administered at birth and booster vaccines administered to adolescents and adults at ten-year intervals (80 percent effective).

### Development and Production Costs

For the purposes of this analysis, we assumed production costs would be $0.50 to $2 a dose for a BCG-replacement and $5 to $10 a dose for a subunit booster vaccine. In addition, 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. Non-attrition-adjusted development costs (that is, the cost to bring a single, successful product to market) are estimated at $194 million for a BCG-replacement vaccine and $203 million for a booster vaccine. (See Table 1 and Appendix II.) From the perspective of a single, successful vaccine candidate, this suggests that a total investment of several hundred million dollars is necessary when the costs of manufacturing capacity are included. Depending on the amount of current manufacturing capacity that can be utilized for a new vaccine, an additional investment of as much as $200 million may be necessary to meet global demand.

### Timing

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. The longest and most costly stage of clinical development is Phase III trials. To demonstrate protection in a large sample of at-risk individuals, Phase III trials are expected to take three to four years. (See Appendix I.)

### Pricing and Market Penetration

Ensuring developing world access to a TB vaccine will require different price levels by each market segment.

**PUBLIC-SECTOR MARKETS IN LOW- AND MIDDLE-INCOME COUNTRIES:** In low- and middle-income countries, public officials are well aware of the costs of controlling TB. Therefore, we estimate that public officials generally will be willing to pay for a new TB vaccine to avoid the costs of treatment ($14 to $15 per regimen in middle-income countries and $3 per regimen in low-income countries, respectively). For countries not supported by the Global Alliance for Vaccines and...
Immunization (GAVI) that pay for their own vaccines, cost is certainly a critical driver in the decision about whether to adopt a vaccine. 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. GAVI-funded countries, even if they are not currently paying for their own vaccines, are also sensitive to price. These low-income countries may not choose to adopt a vaccine unless the long-term price is sustainable after donor funding ends.

PRIVATE MARKETS IN LOW- AND MIDDLE-INCOME COUNTRIES: In low- and middle-income countries, our interviews suggested that three factors primarily drive vaccine uptake in private markets: unavailability of the vaccine in the public market, perception that the product is an improvement over existing products, and a willingness by the middle- and high-income populations to pay out-of-pocket for vaccines. Individuals in these private market segments tend to view vaccines from a personal finance perspective, not from a public health perspective, and may pay for a TB vaccine ($26 to $29 per regimen) to avoid the risk of lost wages. In fact, we found that individuals in low- and middle-income countries are often willing to adopt vaccines before they are incorporated into the public health program, and they may continue to pay the private-sector price even after adoption by the public sector.9

MARKETS FOR HIGH-RISK INDIVIDUALS IN HIGH-INCOME COUNTRIES: In industrialized countries, we took a conservative approach and assumed that a highly efficacious vaccine would only be adopted for high-risk populations such as health-care workers, prison populations, nursing home residents and staff, those in homeless shelters, individuals with HIV, and immigrants. We estimate that the public sector’s willingness to pay for a vaccine (at $50 to $100 per regimen)10 will be based on how much they are willing to pay to avoid the costs of existing control measures.11

Distribution Channels
A BCG-replacement vaccine could use the same vaccine distribution channels as the current BCG vaccine, resulting in extremely high uptake. A vaccine that boosts the immune response, protecting against TB infection, can be given during one or more of the visits scheduled for the WHO Expanded Program on Immunization (EPI)—typi-
cally up to three doses of a vaccine before age one. Further boosts in late childhood or adolescence would not fit into the existing EPI delivery system, which is geared only for infants and children. School vaccination programs may prove successful, and the ability to work through schools is being evaluated in adolescent epidemiology studies currently ongoing in South Africa and India.

**Market Demand**

Applying our assumptions to the BVGH market-demand model, we derived the following global market-demand estimates for the three product profiles tested. (See Figure 3.) In the case of a BCG-replacement vaccine, the majority of market demand is likely to come from developing countries. In contrast, if a booster vaccine were available, the middle-income markets would demand the bulk of the doses. If both vaccines were available—a prime-boost strategy—countries would likely demand both vaccines, although some markets might still choose to adopt only one of the vaccines. See “The Business Case for Investment” for a more detailed discussion of these markets.

### Table 2. Summary of Financial Returns for Three Scenarios

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BCG-Replacement Vaccine</th>
<th>Booster Vaccine</th>
<th>Prime-Boost Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market NPV in 2005 at 20%</td>
<td>$35 MM</td>
<td>$125 MM</td>
<td>$41 MM</td>
</tr>
<tr>
<td>Market IRR (2005 dollars)</td>
<td>25%</td>
<td>32%</td>
<td>22%</td>
</tr>
<tr>
<td>Total doses delivered (2013-2030)</td>
<td>923 MM</td>
<td>601 MM</td>
<td>1,540 MM</td>
</tr>
<tr>
<td>Optimistic Case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market IRR (2005 dollars)</td>
<td>43%</td>
<td>40%</td>
<td>—</td>
</tr>
<tr>
<td>Total doses delivered (2013-2030)</td>
<td>1,241 MM</td>
<td>1,233 MM</td>
<td>—</td>
</tr>
<tr>
<td>Pessimistic Case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Market IRR (2005 dollars)</td>
<td>14%</td>
<td>26%</td>
<td>—</td>
</tr>
<tr>
<td>Total doses delivered (2013-2030)</td>
<td>813 MM</td>
<td>509 MM</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE: Estimates for potential analysis only; information not provided by industry.
Source: BVGH/BCG analysis

**The Business Case for Investment**

Our objective is to define the market for TB vaccines and, if the market proves attractive, catalyze the entry of new innovators—particularly the major pharmaceutical and biotech companies that have extensive proven development capabilities in vaccines. Our hope is to increase the number of promising products in the pipeline through a data-driven, industry-standard analysis and discussion of the estimated market for new TB vaccines. As this chapter shows, our analysis revealed that, for each scenario modeled, significant value exists within this market, with product net present values (NPVs) ranging from $35 million to $125 million and internal rates of return (IRR) in excess of 20 percent between 2013 and 2030.

Our team examined a base (expected) case for each vaccine profile (the BCG-replacement vaccine, booster vaccine, and prime-boost strategy) and then ran sensitivity analysis to outline both optimistic and pessimistic scenarios.

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.

Our analysis included a range of discount rates for developers, including 10 or 15 percent for pharmaceutical companies and 20 or 25 percent for a typical biotech company. Biotech companies frequently use a higher discount rate than pharmaceutical companies due to the increased risk associated with their business, which drives up their cost of capital. However, if a company receives R&D funding from a donor or product development partnership, it can apply a substantially lower discount rate since a lower cost of capital is required for projects.

For any developer, both development costs and expected return depend on the number of products put into development and on each product’s probability of success. For each product, we calculated returns given estimated probabilities of success at each stage. The results of this analysis are presented in Table 2.

**Base (Expected) Case**
The expected base case scenario represents BVGH’s best estimate of the potential market for a TB vaccine.

**BCG-REPLACEMENT VACCINE**: We estimated that the global annual market for a BCG-replacement vaccine is about $450 million at market peak and almost 60 million doses. At market peak, high-income markets would generate about half of the global revenue. The remainder would be generated from doses needed for low- and middle-income markets (public and private). The public market in low-income countries is expected to generate nearly $90 million. (See Figure 5.) At a 20 percent discount rate, a company could realize an NPV of $35 million and an IRR of 25 percent. (See Table 2.)

**BOOSTER VACCINE**: The estimated peak annual global market for a booster vaccine (which boosts the existing BCG vaccine) is nearly $800 million and about 40 million doses, with high-income markets (at $400 million) again driving revenues. (See Figures 3 and 5.) Given the high estimated cost of the booster vaccine, private markets in low- and middle-income countries and public-sector markets in middle-income countries would drive the remainder of the revenues. Because of the high cost of the booster vaccine, however, we assumed that low-income countries would not adopt the vaccine, even with GAVI support. (See Figure 4.) At a 20 percent discount rate, a company would realize an NPV of $125 million and IRR of 32 percent. (See Table 2.)

**PRIME-BOOST STRATEGY**: The estimated peak annual market for a prime-boost strategy (a BCG-replacement vaccine combined with booster vaccine) is around $1 billion and nearly 100 million doses. High-income markets as well as private markets in low- and middle-income markets would drive the majority of the revenues at peak. As is the case with the booster vaccine, however, we expect that low-income countries will only adopt the cheaper BCG-replacement vaccine and not the prime-boost strategy. At a 20 percent discount rate, a company could realize an NPV of $41 million and IRR of 22 percent. (See Table 2.)

When applying different discount rates under nearly every scenario, the expected returns cover both development costs and the cost of capital. For example, with a discount rate of 10 percent, a pharmaceutical company could expect an NPV of $333 million for the BCG-replacement vaccine, $830 million for the booster vaccine, and $769 million for the prime-boost strategy. Using a more typical biotech
Figure 5. Cash Flow by Year and Market for Three Vaccine Scenarios

**BCG-Replacement Vaccine**
Estimated Total Market Peak over $400 MM (2013 – 2030)

- Facility infrastructure cost cash flows incurred over the previous year are projected forward at 15% cost of capital and capitalized in vaccine launch year; the value of R&D cost cash flows incurred over a period of 14 years, projected forward at 15% cost of capital and capitalized in vaccine launch year.

Source: BVGH/BCG analysis

**Booster Vaccine**
Estimated Total Market Peak over $700 MM (2013 – 2030)

**Prime-Boost Strategy**
Estimated Total Market Peak over $900 MM (2013 – 2030)

Note: Facility infrastructure cost cash flows incurred over the previous year are projected forward at 15% cost of capital and capitalized in vaccine launch year; the value of R&D cost cash flows incurred over a period of 14 years, projected forward at 15% cost of capital and capitalized in vaccine launch year.

Source: BVGH/BCG analysis
discount rate, companies can still generate positive returns. Assuming a 25 percent discount rate, potential NPV is $1 million for the BCG-replacement vaccine and $41 million for the booster vaccine. Only the prime-boost strategy had a negative NPV of -$27 million, suggesting that it would not be a favorable investment. However, as noted earlier, the availability of funding from public donors and product-development partnerships can lower the discount rate that companies need to use.

**Optimistic Case**

To determine the upper bound of the estimates, we modeled the following scenarios for both BCG-replacement and booster vaccines.

BCG-REPLACEMENT VACCINE: We modeled four possible events that could raise the IRR to 43 percent from the base case of 25 percent: (1) accelerating uptake by the developing world market by one year could increase IRR 2.2 percent; (2) delaying when the competitive event occurs (for example, when another vaccine comes on the market) by three years (to 2025) could raise IRR by 2.7 percent; (3) reducing R&D costs to $350 million could raise IRR by 9.8 percent; and (4) assuming that public-market recognition of lost productivity increases, country willingness to pay for a new vaccine could raise IRR by 3.2 percent.

BOOSTER VACCINE: We modeled four possible scenarios that could raise the IRR to 40 percent from the base case of 32 percent: (1) accelerating uptake by the developing world market by one year could increase IRR 1.5 percent; (2) reducing initial production costs to $3.50 per dose could increase IRR by 2.9 percent; (3) increasing vaccine efficacy to 85 percent could increase IRR by 1.3 percent; and (4) delaying when the competitive event occurs to 2025 could raise IRR by 2.2 percent.

**Pessimistic Case**

To determine the lower bound of the estimates, we modeled the following scenarios for the BCG-replacement and booster vaccines.

BCG-REPLACEMENT VACCINE: We modeled four possible events that could lower IRR to 14 percent: (1) a one-year delay in FDA/EMEA approval could lower IRR by 2.3 percent; (2) an additional delay in uptake by developing countries could lower IRR by 1.7 percent; (3) a competitive event occurring three years earlier than expected could lower IRR by 6.6 percent; and (4) if the developer chooses to sell to India and China at prices below $1, IRR could decrease by 0.3 percent.

BOOSTER VACCINE: We modeled three possible events that could reduce IRR to 26 percent: (1) a one-year delay in FDA/EMEA approval could lower IRR by 2.3 percent; (2) an additional delay in uptake by developing countries could lower IRR by 1.1 percent; and (3) a competitive event occurring three years earlier than expected could lower IRR by 2.2 percent.

**Figure 6. TB Vaccine Strategies Could Significantly Reduce Projected Annual Deaths in Asia and Sub-Saharan Africa**

Note: These estimates assume coverage rates of 85% for BCG-replacement vaccines and 66% for booster vaccines necessary to accrue full benefits. Sources: Murray and Salomon; BVGH/BCG analysis.
TUBERCULOSIS VACCINES: THE CASE FOR INVESTMENT

The Social Case for Investment

TB vaccines could have a substantial impact on public health, saving millions of lives each year. (See Figure 6.) For example, in Asia and Sub-Saharan Africa, our model shows that a BCG-replacement vaccine could lead to a 17 percent reduction in TB deaths and a 20 percent reduction in disability-adjusted life years (DALYs) by 2029. Booster vaccines following initial prime with a BCG vaccine could lead to a 40 percent reduction in TB deaths and a 22 percent reduction in DALYs. Combining both approaches together in a prime-boost strategy (the BCG-replacement vaccine and booster vaccines), given existing infection rates, could lead to a remarkable 62 percent reduction in TB deaths and 45 percent reduction in DALYs by 2029.

Our results also show that investments in TB vaccines can be highly cost effective for public-sector donors. While there does not seem to be strong consensus in the public health community about the threshold for cost-effectiveness, the World Bank considers health interventions that cost less than $100 per DALY in developing countries to be cost-effective interventions. Under our analysis, the cost per DALY averted in Sub-Saharan Africa is $6 to $10 for the BCG-replacement vaccine and $21 to $26 for the booster vaccine—well within the World Bank’s range. Investments in Asia are similarly cost effective. The cost per DALY averted in Asia ranges from $5 to $16 for the BCG-replacement vaccine. The estimates for a booster vaccine in Asia ($18 to $235) show a much wider range, however, and it is less clear whether a more expensive booster vaccine such as the one modeled here is cost effective in this region. Additional modeling may be necessary to get a more targeted estimate. (See Figure 7.)

Challenges and Opportunities

Challenges

There are several significant development and deployment hurdles for TB vaccines along the vaccine development and supply chain. (See Figure 8.) Three in particular pose major challenges for developers.

LACK OF SURROGATE MARKERS THAT PREDICT CLINICAL EFFICACY OF A VACCINE: For many vaccines, the presence of surrogate markers for protection (or “biomarkers”) are used to predict the efficacy of the vaccine. No such surrogate markers exist for TB vaccines. Without surrogate markers, clinical researchers can only use evidence of disease over time to show the efficacy of a vaccine. Thus, they have no way to reliably predict whether a vaccine could offer protection against the disease. As a result, Phase III clinical trials for TB vaccines are anticipated to be long (three to four years) and will require large patient populations. The risk and cost of such trials will, thus, be particularly high compared to those for other drugs and vaccines that are developed with shorter or smaller trials. Investment in new, highly predictive biomarkers that correlate with protection from disease could have a dramatic impact in reducing the length of clinical trials and the risk to developers.
SHORTAGE OF TRIAL SITES: Despite significant progress by the Aeras Global TB Vaccine Foundation in setting up clinical trial sites in India and South Africa, there is still a need for additional sites to support the current pipeline of TB vaccines. Currently, only one to two Phase III trials can be started in the next two to three years, creating a serious bottleneck. Recent plans by the European and Developing Countries Clinical Trials Partnership to fund development of additional trial sites may begin to ease this bottleneck. It is anticipated that these trial sites may be ready in three years.

LIMITED PUBLIC-SECTOR FINANCING TO ASSIST LOW-INCOME COUNTRIES WITH TB VACCINE PURCHASE: A shortfall in support from nongovernmental organizations (NGOs) and international organizations would mean slower adoption of the BCG-replacement vaccine in low-income countries. And without significant public-sector commitment, our analysis shows that a booster vaccine, assuming costs well exceeding $1 per dose, would not even be administered in low-income countries. The pressure on public-sector resources, however, will likely increase as additional vaccines for other critical diseases become available. Strategists will need to campaign hard for funding increases and to pursue new possible financing mechanisms, such as Advance Market Commitments (AMCs).

Pathways and Opportunities for Innovation

Despite the real challenges, our analysis shows that there are several key pathways and opportunities to accelerate TB vaccine innovation.

STRONG DONOR COMMITMENT TO TB VACCINE DEVELOPMENT: The Bill & Melinda Gates Foundation is the largest private provider of funds for TB vaccine development. In 2004, the Bill & Melinda Gates Foundation invested $82.9 million in the development of TB vaccines through the Aeras Global TB Vaccine Foundation. In addition, the United States is the largest public provider of R&D support, and the European Union has made significant commitments as well, although most of these funds are directed toward basic research. Denmark has funded Aeras, and Norway is expected to provide funds for development work within the next six to nine months.

In addition, the G8 governments are considering whether to create an AMC for TB vaccines, essentially guaranteeing a market for TB vaccines in the developing world (provided countries choose to adopt). BVGH worked directly with the World Bank and GAVI to estimate the size of an AMC necessary to incentivize industry to take on the risk of supplying to these markets. Using the same product profiles for both the BCG-replacement vaccine and booster

Figure 8. Vaccine Development and Deployment Pathways and Hurdles

<table>
<thead>
<tr>
<th>Scientific &amp; technical</th>
<th>Lack of proper animal models</th>
<th>Lack of surrogate markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial &amp; economic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Political &amp; social</td>
<td>Co-development in China and India desired</td>
<td>Clinical trials in China, India, and South Africa required</td>
</tr>
<tr>
<td>Logistical</td>
<td>Lack of sufficient clinical trial sites</td>
<td></td>
</tr>
</tbody>
</table>

Source: BVGH/BCG analysis
Vaccines, the analysis estimated that an AMC of $360 million for a BCG-replacement vaccine and $3.8 billion for a booster vaccine would be needed.

INVESTMENT IN NEW DIAGNOSTICS: Our analysis shows that the availability of a diagnostic would have a significant effect on improving uptake of a booster vaccine. We assume in this analysis that a booster vaccine would not work on people already infected with TB. If public health workers were able to administer a rapid diagnostic in the field to determine whether a person is infected with TB before administering the vaccine, then the vaccine could be more appropriately targeted. While this would decrease the number of people that get the vaccine, it would improve its cost effectiveness, leading more companies to adopt. In fact, the availability of an inexpensive and rapid field diagnostic would increase the number of booster vaccines adopted by 13.3 million doses in public markets. (See Figure 9.)

In interviews with TB experts, we repeatedly heard that such diagnostic innovation is technically feasible and may be available by the time the vaccines in the current pipeline reach Phase III clinical trials. Given the significant impact that diagnostics could have in improving the cost-effectiveness of a booster vaccine, additional investment in these new tools is imperative.

SHORTENING DEVELOPMENT TIMELINES AND REDUCING RISK: Our analysis shows that donors can leverage their funding for TB vaccines by investing in measures that reduce time to development. For example, investing $10 million to develop three new clinical trial sites and another $10 million to address country-specific regulatory hurdles could help accelerate development by one year, leading to an increase in a company’s IRR and improved public health (averting 22,000 deaths and reducing DALYS by 475,000).

ADVANTAGES TO PARTNERING WITH EMERGING MANUFACTURERS: Based on interviews with Indian and Chinese biotech companies, NGOs, and clinical trial coordinators, we found that in order to access Chinese and Indian markets, companies would benefit both from conducting clinical trials in those countries and exploring partnering opportunities with Chinese and Indian manufacturers. Doing so could reduce clinical development costs and smooth the path to licensing within those countries.
Conclusion

Our study builds a strong financial and social case for investment in TB vaccines and highlights how donor involvement can improve the market opportunity as well as the social impact. The global market—driven by both developed and emerging markets, with an estimated peak annual market of over $450 million for a BCG-replacement vaccine and nearly $800 million for a booster vaccine—is sufficient to attract industry investment. In addition, the estimated public health impact of TB vaccines is dramatic. Millions of deaths could be avoided, and morbidity could be significantly reduced, at a cost of only $19-$63 per DALY averted.17

Certain hurdles to development are high, however, and could still deter industry investment. The absence of biomarkers for vaccine efficacy means that clinical trials are expected to be long and risky. Phase III trials could take three to four years and require the participation of thousands of subjects. Steps to reduce development time—particularly the approaches that shorten clinical and regulatory timelines—could help mitigate the development risk, and thereby attract more companies. In addition, funding for new clinical trial sites, steps to smooth product licensure in developing countries, and additional public-sector funding to further reduce the risk of clinical trials are all needed.

Our analysis also shows the significant potential health impact of a booster vaccine—an additional 500,000 lives saved over the number saved by a BCG-replacement vaccine, delivered in infancy. The price of several booster candidates, however, is projected to be beyond the means of the poorest countries, even with the support of donors. To ensure that those in the poorest countries receive the benefits of a booster vaccine, developers should seek practical ways to lower the manufacturing costs of these vaccines. Lower manufacturing costs could increase the adoption of booster vaccines in low- and middle-income public and private markets, which would build the overall market size and improve industry’s return on investment.

Call to Action

INDUSTRY

- Evaluate the opportunity for TB vaccine development.
- Seek efficient development processes that will keep the manufacturing costs down and help make TB vaccines more affordable to resource-poor countries.
- Develop diagnostics and novel biomarkers for TB.

PUBLIC SECTOR

- Support the development of novel biomarkers to predict vaccine efficacy and diagnostics to detect the presence of disease.
- Support the development of clinical trial sites.
- Explore ways to ensure a smooth regulatory pathway.
Bibliography


Kaufmann SH. Rational vaccine development against tuberculosis: “Those who don’t remember the past are condemned to repeat it.” Microbes and Infection 2005;7:897-898.


Endnotes

1 Andersen and Doherty (2005).
2 BCG vaccines are vaccines against TB that are administered at birth. While they have a wide range of reported efficacy, they are generally believed not to be protective against TB in adolescents and adults.
3 A measure that combines healthy life years lost because of premature mortality with those lost as a result of disability.
4 Andersen and Doherty (2005).
5 Andersen and Doherty (2005).
6 Andersen and Doherty (2005).
7 The six TB-endemic countries in which we conducted research are Brazil, China, India, Nigeria, Russia, and South Africa.
8 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.
9 For example, before the Hepatitis B vaccine was offered through the public market in China, 70 percent of all households bought the vaccine for their newborns (at $3 per dose). And in Brazil, while Hepatitis B vaccines are given through the public health care system free of charge, some are still willing to pay even $70 per vaccine.
10 Regimen equals the number of doses provided per vaccine course.
11 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.
12 An investment tool used to rate alternative investments, IRR is defined as the discount rate that gives an NPV of zero.
13 A measure that combines healthy life years lost because of premature mortality with those lost as a result of disability.
15 Assumes that the bulk of vaccine development is covered by the public sector through Aeras.
16 Assumes that the cost would be as low as $1.75 per booster vaccine.
17 Our model examined cost-effectiveness for Sub-Saharan Africa and Asia.
Appendix I. TB Vaccine Pipeline

The current TB vaccine pipeline includes about a dozen candidates, half of which aim to replace the existing BCG vaccine and half of which are designed to boost immunity in individuals primed with either the BCG vaccine or a BCG-replacement vaccine.

### TB Vaccine Pipeline

#### BCG-Replacement Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Source</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aeras 403</td>
<td>Aeras</td>
<td>Pre-clinical</td>
<td>Recombinant BCG which over expresses antigens 85A, 85B, and 10.4 with endosome escape</td>
</tr>
<tr>
<td>BCG::RD1</td>
<td>Institute Pasteur</td>
<td>Pre-clinical</td>
<td>BCG into which the RD1 locus was reintroduced, allowing secretion of ESAT-6-CFP10</td>
</tr>
<tr>
<td>rBCG::(\Delta u)reC(\Delta h)ly</td>
<td>Max Planck Institute</td>
<td>Pre-clinical</td>
<td>Urease-deficient BCG mutant expressing listeriolysin O gene from (L.\ monocytogenes)</td>
</tr>
<tr>
<td>6020 and 6030 attenuated Mtb</td>
<td>Albert Einstein College of Medicine</td>
<td>Pre-clinical</td>
<td>LysA, PanCD and RD-1, PanCD double deletion mutants of (M.\ tuberculosis)</td>
</tr>
<tr>
<td>(\Delta phoP/R)</td>
<td>Institut Pasteur/ TB-Vac</td>
<td>Pre-clinical</td>
<td>(phoP) virulence factor inactivated by the insertion of an antibiotic gene into (M.\ tuberculosis)</td>
</tr>
</tbody>
</table>

#### Booster Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Source</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA-85A</td>
<td>Oxford University</td>
<td>Phase II</td>
<td>Recombinant, replication-deficient vaccinia virus expressing antigen 85A from (M.\ tuberculosis) to boost BCG</td>
</tr>
<tr>
<td>72f (M72)</td>
<td>Aeras/GSK</td>
<td>Phase I</td>
<td>Fusion molecule comprised of two proteins, with the PFE family member Rv1196 inserted into the middle of the putative serine protease Rv0125 to boost BCG</td>
</tr>
<tr>
<td>Hybrid 1</td>
<td>SSI/Intercell</td>
<td>Phase I</td>
<td>Recombinant Mtb antigens 85B and ESAT-6 combined with adjuvant IC31 to boost BCG</td>
</tr>
<tr>
<td>Aeras 402</td>
<td>Crucell/Aeras</td>
<td>Pre-clinical</td>
<td>Recombinant adenovirus35 which expresses antigens 85A, 85B, and 10.4 to boost BCG</td>
</tr>
<tr>
<td>HyVac 4</td>
<td>SSI/Intercell and Aeras</td>
<td>Pre-clinical</td>
<td>Recombinant Mtb antigens 85B and 10.4 combined with adjuvant IC31 to boost BCG</td>
</tr>
<tr>
<td>Shigella RNA capsids</td>
<td>Aeras</td>
<td>Pre-clinical</td>
<td>Mtb antigens delivered by RNA capsid system to boost BCG</td>
</tr>
</tbody>
</table>

Source: BVGH
Appendix II: Methodology

Methodology Used to Analyze Market Demand

To obtain a realistic picture of market demand, we first estimated the need for a particular TB vaccine and then made assumptions about the ability of the modeled vaccine to address that need, the ability of those in need to access the vaccine, and different market segments’ attitudes toward the vaccine. For example, the need for a TB vaccine may be great across a population, but the actual demand will be tempered by the vaccine’s target population. Access will also differ from country to country, depending upon factors such as infrastructure and per-capita healthcare expenditure. And attitude plays a role as well—for example, whether the disease is recognized as a priority issue in a particular country.

To identify whether countries will adopt a particular vaccine, we employed cost-effectiveness analysis for three different market segments.

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

In analyzing public-sector markets in low- and middle-income countries, we took a health-system perspective—given that government officials are concerned with avoiding treatment costs and reducing infection and active cases.

In assessing private markets in low- and middle-income countries, we took a personal-finance perspective—since these individuals are more concerned about loss of wages and the health of their children than with reducing the risk of TB transmission across the population.

In evaluating markets in high-income countries, we again took a health-system perspective—because concern is focused on avoiding treatment costs and on the risk of transmission. In this case, we assumed that a TB vaccine would be adopted for high-risk populations only.

For public markets (in low-, middle- and high-income countries), we calculated a threshold willingness to pay for the vaccine based on the endemic rate of TB within the country, the incremental efficacy of a new vaccine product over the BCG vaccine, the duration of protection of the

Three Product Profiles Tested Addressing Different Target Populations

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<thead>
<tr>
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<tbody>
<tr>
<td>Low- and Middle-Income Countries: Neonates/Children</td>
<td>Effective neonatal vaccine</td>
<td>Effective childhood boost vaccine to BCG</td>
<td>Combination neonatal vaccine and childhood boost vaccine</td>
</tr>
<tr>
<td>Low- and Middle-Income Countries: All Ages</td>
<td>Assumed not to be effective adolescent and adult vaccine</td>
<td>Effective adolescent and adult vaccine</td>
<td>Effective adolescent and adult vaccine</td>
</tr>
<tr>
<td>High-Income Countries: High-risk Individuals</td>
<td></td>
<td>Effective primary vaccine in adults in developed nations — 1 dose every 10 years</td>
<td></td>
</tr>
</tbody>
</table>

Key Features

- **Product profile 1: BCG Replacement**
  - Efficacy 70%
  - Safety Equivalent to BCG
  - Includes HIV(+)
  - 1 Dose at Birth
  - Effective for 10 years

- **Product Profile 2: Booster**
  - Efficacy 70%
  - Safety Equivalent to BCG
  - Includes HIV(+)
  - 1 Dose Every 10 years
  - 1st Boost at 14 weeks

- **Product Profile 3: Prime Boost**
  - Efficacy 70-90%
  - Safety Equivalent to BCG
  - Includes HIV(+)
  - Prime at Birth + 1st Boost at 14 weeks

Source: BVGH/BCG interviews
product, and an estimate of additional cases avoided through vaccination. We calculated cost avoidance for public-sector markets in low- and middle-income countries by using published WHO DOTS program costs (with appropriate proxies for countries with missing data). We based high-income market willingness to pay for a vaccine on the cost of treatment for high-risk individuals.

For private markets in low- and middle-income countries, we based costs on a risk-adjusted estimate of individual productivity lost from contracting TB. For cost-effectiveness analysis for individual companies, we derived an adoption price and estimated the portion of the population willing to pay using the following key variables:

- Risk of active TB (incidence per capita);
- Productivity lost through TB (~6.5 months);
- Health utility index for pulmonary TB (0.89); and
- Vaccine attributes (incremental benefit of 40 percent).

We calculated the percentage of the high-risk U.S. population for whom risk-adjusted wage loss exceeds vaccine price based on a Lorenz curve distribution of income per capita in the population. We then extrapolated an uptake rate based on proxies of EPI vaccine coverage rates, triangulated these willingness-to-pay estimates and validated them through interviews with public health officials, NGO representatives, and global donors, as well as through proxies and analogies of willingness to pay for other vaccines.

**Methodology Used to Calculate Social Return on Investment**

To gauge social return on investment, we calculated two cost-effectiveness measures: the cost to avert a death and reduce a DALY. In other words, how much has to be invested in a TB vaccine to save one life, and how much to add one year of useful life? To arrive at these measures, we leveraged two models—the BVGH demand model and the Murray/Salomon model.

The Murray/Salomon model was developed during the 1990s to calculate the relative DALY and mortality impact of a series of hypothetical interventions for TB for the 1998 to 2030 time period. While it did not specifically address a vaccine with the product profiles we tested, we worked with Joshua Salomon at Harvard University to extrapolate its results and apply them to our demand model.

Our study calculated the figures for the years 2013 to 2030 for two regions—Asia and Sub-Saharan Africa—for each of the three vaccine scenarios: BCG-replacement vaccine (prime), booster vaccine, and the prime-boost strategy. The formula is straightforward: total vaccination cost divided by number of TB deaths/DALYs averted.

The total vaccination cost is made up of the sales price (production costs and margin) and the fees for administration and distribution.

We limited our analysis to these two regions for two reasons: they bear the bulk of the global TB burden (about 78 percent) and their epidemiologic pattern has remained fairly steady since the Murray/Salomon model was established in the 1990s. In most of the other regions—Latin America, the former Soviet republics, and the Middle East—the epidemiologic patterns have changed dramatically, with a great surge in incidence.
Appendix III. Vaccine Procurement Process

Complex Coordination of Entities to Supply Vaccine through UNICEF for Low-Income Countries

1. Qualifying countries submit proposals to be considered for funding
2. GAVI evaluates and submits recommendation to the Vaccine Fund
3. The Vaccine Fund approves purchase recommendation and provides funding through UNICEF
4. UNICEF supply division procures all vaccines after negotiating directly with suppliers
5. Suppliers ship directly to recipient countries or via UNICEF


Source: GAVI, UNICEF, Vaccine Fund websites; BVGH/BCG interviews
Appendix IV: BVGH Team and Advisers

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