Executive Summary

The purpose of this *Business Case* for investment in TB research and development is to demonstrate that a viable global market exists for new TB vaccines and to initiate discussions among various key stakeholders, including donors, pharmaceutical companies, vaccine developers, the WHO, and representatives from high disease burden countries, and civil society. This is an effort to ensure adequate finance and risk-sharing among the public and private sectors, and to advocate for the portfolio management approach as the most efficient and effective mechanism for facilitating the development of new TB vaccines.

The Business Case incorporates outputs from a dynamic model that was developed to address four key objectives: (1) To identify a product development strategy that maximizes the public health impact of new TB vaccines; (2) To conduct a strategic market analysis to assess the commercial viability of new TB vaccines; (3) To evaluate portfolio development costs in order to inform on investment strategies by phase of development over time, to support the successful commercialization of at least one new TB vaccine; and, (4) To demonstrate the cost efficiencies of implementing a portfolio management approach.

Contagious and airborne, *M. tuberculosis* is a resilient and highly adaptable microorganism that has survived and thrived alongside its human host for centuries. Tuberculosis (TB) was first reported in the Greek literature by Hippocrates as the most widespread and fatal disease of the times. Historically described as the "Great White Plague", TB was the cause of more deaths in industrialized countries than any other disease during the 19th and early 20th centuries. By the late 19th century, 70-90% of the urban populations of Europe and North America were infected with the TB bacillus, and about 80% of those individuals who developed active TB died of it. Today, more than 2 billion people, almost a third of the world's population, are infected with the same TB bacillus, and this number will continue to grow without effective preventative measures.

Intensified and heroic efforts by the public health community to reduce disease burden have resulted in a 45% reduction in TB related deaths over the past two decades. However, there are nearly a million more cases of TB in the world today than when the World Health Organization (WHO) declared TB a global emergency 20 years ago, with 7.8 million cases in 1990 and 8.6 million cases in 2012. Today, TB is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent.

M. tuberculosis has evolved and become more challenging to cure, as evidenced by increasing cases of drug-resistant TB strains now present in almost all countries surveyed worldwide. Alarmingly, recent reports from India and South Africa of apparently untreatable cases, referred to as totally drug resistant (TDR), are raising international concerns around the emergence of a manmade superbug, with higher mortality rates being reported than the more highly publicized Ebola and SARS viruses.

While predominantly a disease of the poorest and most vulnerable, TB is poised to spread through migration and urbanization as evidenced by a highly publicized

London TB hotspot adjacent to the home of some of Europe's largest banks, and the recent outbreak in downtown Los Angeles. Situations like these are waking up policy makers to the fact that there is no way to adequately protect those who are exposed to a contagious individual from becoming infected with the TB bacillus. Leveraging this growing public concern to catalyze political will and resources for intensified control efforts and the development of new vaccines, drugs and diagnostics could significantly accelerate global efforts to eliminate this ancient plague.

With TB killing 2-3 people a minute worldwide, there is little doubt that the disease remains a serious public health threat. The ongoing economic impact of the epidemic, however, is also a matter of grave concern, even for those not directly affected by the disease. In the European Region[1], for example, there are 49 new TB cases and 7 TB-related deaths every hour. According to a study published in 2013 in the European Respiratory Journal, the consequent economic cost of this regional disease profile is estimated to be more than € 5 billion per year due to lost productivity and treatment costs (Diel).

To reduce this economic burden, and scale up TB care and control efforts, the WHO estimates that upwards of US $8 billion per year will be required to support low- and middle income countries through 2015. However, without a vaccine to prevent the spread of pulmonary TB, transmission will continue. For the foreseeable future, efforts to save lives and reduce disease burden will be increasingly difficult and expensive to address.

Ultimately, it is innovation that will drive progress across the entire value chain from delivery science, operational research and R&D in vaccines, to drugs and diagnostics. Already there have been some tremendous breakthroughs with the approval of GeneXpert, a new rapid diagnostic, and bedaquiline, the first new antibiotic for TB approved in 50 years. However, these successes are not enough. We cannot let complacency take hold. At current R&D investment levels we remain vulnerable and ill-equipped to deal with an increasingly drug-resistant superbug, or to significantly reduce the spread of disease in the highest disease burden countries.

New vaccines sit at the center of future TB elimination efforts. Like every other major infectious disease in the history of mankind, prevention through vaccination has been the most cost-effective tool in eradicating and controlling these diseases. The ultimate austerity measure is prevention.

Significant scientific progress in vaccine R&D is well underway. Investments of more than US $600 million over the past decade have resulted in a robust global TB vaccine portfolio comprised of more than 25 early stage discovery leads and preclinical candidates, and more than a dozen candidates for which clinical trials are underway. New capacity in high disease burden countries to manage complex, large-scale efficacy trials has been established, and historical clinical trials offer crucial insights into the biology of TB.

A new model incorporating data from 183 countries demonstrates that a partially efficacious (60%) adolescent and adult preventative vaccine, delivered to a mere 20% of the target population, could potentially avert as many as 30-50 million new cases of TB by 2050, depending on the year of vaccine introduction. A significantly improved infant vaccine, relative to the 90-

[1] Full list of 53 World Health Organization European Region Countries http://www.euro.who.int/en/where-we-work

year-old Bacille Calmette-Guérin (BCG), could potentially avert an additional 7-10 million new cases over that same period of time. New TB vaccines would be our single greatest preventative tool in the fight against TB for decades to come.

Renewed commitments to funding future clinical trials and capacity building at trial sites by the European Commission's flagship European & Developing Countries Clinical Trials Partnership (EDCTP), as well as funding from the Bill & Melinda Gates Foundation and the Dutch, British and US governments, will help ensure that resources are available to support vaccine development efforts in the near term. However, funding gaps remain creating an urgent need to ensure long-term financial support, covering all phases of development, so that new TB vaccines will be available as soon as is feasibly possible.

This *Business Case* addresses these challenges by promoting the efficient use of finance and effective portfolio management as the best means of advancing the global TB vaccine portfolio. Implementing effective portfolio management is achieved by applying rigorous stage-gating criteria and innovative trial designs that facilitate the expeditious down-selection of candidates, and preserving scarce resources by advancing only the most promising candidates into the more expensive, later-stage trials. Aligning public and private sector interests will also be paramount in catalyzing vaccine development efforts. While governments may have a strong economic and public health incentive to introduce new TB vaccines, it is the relatively few multi-national pharmaceutical companies that possess the capabilities and experience to globally introduce a new TB vaccine.

Given these dynamics, Aeras and TB Vaccine Initiative (TBVI) are working together to evaluate the market potential of new TB vaccines and to recommend investment strategies that balance commercial and public sector interests. EDCTP has been recently invited to join the collaboration. The European Commission has requested that the Advisory Services of the European Investment Bank (EIB) facilitate the collaborative process and provide technical and financial advice.

Initial market assessments indicate that the market for a preventative TB vaccine targeted toward adolescents and adults could be substantial. Utilizing conservative estimates on price and vaccine coverage rates, the 10 year market opportunity is projected to be US $12-13 billion, with approximately 50% of these revenues being generated in the high- and upper middle-income countries, although these segments would consume less than 25% of the total projected doses.

The potential market for an infant vaccine is projected to be approximately US $700 million to $1 billion over ten years, with the majority of these revenues generated in middle-income countries.

Despite the significant market potential for new TB vaccines, the high degree of scientific uncertainty from discovery through phase 2b proof-of-concept proves to be a significant barrier to attracting priority interest from pharmaceutical companies. The public sector can mitigate these risks by offering well-targeted push and pull mechanisms along the value chain. Push mechanisms utilize grants to finance the high-risk, early-mid phases of development, and pull mechanisms seek to increase commercial rewards for the development of an effective vaccine in key markets, thereby leveraging greater investment by the pharmaceutical industry in

the more expensive, later-stage clinical trials. Blended capital utilizing debt and/or equity as part of a well-structured pull mechanism in the later stages of development might offer an additional option to filling the funding gap.

In order to test and validate the assumptions and proposals made in this business plan, the Collaboration Partners propose the following next steps:

- Holding bilateral meetings with the major donors to discuss a coordinated global governance structure and portfolio management principles;
- Seeking recommendations from the various stakeholder groups on necessary changes that need to be considered by the funding community and, in particular, among the major donors (Bill & Melinda Gates Foundation, European Commission, NIH, etc.);
- Vetting various push and pull mechanisms with major vaccine manufacturers to optimize alignment;
- Validating the market among various high- and upper middle-income countries within the EU and other regional countries;
- Assessing year-over- year (YOY) portfolio funding needs and identifying investment strategies to close gaps;
- Engaging the broader scientific community to update them on the potential for future funding and test the feasibility of establishing a global governance structure;
- Refining the business case to include key stakeholder feedback.

Making new TB vaccines available to the world over the next 10-15 years is estimated to cost less than US $800 million, utilizing a highly efficient portfolio management approach. These costs pale in comparison to the estimated US $8 billion a year required to provide TB treatment and care. While no one should be denied access to life-saving treatment today, austerity measures demand that we invest in longer-term strategies that could ultimately save billions in treatment costs while protecting future generations from one of the longest lasting and deadliest epidemics of mankind.

It is only on the brink that people find the will to change. Only at the precipice do we resolve to act. This is the moment for TB.

2. The Global Need for New TB Vaccines

2.1 Overview

The global TB epidemic requires novel approaches, new tools and sufficient resources to mitigate what is now an even more challenging and expensive disease to control than when the WHO declared TB a global emergency 20 years ago. Although the international community has made significant progress in decreasing TB-related deaths by 45% since 1990, the global incidence relative to population growth has remained relatively flat with the exception of a few countries (Figure 1).

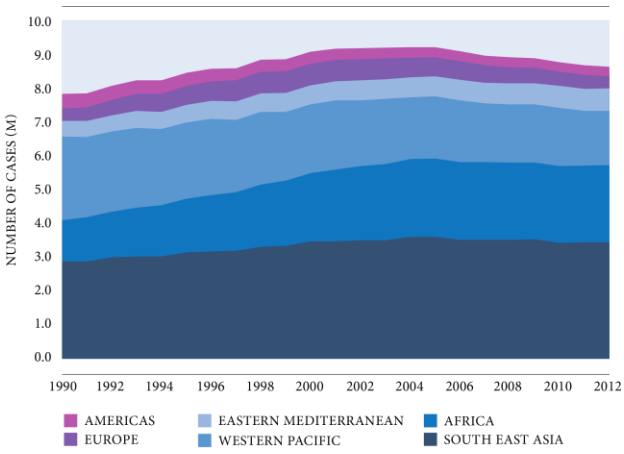
In 2012, an estimated 8.6 million people fell ill with active TB, with a third of those cases remaining both undiagnosed and untreated, confounding efforts to stop the spread of this deadly airborne disease (WHO, 2013). In addition, multi- and extensively drug-resistant (M-XDR) TB threatens to halt overall progress, given that treatment for drug-resistant disease can be as much as 1,000 times more expensive and require two or more years of continuous therapy (WHO, 2007).

A vaccine that could prevent adolescents and adults from acquiring, developing and transmitting disease would be the single most cost-effective tool in mitigating this epidemic.

Treating our way out of this epidemic is neither possible nor affordable for most countries, given the limitations inherent in the tools used today, as well as the requisite costs for scaling up and achieving universal access to M-XDR TB treatment and wide-scale access to preventive therapy. It is for this reason that R&D investments in new tools and approaches remain the cornerstone to reaching global elimination targets within the coming decades.

The most effective way to stop the spread of TB is to prevent its spread. And while the current vaccine *M. bovis* Bacille Calmette-Guérin (BCG) – the most widely used vaccine in the world – protects against severe progressive TB in children, it is inconsistent in protecting against the predominant adolescent and adult form of TB, that is pulmonary TB. This contagious form of the disease is largely responsible for the global epidemic. New vaccines are urgently needed to protect against all forms of TB, in all age groups and in all global populations. However, a vaccine that could prevent adolescents and adults from acquiring, developing and transmitting disease would be the single most cost-effective tool in mitigating this epidemic (Tseng, 2012).

Figure 1. Global Incident TB Cases 1990-2012



Today, we stand at the precipice of a new paradigm in fighting this ancient scourge. Since 2005, global investments of more than US $600 million have allowed more than 15 TB vaccine candidates to be tested in more than 50 human trials (TAG, 2012). In addition, promising activities for the development of new biomarkers have emerged; capacity for vaccine production and carrying out large-scale clinical trials is present particularly in disease endemic countries; there is broad and widely-accepted local community support for research among communities where clinical trials are being conducted; and basic information on safety and immune responses to a variety of first-generation TB vaccine candidates is now available. The effectiveness of these vaccine candidates in preventing TB will be revealed over the next decade, and plans for regulatory approval and delivery of effective vaccines are being established.

Today, there is robust global portfolio comprised of more than 25 early stage discovery leads and preclinical vaccine candidates, and more than a dozen candidates for which clinical are trials underway (Annex 1). In addition, advanced TB vaccine programs now exist among major multi-national pharmaceutical companies, biotechs, Indian and Chinese public and private organizations, and a myriad of academic and public institutions. Paramount to these global achievements are the resources and technical expertise required to advance technologies through the infamous 'valley of death' – which occurs when 'non-economic' investments (such as government expenditures on basic research) are made in very early stage research without sufficient attention to the likely investment decisions at later stages focused on product development and commercialization (Beard, 2009). Aeras and TBVI are providing these translational capabilities and critical resources through the generous support of major donors such as the Bill & Melinda Gates Foundation, the UK Department for International Development, the Netherlands' Ministry of Foreign Affairs, the European Commission, the US National Institutes of Health (NIH), and a range of other governments.

The next phase of vaccine development will prove to be most crucial, as limitations of resources, both financial and clinical, demand a structured and transparent 'rational selection' process for advancing the best TB vaccine candidates. This cannot be the work of a single foundation or a small set of governments or biotech partners, but must involve the larger global public and private community. It requires a shift in will, not simply from policymakers and traditional grant-makers but also from financial institutions, to make innovation across all sectors a priority in the fight against TB.

2.2 Disease Description

TB spreads through the air like the common cold. A TB patient with active disease can infect up to 15 people simply by coughing, sneezing or talking. Although most TB cases and deaths occur in developing and emerging countries, TB is not limited by national boundaries. In the WHO European Region alone, TB

causes 49 new cases and kills 7 people every hour. Fifteen of the 27 high multidrug-resistant TB (MDR-TB) burden countries in the world are in the WHO European Region (WHO: Tuberculosis in the European Region).

The global burden of disease remains enormous, and the decline in incidence is so slow that at current rates, and with the current tools available to us, it will take a millennium to end TB, if elimination can be achieved at all (Figure 2).

Confounding efforts to achieve Millennium Development Goal (MDG) 6 - combat HIV/AIDS, malaria and other diseases – is the HIV/TB syndemic[2] and the spread of drug-resistant TB. In addition, new and troubling findings from a robust, multi-country study show that counterfeit and poorly made drugs are widely used to treat TB across the 17 countries analyzed (Bate, 2013).

Figure 2: Projected TB Incidence

The study found that 16.6% of the TB drugs in Africa, 10.1% in India and 3.9% in the other middle-income countries were "failures," meaning they contained less than 80% of the active ingredient necessary to treat the disease (Bate, 2013). These substandard drugs are almost certainly making the disease more resistant to drugs, posing a grave health threat to communities around the world.

In regards to MDG 4 - reducing child mortality - and MDG 5 - improving maternal health - childhood TB remains a hidden epidemic in most countries. Every year, approximately 530,000 children develop TB, and 74,000 die from the disease. In 2010, there were more than 10 million left orphaned from TB.

> *"We are on the brink of another epidemic, and it has no treatment. If TDR spreads, we will go back to the Dark Ages."*
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> - *TIME Magazine March 4, 2013*

TB is also the third leading cause of death of women of reproductive age (15-44 years) worldwide, killing 410,000 women in 2012 (WHO, 2013). It is a known risk factor for pregnant mothers and their infants. Babies born to women with TB are more likely to be premature or low-birth weight, increasing the risk of neonatal death, and pregnant women with active TB are more than four times more likely to die in childbirth. Transmission from mother to child is estimated to be 15% within the first three weeks of birth. (Fleischman, 2010).

Unique among 'neglected diseases of poverty,' TB exacts an enormous toll on the BRICS emerging

[2] A syndemic is defined as the convergence of two or more diseases that act synergistically to magnify the burden of disease (Kwan & Ernest, 2011).

economies, with 60% of the world's cases of MDR-TB occurring in South Africa, Russia, India and China (WHO, 2012). China's first national survey revealed that a third of new TB cases and half of previously treated cases were MDR-TB, representing 25% of the world's total MDR-TB cases (Zhao, 2012). Three areas in Russia have the highest rates of MDR-TB ever recorded, and in India, recent outbreaks of what doctors have dubbed "totally drug-resistant TB (TDR)" have rippled through the global media headlines and alarmed health officials around the world. This form of TB, which has also been identified in Iran, Italy and South Africa and is likely present elsewhere, is virtually untreatable with existing drugs, leading in most cases to death.

Perhaps no other country suffers a greater challenge in controlling TB than South Africa. Over the past 15 years, TB incidence has increased by 400% (UNAIDS, 2012). TB incidence in South African mines ranks as one of the highest in the world, at 3,000 to 7,000 cases per 100,000 population, highlighting a complex political economy that interconnects health, employment opportunities, worker rights and migration policies in Southern Africa. Confounding efforts to control South Africa's TB epidemic, 73% of people with HIV are co-infected with *M. tuberculosis* (Stop TB Partnership: HIV/AIDS in South Africa).

Globally, the WHO reports that MDR-TB cases are on the rise in most of the high disease burden countries. The highest proportions of TB patients who have MDR-TB are in Eastern Europe and Central Asia, where up to 20% of new TB cases and more than 50% of previously treated cases are MDR-TB (WHO, 2013), as well as in several African countries. It is estimated that only 10% of cases of MDR-TB are currently identified worldwide and only half of them receive appropriate treatment (Zumla et al, 2013). Extensively drug-resistant TB (XDR-TB), which is resistant to first- and second-line drugs, has been identified in 92 countries (WHO, 2013).

TB remains one of the deadliest and most disabling diseases in the world today. Although its burden is spread across all age groups, it exacts its greatest toll on individuals during their most productive years, from 15-44 years of age. It is for this reason that the impact of TB on families is often economically devastating. In high-burden countries, this translates to significant annual losses in GDP.

2.3 The Economics of Tuberculosis Disease Burden and Control

TB places an extraordinary burden on those afflicted by the disease, their families and their communities, as well as on government budgets. The greatest burden of TB falls on working adults, who, once infected, are weakened and often unable to work for long periods of time. The burden of taking care of sick individuals usually falls to other family members, putting them at greater risk of infection, lowering their productivity and perpetuating the cycle of poverty.

Adult deaths place an especially high economic burden on societies. Studies found that more than two-thirds

of pre-industrialized European economic growth between 1700 and 1820 was accounted for by reductions in adult mortality (Laxminarayan, 2007). Greater adult mortality results in a lower rate of return to human capital investments, which in turn is a determinant of economic growth (Boucekkine, 2003).

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TB's costs to society can be measured by both the costs of controlling the epidemic with currently available tools and methodologies, and the costs associated with lost productivity and the economic burden of deaths. A World Bank cost-benefit analysis conducted in 2007 found that the economic benefits of implementing the WHO's 'Directly Observed Therapy Short-Course' (DOTS), and *The Global Plan to Stop TB,* in the 22 high-burden countries would result in an estimated economic gain of around $1.6 trillion over the period 2006-2015. The economic impact of TB deaths and the benefits of control were calculated to be greatest in China and India, in which the combination of growing incomes and high numbers of TB deaths translates into a significant economic effect.

While the World Bank study did not include a cost-benefit analysis around the more expensive treatments for deadlier drug-resistant TB strains, a recent systematic review of the cost and cost-effectiveness of treatment for MDR-TB noted that treatment can be cost-effective in low- and middle-income countries. However, the author noted that more data are required from Africa and Asia, especially India and China (Fitzpatrick, 2012).

The cost of treating MDR-TB is up to 200 times greater than for treating drug-sensitive TB, often requiring up to two years of treatment, daily injections and in-patient care (WHO, 2010). XDR-TB can be up to 1,000 times costlier (WHO, 2007).

Within the context of national budgets, South Africa spends nearly a third of its total control budget on MDR-TB, which makes up only 2% of actual cases (Pooran, 2013). The WHO European region alone spends an estimated €2 billion a year on treatment (WHO, 2010). In London, the total number of cases of MDR-TB has increased by over 50% in the last 10 years, and although the total number of cases remains relatively small, the overall cost of treating each case ranges from £50,000-70,000 per patient (London Health Programmes, 2011).

The WHO European region alone spends an estimated €2 billion a year on treatment, where the cost of treating MDR-TB can be 200 times that of drug-sensitive TB.

In the United States, the cost of hospitalization for one XDR-TB patient averages nearly US $500,000, and because of the limited responsiveness of drug-resistant strains to available antibiotics, mortality rates among patients with XDR-TB are similar to those of TB patients in the pre-antibiotic era (CDC, 2009). Treating one case of MDR-TB in the US costs an average of US $250,000, and in the early 1990s, an outbreak of MDR-TB struck New York City, costing at

least US $1 billion to treat patients and prevent further spread of the disease.

In 2014 and 2015 upwards of US $8 billion per year will be needed in low- and middle-income countries to cover TB care and control.

The WHO's *Global Tuberculosis Report 2013* states that in 2014 and 2015, upwards of US $8 billion per year will be needed in low- and middle-income countries to cover TB care and control. They cite a funding gap of up to US $2.3 billion per annum. During these challenging economic times, it is critical not only to adequately fund TB control programs, but also to take into consideration the future costs to society. Under-investing in new tools such as vaccines, drugs and diagnostics will impose a heavy economic burden on future generations, who will need to sustain and finance global TB control efforts for the next millennium. A vaccine that prevents adolescents and adults from developing and transmitting TB disease could potentially save public health systems billions of dollars in treatment costs over time.

The greatest austerity measure is prevention. To further evaluate the economic case for investment in TB vaccine R&D, Aeras has commissioned the London School of Hygiene & Tropical Medicine to conduct the first global analysis of the cost-effectiveness of future TB vaccines. This study will assess the current and future health and economic burden of TB over the next 60 years. Results from this landmark study will be published in 2013.

Understanding the societal value of having new TB vaccines in terms of savings in healthcare costs and reductions in lost productivity and deaths will enhance the investment case and lay the groundwork for improved downstream market adoption in countries with high burdens of disease and among at-risk populations.

2.4 TB Vaccine Development Approach

After decades of complacency in TB vaccine R&D, in 1998, the US NIH led an effort revamp efforts resulting in the publication of the first *TB Vaccine Blueprint* (Sizemore, 2012). Based on those early recommendations, in 2002, global experts and donors moved rapidly to advance the first generation of new TB vaccine candidates into human testing. During those initial years, the field prioritized TB vaccine candidates primarily based on their proximity to generating human data, and put an emphasis on building clinical trial capacity at sites with a high incidence of TB and stable populations who could be followed over a prolonged period of time (Small, 2012). Researchers recognized that these first vaccine candidates were not optimized for diversity and that there was a low probability that these frontrunners would make it through to commercialization. However, it was necessary to generate human data to better understand the mechanisms of protective immunity from TB.

Consequently, and in order to achieve the goal of bringing to market new and more effective TB vaccines, it was deemed critical that vaccine development efforts focus on developing a diverse and robust portfolio of next-generation vaccine candidates, informed by what was being learned through those early clinical trials. To meet these challenges, Aeras shifted its strategy away from vaccine discovery to one of applied research, working globally with academic researchers and biopharma to advance their novel discoveries. TBVI further advanced the TB vaccine portfolio by providing coordination, technical assistance and resources for EU researchers, particularly focused on earlier stage development work.

Efforts to address the scientific challenges have resulted in establishing comprehensive, measurable and globally acceptable criteria for selecting, assessing and advancing the best vaccine candidates in the pipeline (Barker et al, 2012). These published 'stage-gating criteria' (Annex 5) provide specific points at which a decision to invest significant funds is required to advance the product to the next stage. Head to head comparisons within an agreed-upon model system can help in decision making and in achieving portfolio diversification objectives, as can robust critical assessment of each product's characteristics.

These 'stage-gating criteria' provide specific points at which a decision to invest significant funds is required to advance the product to the next stage.

Target product profiles (TPPs) for each vaccine candidate in the clinical pipeline have been developed to prioritize within the global vaccine portfolio. Discovery leads and vaccine candidates are prioritized based on whether or not their design and immunological profiles vary enough from existing candidates to be included in the portfolio. Vaccine development strategies aim to minimize cost of goods, and maximize potential public health impact.

"One can't rationally develop an effective vaccine if one doesn't understand the nature of protective immunity and one can't determine the nature of protective immunity without an effective vaccine."

- *Peter Small, TB Vaccine Blueprint, 2012*

Today's TB vaccine portfolio, selected by experts from Aeras and TBVI and hereafter called the 'Global Portfolio,' represents a diversity of approaches and strategies including recombinant BCG, rationally attenuated *M. tuberculosis*, viral-vectored platforms, recombinant purified proteins, and novel adjuvants as well as novel delivery systems such as RNA or DNA combined with electroporation (Annex 1).

Clinical trials are underway for around a dozen candidates, with the first proof-of-concept, Phase IIb efficacy trial of a modern TB vaccine in almost a

century recently completed in South Africa. Vaccine candidates that fail to advance to the next phase of development offer critical insights into the biology of TB and inform on future portfolio decision-making.

Box 1: Tuberculosis Vaccines: A Strategic Blueprint

In March 2012, the Stop TB Partnership's Working Group on New TB Vaccines published *Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade.* The *Blueprint* outlines the major scientific challenges and priorities, critical activities and crucial questions that need to be addressed to develop life-saving TB vaccines in five key priority areas:

1. Creativity in research and discovery. The major question to be answered is why certain individuals infected with *M. tuberculosis* are resistant to TB disease.
2. Correlates of immunity and biomarkers for TB vaccines. Here the focus is on identifying correlates of immunity for TB vaccines.
3. Clinical trials: harmonization and cooperation. The main question to be addressed is whether TB vaccines can effectively reduce the transmission of *M. tuberculosis.*
4. Rational selection of TB vaccine candidates. This priority area tackles the challenge of having all developers of vaccines agree to standardized criteria for the selection and development of novel TB vaccines.
5. The critical need for advocacy, community acceptance and funding. Here the emphasis is on innovative approaches to mobilizing funding for TB vaccines.

The blueprint is designed to initiate a renewed, intensified, and well-integrated international effort to develop TB

2.5 Scientific Challenges and Risks in TB Vaccine Development

In March 2012, *Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade* was published, mapping out the top five key research and development priorities for the next decade (Box 1). Top among these priorities is the discovery of biomarkers and correlates of protection that could help predict vaccine efficacy before large-scale clinical trials (Brennan & Thole, 2012).

After a decade of great progress in the laboratory and the field, TB researchers still have limited understanding of what constitutes protective immunity in different age groups and among heterogeneous populations. Neither animal models nor early stage clinical trials have been able to predict protection, necessitating the evaluation of efficacy in long, protracted and costly late-stage clinical trials (Brennan & Thole, 2012).

Researchers are optimistic that biomarkers and correlates of protection could be better identified within the next several years with intensified efforts and adequate resources. Aeras and TBVI have initiated a Biological and Correlates Working Group (BCWG) to accelerate these efforts. The impact on the Global Portfolio would be substantial. Today, the probability

of success in Phase IIb is estimated to be 33%. However, with new biomarkers and correlates of protection, the probability of success could improve to 50%, saving considerable resources and time. Efforts by the US NIH, US FDA, EC, EU member states, and the Bill & Melinda Gates Foundation are funding programs to address this critical research priority.

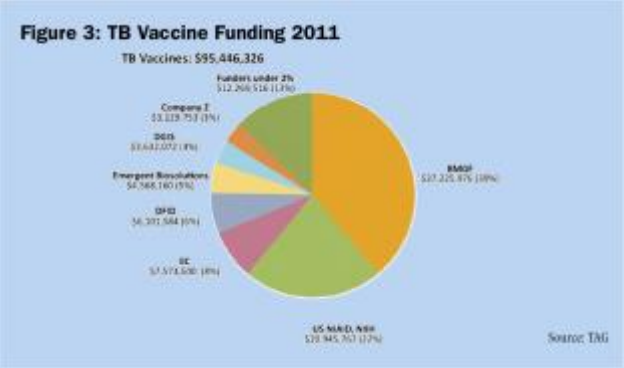
Another critical challenge facing the TB vaccine research field is having reliable TB prevalence and incidence data, in order to select clinical trial sites and choose target populations to support large-scale efficacy trials. The quality of epidemiological data in many of the high disease burden countries is weak, requiring further epidemiological analysis before committing to moving ahead with a new clinical trial site. The cost and time of epidemiological studies can hamper development timelines and represent a significant challenge when multiple late-stage trials are expected to begin within a relatively close timeframe. While a few dedicated clinical trial sites have been set up for future Phase III trials, more will be needed given the pipeline of TB vaccines and the large number of clinical trial participants that will be required (Brennan & Thole, 2012). It is therefore urgent to address the issue of capacity building and site development to support an advanced TB vaccine pipeline, and these efforts will require significant time and financial investment. Aeras and its partners are working on innovative ways to address these knowledge and resource gaps, including collaborating with existing site networks that support research for other disease areas, such as HIV and malaria.

Finally, while the *Blueprint* highlights additional challenges and opportunities, it is worth noting that levels of funding for TB vaccine research remain well below what will be needed to advance at least one new TB vaccine to commercialization within the next decade. Today, there are a small number of donors supporting TB vaccine R&D (TAG, 2012). Coinciding with this funding shortfall is the absence of a robust constituency of advocates and champions within donor and disease endemic countries. Intensified efforts are needed to develop and sustain political will and improve policies and resources. This *Business Case for Investment* is representative of commitments by key partners and donors, such as the EC and EIB, to explore ways of financing the Global Portfolio.

2.6 Current and Historical Funding for TB Vaccine Development

The Treatment Action Group (TAG) reports that more than US $600 million was invested in TB vaccine R&D between 2005 and 2011 (TAG, 2012). In 2011, the top five institutions/agencies provided nearly 80% of funding (Figure 3). These data highlight the relatively small number of governments and foundations committing significant resources to TB vaccine R&D globally. Data from high disease burden emerging markets such as China and India are not included in these figures and, although there is research activity underway, there is limited public data available on the amount they invest in TB vaccine R&D. Finally, although not one of the largest donors, the Wellcome Trust, a British foundation, has played a pivotal role in

supporting the development of the MVA85A vaccine candidate.



It is also important to note that substantial investments by multilateral initiatives such as the European and Developing Countries Clinical Trials Partnership (EDCTP), disease-endemic country governments and biopharma companies are being leveraged as a consequence of donor funding. To date, EDCTP has invested approximately €42 million towards site preparedness and capacity building for TB vaccines in Africa, with additional direct funding for specific clinical trials (EDCTP, 2011). Likewise, industry partners such as Emergent BioSolutions, GlaxoSmithKline (GSK), Sanofi Pasteur, Crucell, Institute Merieux/Transgene, BIOFABRI and others have contributed resources and expertise to advance TB vaccine candidates, providing a significant cost offset for public funders.

The EC and member states are major funders of poverty-related and neglected diseases (PRND), such as TB, contributing almost a quarter of government R&D investments worldwide and 15% of total global investment (~ €341 million/year), with 73% contributed by member states and 27% contributed by the EC (Policy Cures, 2012).

Since 2000, the EC has contributed more than €34 million to TB vaccine development, supporting a broad consortium of European researchers. These EU researchers and their respective institutions play a central role in advancing TB vaccine R&D as evidenced by the fact that more than 75% of the Global Portfolio either originated in Europe or is being developed in partnership with European academic institutions, biotechs and/or pharmaceutical manufacturers (Annex 1). TBVI was created as an initiative of the EC to provide a coordinating function across member states to manage the program of work, administer the financial arrangements and provide the communication channel between the partners and the EC. Today, TBVI supports a consortium of 34 European partners and collaborators.

More than 75% of the Global Portfolio either originated in Europe or is being developed in partnership with European academic institutions, biotechs and / or Pharma.

In addition to new PRND technologies which have the potential to save millions of lives, these investments are also contributing to the next generation of EU researchers and small to medium size enterprises (SMEs). According to a Policy Cures report, €0.66 cents of every euro invested by EU governments is reinvested back into the EU laboratories, universities and companies, creating nearly 13,000 new jobs between 2002-2010 (Policy Cures, 2012). Each euro invested leverages a further €1.05 in investments from companies, philanthropic organizations and governments, often outside Europe (Policy Cures, 2012). Impressively, EDCTP funding has leveraged a further €1.50 for every euro invested in PRND funding

in Africa. The portfolio of EC and member state investments catalyzes cooperative efforts among EU member states and international institutions spanning all continents. In this regard, it represents a model of collaboration that converges around innovation, economic growth and social impact.

Figure 4: Global Funding Landscape for TB Vaccines

Funder (2005-2011)	Basic Science/ Discovery/Preclinical	Early Stage Clinical Development	Late Stage Clinical Development
BMGF ~$276.6M*	✓	✓	✓
US NIAID, NIH ~$130.2M*	✓		
EC ~$56.8M*	✓	✓	
EDCTP ~$6.5M*			✓
DGIS ~$25.4M*	✓	✓	✓
DFID ~$16.4M*	✓	✓	✓
Wellcome ~$12.8M*			✓

In addition, of the five pharmaceutical companies (GlaxoSmithKline, Merck, Novartis, Sanofi Pasteur, and Pfizer [acquired Wyeth]), providing 80% of the worldwide vaccine market, the only two working on TB vaccines are UK/European-based, GlaxoSmithKline and Sanofi, which could offer future economic returns for the EU economy.

The Dutch and British governments are providing the most funding for the advancement of the TB vaccine portfolio within the EU. Since 2006, the Netherlands' Directorate-General for International Cooperation (DGIS) has committed over US $40 million through 2014 in support of clinical development, basic and epidemiological research, and capacity building at trial sites in endemic countries. Since 2009, the UK's Department for International Development (DFID) has contributed over US $16 million in support of TB vaccine R&D. In addition to advancing the vaccine pipeline, Dutch and British governments' support has been instrumental in building clinical research capacity in endemic countries through infrastructure development and local workforce training, so that new generations of TB vaccine candidates can be tested according to the highest international regulatory standards.

The US government is the largest funder of global health R&D in the world, contributing approximately 45% of the total investment in global health R&D each year, and 70% of government investment worldwide (GHTC, 2012). Over the past decade, the US government has invested $12.7 billion in the creation of new vaccines, drugs, diagnostics and other products for otherwise neglected diseases (GHTC, 2012). This funding, combined with other governments, foundations and biopharma has contributed toward the development of 24 (53%) of the 45 neglected disease products registered between 2000-2010. The majority of US government funding, nearly 60%, goes to HIV/AIDS.

The US NIH is the second largest funder of TB vaccine R&D next to the Gates Foundation, but their remit is to advance basic science, primarily through US academic institutions, to answer critical questions around biomarkers, systems immunology, correlates of protection, epidemiology, animal studies and much more. As noted earlier, these studies are paramount to understanding how to better design, select and test future vaccine candidates, but they support a relatively small amount of the translational activities that are required to advance TB vaccine candidates through the 'valley of death' and into the clinic. The Bill & Melinda Gates Foundation, EC, Dutch and British governments, as well as the biopharma companies themselves have been the largest financiers of the translational work (Figure 5).

Other US funding initiatives and programs, including USAID, the President's Emergency Plan for AIDS Relief (PEPFAR), the NIH's National Center for Advancing Translational Sciences (NCATS) and Vaccine Research Center (VRC), and Obama's Global Health Initiative have not yet provided direct funding for the advancement of the TB vaccine portfolio.

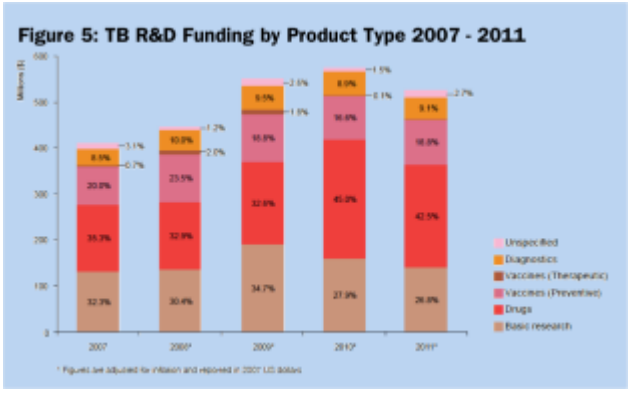
No institution or government, however, has done more to facilitate the development of the TB vaccine portfolio than the Bill & Melinda Gates Foundation. Since making their first grant in 1999, the Foundation has generously invested approximately US $350 million. The majority of these funds have been channeled through Aeras, a product development partnership (PDP) established in 1997 (previously Sequella Global TB Foundation), which received the first Gates Foundation grant in 1999.

Future Investments in TB Vaccine R&D

PDPs have proven cost-effective, contributing to 12 of the products developed in the past decade at a cost of US $4 billion, while saving an estimated $8 billion in development costs if those same technologies had gone through traditional discovery and development processes. However, there are a relatively small number of donors supporting PDPs today, including, principally, the Bill & Melinda Gates Foundation. The shortage of funding sources for PDPs is creating intense competition among diseases and product areas, which is only escalated by the fact that PDP funding has been on a steady decline since 2008 (Policy Cures, 2012). In 2011, funding was US $451 million, down from US $580 million in 2008. Overall, PDPs have seen cuts in the order of US $30-50 million per year over the past three years (Policy Cures, 2012).

PDPs have seen cuts in the order of US $30-50 million per year over the past three years.

As a result of these cuts, many PDPs are experiencing funding challenges, with limited short and long-term opportunities on the horizon. Without exploring new ways of financing both PDPs and the technologies they develop, advocacy efforts have focused on either increasing the amount of funding available through the handful of existing donors, or on encouraging additional high- and middle-income countries to create new PDP funding streams. The appetite for either of these options during such uncertain economic times is proving limited. In addition, fundraising efforts among high-net worth individuals and foundations, outside of the Bill & Melinda Gates Foundation, have had limited success.



Today, the only two G8 governments that are exploring new or increased funding for PDPs are the Germans and Australians. In 2011, the German Federal Ministry of Education and Science (BMBF) opened a financing window for PDPs engaged in PRNDs, committing €20 million through 2014. However, TB and HIV/AIDS R&D were excluded from this first call. BMBF argued that other funders were attending to TB and HIV/AIDS R&D. Incidentally, BMBF does provide

German universities and research institutions working on HIV/AIDS, malaria and TB with about €11 million annually. They also participate in EDCTP, providing nearly €68 million from 2003-2011. The next BMBF PDP funding call is expected in late 2013 or early 2014. Advocacy efforts are underway to increase overall funding and to ensure the inclusion of TB R&D in this second call. Aeras and TBVI are actively working with German civil society groups, key decision makers, and local researchers to improve political will and resources for TB vaccine R&D.

The Australian government is in the final stages of determining what level of support will be included for PDPs through a new AusAID program. They have prioritized PDPs working on malaria and TB for the initial rounds of funding. However, the relative funding amounts for PDPs are small (around $5 million per year) and are shared between malaria and TB PDPs, although the split remains unknown.

Global Perspective

In aggregate, funding for neglected disease R&D was US $3,045 million in 2011, covering 34 diseases and 134 product areas (Policy Cures, 2012). While the public sector represents the majority of global funding, there has been a steadily declining trend among both public and philanthropic funders since the financial crisis. Conversely, multinational pharmaceutical companies (MNCs) have been increasing their investment over the past five years. This may reflect the role public funding has played in catalyzing and de-risking global health technologies during early stages of development. It may also reflect industry trends in moving beyond the high-income markets to explore other disease areas, such as TB, where significant disease burden exists within the emerging markets.

Investment in TB R&D more specifically has seen an 8.3% drop from 2010 (TAG, 2012). The majority of funding is allocated to drugs (42.5%), followed by basic research (26.8%), preventative vaccines (18.8%), diagnostics (9.1%) and therapeutic vaccines (0.01%) (TAG, 2012).

Discussions are now underway around financing and coordination for R&D by the World Health Assembly (WHA). A WHO Consultative Expert Working Group on R&D (CEWG) recently released a recommendation that a global health 'Observatory' be established at the WHO. The Observatory would collect and analyze financial flows for R&D, monitor the current composition of R&D and identify gaps and duplication to foster greater priority setting and promote efficiencies. While the CEWG set out to address R&D to meet health needs in developing countries by strengthening global financing and coordination, the recommendation of creating an Observatory at WHO does not at present seem to address the need for improved resources and mechanisms for mobilizing pooled funds.

U.S. Perspective

It is unlikely that major changes to global health R&D funding from the US will change over the next four years, as austerity measures are being put in place to reduce the US national debt. Most global heath R&D funding will continue to go through the NIH towards basic research and discovery. Across all neglected disease areas, TB receives a meager 12% of all NIH global health R&D funding (GHTC, 2012). However, there is an opportunity to raise the priority of TB

vaccine R&D within the US government, with a new group of global health leaders coming on board in both the US Congress and the Administration, and with PEPFAR's reauthorization occurring in 2013. Moving forward, finding ways to link TB and HIV vaccine R&D efforts while increasing resources for TB vaccines could have a tremendous impact on both diseases since TB remains the number one killer of people living with HIV – causing 1 in 4 deaths.

EU Perspective

At the European Union level, the new policy framework Horizon 2020 – the EU's programme for research and innovation for the years 2014-2020 - is under negotiation among the EU Member States and European Parliament. Horizon 2020 outlines the high-level priorities for funding of research and innovation activities within the EU. The decision on Horizon 2020 is expected during the third quarter of 2013, allowing an official start of the programme by 1st January 2014.

The European and Developing Countries Clinical Trial Partnership (EDCTP), a joint initiative between EC and 16 European Countries, and the next phase of the Innovative Medicines Initiative (IMI), a public-private partnership between the European Commission and European Federation of Pharmaceutical Industries and Associations (EFPIA), have been identified among the priorities for funding by Horizon 2020. The EDCTP2 programme will focus on supporting research and development of new or improved diagnostics, drugs, microbicides and vaccines against HIV/AIDS, TB, malaria and neglected infectious diseases. EDCTP2 will have the potential to provide support to all phases of clinical trials (phases I-IV) in collaboration with sub-Saharan Africa, including multi-center, multinational trials, in conjunction with other funders. The other main activity of EDCTP2 will be to provide support to clinical capacity building in sub-Saharan Africa.

Current assessments by Aeras and TBVI suggest that there is a funding gap across the full research cycle for product development. The consequence of these funding shifts could be significant. After investing more than €34 million in TB vaccine development over the past 12 years, which resulted in a global portfolio comprised of more than 75% of vaccine candidates coming from the EU region, the act of dissolving the disease specific funding and subsequent central coordinating function and pooled technical expertise could have serious consequences on the prospects of having a new TB vaccine within the next 15 years. At present, funding for both NEWTBVAC, an integrated project for new TB vaccines established by previous EU frameworks, and its coordinating entity - TBVI - will cease January 2014.

BRICS perspective

The BRICS represent a major opportunity to mobilize resources for both TB vaccine R&D and the utilized infrastructure required to execute large, late-stage clinical trials. Unique perhaps compared to any other poverty-related disease, the BRICS, except for Brazil, account for 60% of the global disease burden for MDR-TB alone. Upper middle-income countries in Eastern Europe can also play a pivotal role, given that they are listed among the 22-high disease burden countries.

New financing mechanisms are required to attract pools of private capital that could not only help bridge the funding gap for global health R&D, but could help biopharma achieve their goal of expanding beyond traditional high-income markets and into the emerging markets.

In January 2013, at the Second BRICS Health Ministers' Meeting held in Delhi, Ministers placed a focus on TB, including MDR TB and TB/HIV, as major health threats in need of urgent attention. The Ministers resolved to "…collaborate and cooperate for development of capacity and infrastructure to reduce the prevalence and incidence of tuberculosis through innovation for new drugs/vaccines, diagnostics and promotion of consortia of tuberculosis researchers to collaborate on clinical trials of drugs and vaccines, strengthening access to affordable medicines and delivery of quality care." Efforts to catalyze funding and pool technical expertise to facilitate the objectives set forth in the communiqué are urgently needed to leverage the political will and commitment of these governments. This could be the greatest single opportunity for the TB vaccine field for R&D, vaccine utilization and public health impact. According to McKinsey, by 2025 annual consumption in emerging markets will reach $30 trillion – the biggest growth opportunity in the history of capitalism (McKinsey, 2012).

South Africa is already playing a major role in designing and executing TB vaccine clinical trials in adults and infants. World renowned for their work in managing these clinical trials, attaining the highest international quality standards, South Africa is a model for what can be achieved by other BRIC countries. Deepening collaboration with South Africa's Department of Science and Technology and Ministry of Health with BRIC ministries and international organizations could result in greater global capacity, expertise and resources to support these collaborative efforts.

China, perhaps unique to any other country in the world, has the opportunity to both accelerate efforts to reduce disease burden through improved public health measures, and to play a leading role in driving innovation through TB vaccine R&D efforts. China is now the world's largest vaccine manufacturing country, producing more than one billion doses a year (Wang, 2005). The vast majority of China's vaccine manufacturing serves their domestic market. However, China's ability to develop, test and manufacture novel vaccines that meet international standards may, over the coming years, provide an unprecedented opportunity to accelerate the development and testing of new TB vaccines.

A new funding partnership between the Bill & Melinda Gates Foundation and the Chinese Ministry of Science and Technology (MoST) was established, to combine resources and accelerate the development and delivery of China health and development solutions. This new funding partnership will issue up to US $300 million in grants in the first five years of the partnership, with non-grant funding possible through the Cooperation Fund Mechanism. The Chinese MoST budget was US $3.9 billion in 2011, much of it used as matching funds to guide the investments of other government bodies. TB is listed as an investment priority by MoST. Today, their efforts have been

largely directed toward drug development and basic research.

The BRICS represent a major opportunity to mobilize resources for both TB vaccine R&D and have the infrastructure required to execute large, late stage clinical trials.

To further advance TB vaccine R&D efforts in China, Aeras has established an office in Beijing and initiated a partnership with China's largest biotechnology corporation, the China National Biotec Group (CNBG), to develop, manufacture and distribute next-generation TB vaccines for the Chinese population and potentially globally. Aeras also has partnerships with CanSino Biotechnology Inc. on a novel vaccine candidate, and Fudan and Wuhan Universities to strengthen epidemiology data and preclinical animal studies.

Additional trends

Finally, we are in the midst of a new trend among foundations, such as the Bill & Melinda Gates Foundation, which have established program-related investments (PRIs) to support charitable activities that involve the potential return of capital. PRIs include financing methods commonly associated with banks or other private investors, such as loans, loan guarantees, linked deposits, and even equity investments in charitable organizations or in commercial ventures for charitable purposes. PRI funding could be an option downstream if a new funding mechanism is established to advance the Global Portfolio.

Regardless of where and how the community mobilizes public funds for global health technologies, new financing mechanisms are required that could attract pools of private capital to not only help bridge the funding gap for global health R&D, but also with the prospect of assisting industry-wide efforts to expand into new markets and disease areas. It is envisioned that not all global health technologies would meet the criteria for such mechanisms, but if there were quasi-commercial opportunities whereby the public funders could reduce risk and or/create incentives that would allow investors to generate moderate returns, the public sector would be wise to use their scarce resources to create such mechanisms in order to leverage greater private investment.

2.7 Financial Engineering for the Social Good

Amid global fiscal austerity measures fueled by the problems of high unemployment, sovereign debt crisis in Europe, and the existing fragility in the international financial system, new challenges around how to best finance economic development are being explored. These same uncertainties are also leading to greater risk aversion among the private sector and investors, further perpetuating the slow growth trend that is expected to persist into the foreseeable future (UN, 2012). And yet, innovation often accompanies

scarcity, catalyzing shifts in industry business models and capital flows, often culminating in a new generation of financial products and strategies to address the world's most challenging problems.

Today, Endure the Paradox claims that growth in purchasing-power parity among the emerging markets over the next decade represents the biggest opportunity in the history of capitalism (McKinsey, 2012). Meanwhile, during this moment of opportunity, diseases like TB will be wreaking havoc on many of these emerging market economies. According to *The Conference Board Global Economic Outlook 2013*, emerging markets like India and China show slowing growth trends projected to range from 4.8% to 3.6% and 6.5% to 4.3%, respectively, through 2025. Of the 25 emerging markets listed in the report, growth is projected to slow to 3.6% on average during that same period of time.

Public private partnerships supported by innovative financial products that blend traditional grant making with loans and/or equity mechanism could have a catalytic effect on the development of these new tools.

Given that TB disease trends show a modest reduction in new cases of TB through over the next decade in high disease burden emerging economies, with the confounding issue of high rates of the deadlier and more costly M-XDR TB, one should consider how the TB epidemic will impact prospects for growth over the coming decades in these emerging markets. Layer on the costs of TB control, estimated to be US $8 billion a year in 2014 and 2015 for low- and middle-income countries, and one can easily deduce that new mechanisms are urgently needed to finance R&D and the delivery of next generation TB control and prevention tools. Public private partnerships supported by innovative financial products that blend traditional grant making with loans and/or equity mechanisms could have a catalytic effect on the development of these new tools.

In order to understand how to best design and blend various types of finance, one must first assess the risk-return profile of those potential investments, as well as the time horizons and current and potential costs, and match them with an appropriate investor class. Blending capital to create incentives along the R&D development phases can facilitate the use of grant funding to 'de-risk' candidates as they move from early to late stage testing. This in turn could enable other types of financial vehicles that include loans and/or equity arrangements to be utilized as the cumulative success rate goes up in the later stages of development (Figure 6).

Figure 6: Blended Capital for the Global TB Vaccine Portfolio

With the current low-interest-rate and stagnant economic climate, multinationals, governments and foundations are structuring mechanisms that can give either concessionary returns, as part of a philanthropic portfolio, or market rates of return for more traditional investors. According to the Milken Institute, "With 10-year Treasury yields around 1.6%,

a 4% return no longer seems massively concessionary" (Milken, 2012).

To further explore the use of alternative sources of capital to advance the TB vaccine portfolio, a sophisticated model was developed to assess the market potential of commercialized TB vaccines and their corresponding public health impact. This model, and the implications of these findings, serves to inform financiers and vaccine developers on innovative ways to both increase and also blend public and private funding sources to support the advancement of the Global Portfolio.

3. Defining the Market for TB Vaccines

3.1 Overview and Strategy for Vaccines

The processes to globally adopt and introduce new TB vaccines are complex and lengthy, at times requiring a decade or more to generate the evidence-base necessary for sound policy development and building a business case for investments. While product development timelines most often dictate the pace of new vaccine introductions, early market access strategies have the potential to influence and accelerate global vaccine introduction with a high degree of confidence among stakeholders and ensuring market security.

Since new TB vaccines are early to midway in the product development cycle, Aeras developed a range of strategic market assessments to evaluate potential market value and health impact of new TB vaccines. A base case and a more conservative scenario were modeled by varying the years of vaccine introduction, based on probabilities that candidates will successfully progress from one stage to the next in the Global Portfolio, as it exists today. Country introduction dates, vaccine efficacy and coverage rates for new TB vaccines are key drivers for health impact and revenue potential.

Strategic market assessments for TB products are developed with a time horizon of 10 to 20 years and created early in the product's development life cycle. The assessment is 'top down' and needed to inform not only product development strategy, but also critical investment decisions by industry, donors, and eventually countries, to minimize delays often associated with the introduction of new vaccines relating to vaccine capacity and supply, budget

allocation, financing, and health infrastructure. Overall, strategic market assessments can help both the private and public sectors develop vaccines more efficiently and provide evidence-based data to major stakeholders.

3.2 The TB Vaccine Market and Financial Model

With the assistance of Applied Strategies (AS) and KPMG, we have designed a dynamic and flexible financial model to assess the market and public health impact of two types of TB vaccine profiles: (1) an infant vaccine that would replace the current BCG vaccine, and (2) an adolescent and adult pre and post-exposure vaccine that would provide some protection against acquiring and developing disease. These outputs inform TB vaccine R&D efforts and financiers on:

- Vaccine design and delivery approaches and their respective public health impact on a global, regional or national level.
- The range in time and costs to advance the Global Portfolio to reach successful commercialization of one or two vaccines.
- The global market potential and estimated revenue generated over the commercialization timeframe for each of the infant vaccine and the adolescent and adult vaccine.
- Investment strategies to advance the Global Portfolio with targeted push and pull mechanisms to ensure an adequate sharing of risks and rewards among the public and private sectors.
- The cost efficiencies of implementing a rational portfolio management approach.

The following sections contain details around the design, inputs and outputs of the model. References related to benchmarking and baseline assumptions can be found in Annex 3.

Public Health Inputs and Outputs

The model is pre-populated with data from 183 countries for each year from 2020 to 2050 with TB and HIV epidemiology, including contact and treatment rates, M-XDR TB, demographic data by age cohort, high-risk groups in HICs, BCG vaccine coverage rates, and birth and population data. The user enters assumptions into the model such as vaccination strategies, vaccine duration of protection, vaccine efficacy, vaccine prices, vaccine introduction dates by country, new TB vaccine coverage rates, vaccine regimen, and the split between private and public sector payers.

Based on the input data, the model generates outputs such as the potential vaccine market in terms of vaccine demand, the number of subjects expected to be vaccinated, vaccine cost to donors and countries based on forecasted demand, vaccine impact in terms of incident and prevalent cases and deaths prevented/1000 vaccinated people.

3.3 Projected Vaccine Pricing

Vaccine pricing is of particular importance to all stakeholders in strategic market assessments. Pricing is a key driver for future revenue and gauges the interest of suppliers, donors, countries, and potential investors in the TB vaccine market. The estimated prices for new TB vaccine input into the model were derived from two sources: a review of historical prices for new vaccines launched in HICs, MICs, and LICs, used as an indicator of 'what the market will bear' (Figure 7); and second, crude estimates of new TB vaccine 'cost of goods' (COGs) based upon the technology and manufacturing processes used in the production of TB vaccines.

Figure 7: Current Pricing of Pediatric and Adult Vaccines

VACCINE	HIGH-INCOME PRIVATE MARKET PRICE/DOSE	HIGH-INCOME PUBLIC MARKET PRICE/DOSE	MIDDLE-INCOME PRIVATE MARKET PRICE/DOSE	MIDDLE-INCOME PUBLIC MARKET PRICE/DOSE	GAVI PRICE/DOSE
Pentavalent	$80.00	$55.00	-	$3.35	$2.94
BCG Infant	$45.00	-	-	$0.21/$0.11	$0.10
13 valent pneumococcal	$120.00	$102.00	$20.00	$16.34	$7.00
Hep A Adult	$63.00	$21.00	$15.00/$18.00	$11.00	-
Rotavirus (2 dose regimen)	$106.00	$91.00	-	$7.50	$2.50
Rotavirus (3 dose regimen)	$69.59	$59.18	-	$5.15	-
HPV (2 dose regimen)	$130.00	$92.00	-	$14.25	-
Influenza Adult	$14.00/$11.00	$5.30/$2.50	$14.00/$11.00	$5.30/$2.50	-

Source: UNICEF/PAHO/CDC pricing as of July 2012

While COGs is difficult to estimate in the absence of specific vaccine technology, for purposes of this evaluation, *E. coli* was the underlying technology used to determine vaccine-pricing ranges. The cost/dose included fixed, variable and semi-variable costs at 100% plant utilization, amortized over 10 years. Costing using cell culture, a competing technology, would incur almost twice the *E. coli* COGs and force increases in vaccine pricing to ensure recovery of the cost of R&D. Vaccine pricing estimates were then tiered according to geographic segmentation (Figure 8).

Figure 8: New TB vaccines – Estimated Pricing per Market Segment

Market Segment*	Infant Public Market Price	Infant Private Market Price
LIC	$1.00	$1.00
LMIC	$2.50	$5.00
UMIC	$5.00	$15.00
HIC	N/A	N/A

* India & China prices are assumed at LIC tier

Market Segment*	Adolescent & Adults Public Market Price	Adolescents & Adults Private Market Price
LIC	$1.50	$5.00
LMIC	$5.00	$8.00
UMIC	$10.00	$30.00
HIC	$40.00	$80.00

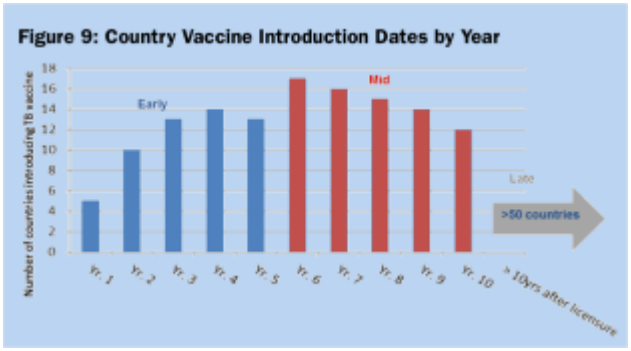
* India & China prices are assumed at LIC tier

The practice of 'tiered pricing', based on the buyer's ability to pay, has been in use by suppliers and organizations such as UNICEF in the global market since the inception of the Expanded Programme on Immunization (EPI) in 1974. The practice allows donors and/or countries to purchase vaccines in middle and low-income countries (MICs, LICs) at significantly lower prices than in high-income countries (HICs). UNICEF, the predominant purchaser, issues tenders separately, wherein the manufacturer can quote different prices for different markets.

3.4 Country Vaccine Introduction

Women, children, working adults and the elderly all stand to benefit from new preventative TB vaccines. Despite the potential benefits of new TB vaccines, not all countries are expected to uptake the vaccine immediately due to competing priorities such as civil unrest or economic instability, or there may be a preference to focus health budgets on other vaccines (e.g., HPV, dengue, malaria). Therefore correlation methods, such as Looks-Like Analysis, using historical vaccine uptake of similar products, disease burden, and political will were used to estimate rates for accelerated country introduction.

In our Conservative Case, the number of countries expected to uptake a new TB vaccine within the first five years of introduction is 55, considered the 'early introduction countries.' In years 6 through 10, it is estimated that an additional 75 countries would introduce new TB vaccines ('mid-introduction countries'). Thus of the 183 countries included in the analysis, 130 are projected to introduce new vaccines within 10 years. The remaining 53 countries, considered 'late introduction countries,' are expected to introduce new TB vaccines 10 years or more after the first licensed vaccine on the market or not at all (Figure 9). The full list of countries and their projected introduction dates are found in Annex 4.



Of the 55 early introduction countries, 28 are in HICs, 18 in UMICs and LMICs and 7 in LICs. These early adopters drive the vast majority of revenues within the global market. India and China are considered separate market segments within the global analysis. Large populations, high disease burden and requirements for in-country vaccine development and manufacturing drive introduction strategies. China, as a UMIC, is a key 'early introduction country' demonstrating a keen interest in working with partners in vaccine development and high political will. Even with estimating new vaccine public sector prices at the lower LIC level, China leads the market in potential revenue and health impact across all market segments. India is considered a 'mid-introduction country,' to account for slower vaccine development, building political will and improving infrastructure to deliver new TB vaccines. Vaccine pricing for India is also calculated at the LIC tier.

3.5 Strategic Demand Forecast

Developing a global strategic demand forecast is a complex challenge, and ensuring predictable demand over time is a risk that all vaccine markets face. Generally, there are two main types of demand forecasts: strategic demand forecasts done early in product development and supply chain conducted 1-3 years before product launch. Early stage products in development employ strategic demand forecasting to assess the risk to manufacturers during development and positively impact capacity decisions thereby reducing the negative impacts of demand uncertainty on price. However, past experience has shown that strategic demand forecasts must be backed by financing to draw new suppliers into the global market.

Combinations of methods were used to prepare the TB strategic demand forecast including:

- Research, data collection, and analysis for the evaluation of the present and future conditions in domestic and international environments for each of the following:
    - TB global environment assessment – macroeconomics and microeconomic
    - Industry – vaccine pipeline, technologies, process development, COGs, and capacity
    - Donor R&D financing strategies

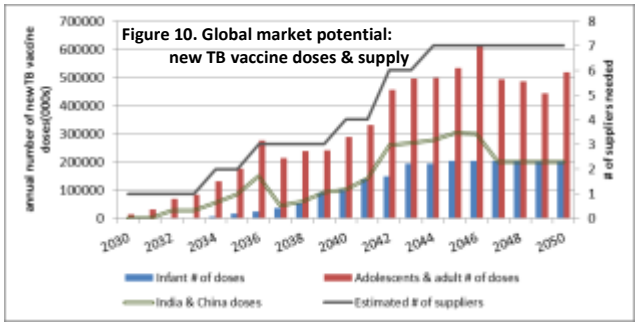
Aeras modeled several strategic market scenarios to inform the TB vaccine environment. Applying a 20% coverage rate for adolescent and adult TB vaccines and using current BCG coverage of 90% or greater as a proxy for new infant vaccines, Aeras ran Base Case and Conservative Case scenarios to assess the global health impact of new TB vaccines. In both scenarios, variables such as 60% vaccine efficacy, 10-year vaccine duration of protection, 2-dose regimen, and 10-year mass vaccination campaigns for adolescents and adults remained constant, while the dates of vaccine introduction varied by 3-6 years (vaccine introduction delayed by 6 years in the Conservative Case, 2030, compared to the Base Case, 2024). In both the base and conservative scenarios, the launch of infant vaccines occurs 3 years after the adolescent and adult vaccine, assuming suppliers' strategy to quickly recoup R&D investments through the adolescent and adult markets first before infants. The introduction year is the first year that a TB vaccine is licensed and prequalified by the WHO.

3.6 Results of Modeling Demand and Revenue

The main finding from the strategic demand forecast is that vaccine introduction with an affordable, sustainable vaccine supply is possible. If country adoption accelerates, the health impact improves, averting more TB cases and saving more lives. However, managing capacity and scale up in the event that demand is high can create challenges for manufacturers.

To meet global demand estimates, it is anticipated that 7 vaccine manufacturers are needed producing at 100% capacity.

The potential demand, assuming 20% vaccine coverage rates, for new TB vaccines shown in Figure 10 illustrates that for the Conservative Case demand builds to ~300 million doses 10 years after the first country introduction. Between 2041 and 2050, the demand grows rapidly, exceeding ~400 million doses per year beginning in 2042 and reaching ~600 million doses by 2050. To meet global demand estimates, it is anticipated that 7 vaccine manufacturers are needed producing at 100% capacity. India and China alone will need 300 million doses per year after 2037 and most likely will require 3-4 vaccine in-country manufacturers.



The demand forecast for vaccine introduction represents a realistic, yet ambitious, picture of investment in new TB vaccines for global populations. Figure 11 shows that by accelerating country introduction only, incident cases averted can improve ~20-30% from the Conservative Case to the Base Case.

Figure 11. Portfolio Development Scenarios: Expected Incremental Health Impact of Investment in New TB Vaccines

Scenario	Incident Cases Averted through 2050	Country Intro Date Infant	Country Intro Date Adolescent & Adult
Base Case	~50-60 M	2027	2024
Conservative Case	~30-40 M	2033	2030

Improving vaccine coverage rates through mass vaccination campaigns would also have a tremendous impact on incident cases averted (Figure 12).

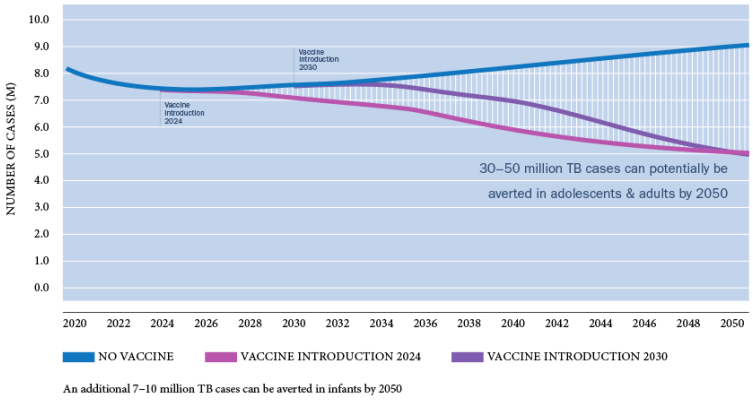
Figure 12: Coverage Rate Sensitivity Analysis and Health Impact

	Coverage Rate	Adolescent and Adult Incident Cases Averted	
Base Case	20%	40-50 M	Base Case
Optimistic - 1	35%	60-65 M	Optimistic - 1
Optimistic – 2	50%	75-80 M	Optimistic – 2

By 2050, and depending on their year of introduction, new TB vaccines will potentially (Figure13):

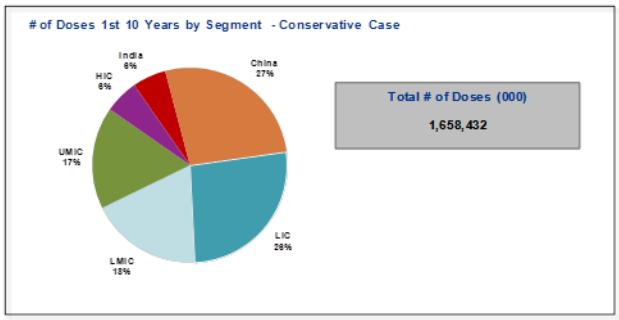
- Avert 30-50 incident adolescent and adult TB cases;
- Avert 7-10 million incident infant TB cases;
- Improve the lives of HIV-infected populations by preventing serious TB disease and complications;
- Prevent additional cases of serious disease and deaths among unvaccinated populations by reducing rates of transmission.

Figure 13. Range of TB Adolescent & Adult Incident Cases Averted



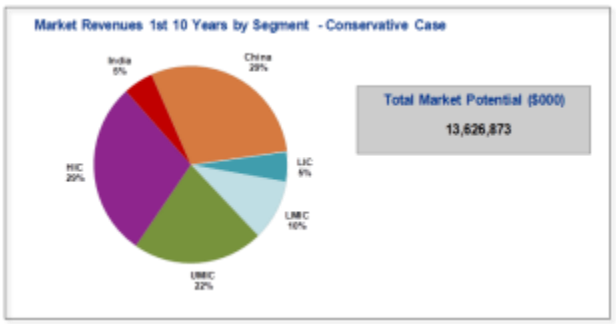
During the first 10 years of commercialization, approximately 50% of the revenue being generated will be in the HIC and UMIC segments, although these segments will consume less than 25% of the total projected doses during the same time period (Figure 14). During this time, the potential revenue of the adolescent and adult market is estimated at US $12-13 billion and the infant market $700 million to $1 billion. These initial assessments indicate that the adolescent and adult market is substantially more sizeable than the infant market.

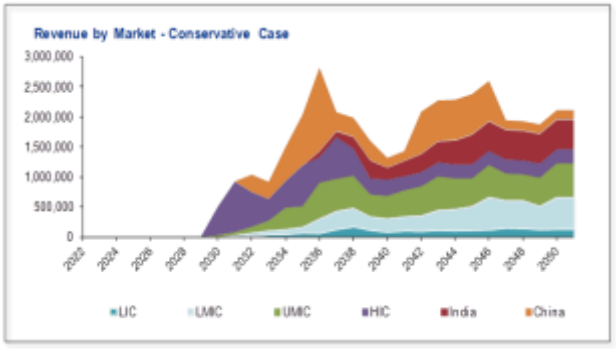
Figure 24: 10-year Global TB Vaccine Market Potential and Number of Doses by Segment



The initial stages of commercialization will be focused on the HIC and UMIC country segments, in which a vaccination campaign focused on health care workers, travelers, military and other high risk populations allows for scaling up capacity and building infrastructure for larger scale immunization campaigns. In addition, the HIC and UMIC country segments have the ability and high political will to introduce early compared to LICs, generating high revenue streams that can offset development costs for manufacturers (Figures 15).

Figures 15: Revenue by Vaccine Category with Market Introduction 2029, adolescent/adult and infant





These revenues assume a market segmentation of 90% public and 10% private across all markets. Our analysis reflects conservative pricing and segmentation assumptions. However, it is important to note that the UMIC and China markets not only have the most to gain by way of public health impact from a new TB vaccine (Figure 16), but they also encompass the economic purchasing power to pay higher prices, at least within a tiered pricing strategy.

Figure 16: Potential Health Impact of New TB Vaccines by Market Segment (2030-2050)

Market Segment	# of Countries	Health Impact Incidence Cases Averted* (millions)	
		Infants 2033-2050	Adolescents & adults 2030-2050
HIC (sub-populations only)	55	-	0.8
UMIC	49	0.9	6.1
LMIC	43	0.7	3.3
LIC	34	1.1	4.8
India	1	0.6	3.0
China	1	1.0	9.5

This is an important finding to note since political will to collaborate on TB R&D and control efforts by all the BRICS is high as noted in the recent 'Delhi Communiqué.' In addition, since a large portion of the population living in UMIC and LMIC are latently infected with TB, including all socio-economic groups, it is possible that there could be substantial demand in the private market for new TB vaccines. If the market were segmented 70% public and 30% private, our model demonstrates that this would result in substantial revenue gains.

3.7 Market Validation

Market validation is a critical step in testing a product concept against a potential target market and should always be done before introduction. For new vaccines it is important to start the evaluation process early to understand how the target market (public and private healthcare providers and their customers) might view and/or evaluate the product benefits, and associated costs, in order to develop an evidence base that facilitates adoption and uptake.

The first study to test the market for new TB vaccines, commissioned by Aeras, was conducting in 2010 by Baird's Communications Management Consultants Ltd, UK. The study sought to assess the market for three different vaccination scenarios. The first was a BCG replacement vaccine that offered no advantage in efficacy but would provide improved safety in HIV positive children. The second was based on a 'prime boost' strategy that included BCG soon after birth, a boost in the first year of life (with a different vaccine) and a second boost in early adolescence. The third assumed that the boosts would be delivered by an aerosol device rather than conventional injection.

The study used the qualitative research method of in-depth interviews. A total of 86 interviews were conducted across 8 countries (Brazil, Russia, India, China, South Africa, Romania, Cambodia and Mozambique). The category of respondents interviewed were senior Ministry of Health (MoH) officials, MoH technical experts (involved in delivering childhood vaccines), senior Ministry of Finance officials, senior public health clinicians/pediatricians who act as advisors to the government, non-governmental agencies involved in public health programs, parliamentarians and senior journalists.

The study showed that the potential market for all three scenarios was quite strong. Toward the end of the interview process, and after having been introduced to the potential impact of new TB vaccines, the respondents were asked if they would re-allocate money from existing health spending to buy the prime-boost regimen. In a remarkable finding, the majority of respondents responded positively. While respondents expressed concern around the obstacles associated with the adolescent boost, most thought that they could be overcome.

Respondents were presented with a proposed $4 vaccine price. In the richer countries, the price was barely worthy of discussion. However, in the majority

of countries at least one respondent thought it was too high and could not be met with in-country health budgets. In the poorer countries, respondents struggled with the price, but most thought that in one way or another countries would find the resources to fund the immunization strategy – ideally with external help but, in extremis and over a longer period, without it.

At least a third of the respondents thought each of the vaccines described would be introduced in their countries within 3 years of first licensure. A third however, were uncertain about introduction noting that the actual efficacy of the vaccine and potential impact within their country would be required to be demonstrated before rapid adoption could occur. For all the skepticism and demands for more data, the study showed that demand for new TB vaccines would be high within 2-3 years of gaining approval in the EU or the US.

There is now a need to retest the market given the latest public health, financial and economic cost-benefit data on the two prioritized TPPS – the adolescent and adult and improved infant vaccines. Understanding the willingness and ability of high- and upper middle-income governments and private health care providers to purchase new TB vaccines will help inform on commercial viability and the feasibility of implementing various R&D investment strategies.

Plans to initiate discussions among a number of European Member States and high-disease burden upper middle-income countries will commence following conversations with industry and major donors.

4. TB Vaccine Portfolio Analysis

4.1 Overview of the Development Process

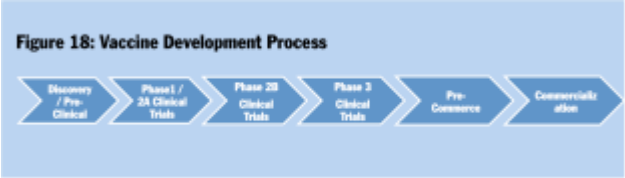
Using the model, inputs to assess the costs to develop the current Global Portfolio to the point of successful global introduction were evaluated (Figure 17). The analysis incorporates the current Global Portfolio of vaccine candidates, phase of development for each candidate and timing, and applies statistical probabilities of moving from one stage of development to the next (and related portfolio attrition). Assumptions were determined in consultation with industry experts and benchmarked against historical figures from Aeras and TBVI. The model is set up to easily change assumptions of these inputs, and can also set a limit to expenditures by phase of development, once an assumed number of candidates pass through various stage gates (e.g. preclinical portfolio diminishes as more candidates reach Phase 3 testing).

Figure 17: Costs to Develop the Current Global Portfolio

Number of Vaccines in Current Portfolio	Probability of moving from one stage of development to the next
• 25+ discovery leads & preclinical candidates • 12 with clinical trials underway • 1.5 new candidates entering the clinical global portfolio each year	• Discovery / Pre-Clinical -20% Success Rate • Phase 1 / 2A – 33% Success Rate • Phase 2B – 33% Success Rate • Phase 3 – 85% Success Rate
Length of each stage (years)	**Development costs per vaccine (phases include multiple trials)**
• Discovery/Pre-Clinical 2 to 4yrs • Phase 1 / 2A - 2 to 3 years • Phase 2B - 3 to 4 years • Phase 3 - 4 to 5 year	• Discovery / Pre-Clinical (portfolio): $15-25 M per year x 8 years • Phase 1 / 2A: $6 - $12 M per vaccine • Phase 2B – $20 - $40 million per vaccine • Phase 3 – $115 - $170 million per vaccine

4.2 Development Process

Reaching successful commercialization requires the completion of one phase of development before proceeding to the next. To determine costs and probabilities of success, the development process was divided into 6 stages defined below (Figure 18).



Discovery / Pre-Clinical Stage 1: Discovery and preclinical stage 1 includes basic research and discovery, assay development, animal testing and early process development. Approximately, US $15 to 25 million a year is required to ensure a robust portfolio of early stage technologies are available to advance 1-2 new vaccine candidates a year into the clinic. Given the status of the Global Portfolio, we expect that this steady-state level of investment will be required for a least the next 8 years, until the clinical portfolio has sufficiently matured and advanced candidates are showing early signs of desired efficacy.

Pre-Clinical Stage 2: Preclinical stage 2 studies include further assay development, GMP pilot scale manufacturing, GLP toxicology testing and regulatory filing to conduct the first safety trial in humans. Each candidate that advances from the discovery/preclinical phase 1 to preclinical phase 2 will require an incremental US $1-2 million to advance to clinical testing.

Phase 1 / 2a Clinical Trials: Phase 1 includes the first testing in humans and starts with a small group of adult subjects to assess safety and immunogenicity. Phase 1 may also include step down studies to reach the target vaccine age (e.g., infants). In Phase 2a, individuals may belong to groups at risk of acquiring the disease. Phase 1/2a can take 3-6 years and cost between US $6-12 million.

Phase 2b Clinical Trials: Phase 2B trials involve a much larger numbers of healthy volunteers (several thousand) to assess safety, immunogenicity and preliminary data on vaccine efficacy. These studies are randomized and double blinded. This stage can take 3-4 years and cost between US $20-40 million. Due to their size, they often include multiple sites in different disease endemic countries.

Phase 3 Clinical Trials: Successful Phase 2B candidate vaccines move on to even larger trials, involving tens of thousands of people. One Phase 3 goal is to assess vaccine safety in a large group of people. Vaccine efficacy is tested as well. Phase 3 can take 4-5 years and cost between US $115-170 million.

Pre-Commerce: This stage involves the introduction of a new TB vaccine to the market. Successful introduction is achieved by developing a comprehensive data package that makes a public health and economic case for TB vaccine adoption into national programs. Often a WHO Strategic Advisory Group of Experts (SAGE) recommendation is required as a prerequisite for adoption in LMICs. Comprehensive data packages include: an evidence for

policy development, advocacy and communication at global and country levels, financing mechanisms to support comprehensive vaccination programs and health infrastructure required for delivery. This body of work can take up to 3 years.

Commercialization: Commercialization is building the value proposition to justify the added benefit of a new vaccine. Activities include ensuring logistical, regulatory, financing, and policy issues are in place. Accurate supply chain forecasting, management of supply and demand to guarantee vaccines are available when countries are ready, review of health infrastructure to support uptake, and monitoring and surveillance systems are also required. Commercialization can take 1-2 years and cost millions of dollars depending on the number of early adopter countries.

4.3 The Current Global Portfolio of TB Vaccine Candidates

Over the past several years, there has been more than US $600 million invested in the development of a global portfolio of vaccine candidates. Currently, there are more than 25 discovery leads and preclinical vaccine candidates, and 12 for which clinical trials are underway (Annex 1). The portfolio includes a diversity of approaches and strategies including recombinant (improved) BCG, rationally attenuated *M. tuberculosis*, viral vectored platforms, recombinant purified proteins and novel adjuvants as well as novel delivery systems such as RNA or DNA combined with electroporation.

4.4 Portfolio Development Timeline

Given the composition of the current global portfolio of TB vaccine candidates, with most candidates in the discovery/pre-Clinical stage of development, it is not likely that a vaccine will be commercialized prior to 2024. As shown in Figure 20, the total time to develop a vaccine candidate from discovery through commercialization is conservatively estimated to be 11 to 17 years. For illustrative purposes, we have utilized the midpoint of the development time period (14 years) as the Base Case assumption.

Figure 20: Clinical Trial Timeline

Time (Years)	Discovery / Pre-Clinical Stage 1	Pre-Clinical Stage 2	Phase 1/ 2A Clinical Trials	Phase 2 B Clinical Trials	Phase 3 Clinical Trials	Pre-Commerce	Total
Range	1 - 2	1 - 2	2 – 3	3 - 4	4 - 5	0 - 1	11 - 17
Base Case	1.5	1.5	2.5	3.5	4.5	.5	14

The assumed success rates by development stage are presented in Figure 21. Given these estimates of success probabilities, the cumulative success rate (i.e. the probability of an individual vaccine candidate moving from the discovery/pre-clinical stage of development to commercialization) is only 2%. Once a vaccine candidate is out of the discovery/pre-clinical

phase, the cumulative success rate for a single candidate is approximately 9%. This improves to approximately 28% after successful Phase 1/2A clinical trials.

Effective portfolio management spreads the development cost risks and ensures sufficient diversity within the portfolio, thereby increasing the probability of success.

Despite the significant market potential of a commercialized TB vaccine, the overall low probability of the successful development of a TB vaccine from discovery/pre-clinical stage 1 to commercialization proves to be a significant challenge for attracting priority interest from pharmaceutical companies. Traditionally, grant based (or other public based) funding is available for earlier stages of development, but the pharmaceutical companies must still make a significant investment in clinical trials. With limited investment resources and a high degree of scientific uncertainty, the pharmaceutical industry historically has not prioritized TB vaccine development within their portfolios. Aeras and TBVI have played a key role in providing early translational and clinical testing technical support and funding to attract pharmaceutical and biotech partners to the process. However, more sustainable, long-term financing is needed to sufficiently de-risk the early phases of vaccine development to incentivize industry to engage in TB vaccine R&D, and to ensure an adequate pipeline of early stage candidates is available to feed the Global Portfolio.

Figure 21: Portfolio Development Attrition and Success Rate Assumptions

Probability of Success	Discovery / Pre-Clinical Stage 1	Pre-Clinical Stage 2	Phase 1 / 2A Clinical Trials	Phase 2 B Clinical Trials	Phase 3 Clinical Trials	Pre-Commerce	Cumulative Probability from Discovery/ Pre-Clinical Stage 1
Base Case	30%	70%	33%	33%	85%	100%	2%

The most efficient approach is to focus on the development of the portfolio as a whole, as opposed to each of the various vaccine IP holders attempting to develop a single candidate on their own. Using a portfolio approach to development, significant synergies can be created compared to individual stand-alone development programs by utilizing predefined gating criteria and testing methodologies that can generate comparability data and help in the down selection process, preserving critical resources for the most promising vaccine candidates. Effective portfolio management spreads the development cost risks and ensures sufficient diversity within the portfolio, thereby increasing the probability of success. Figure 22 below illustrates how, using a portfolio approach, the current vaccine portfolio may evolve over time as certain vaccine candidates fail to move on to the next stage of development. In conducting the analysis, we assumed that two new vaccine candidates enter the Pre-Clinical Stage 2 phase each year. Figure 21 highlights the need for a broad initial portfolio, because the overall attrition rates for vaccines are high, particularly in the early stages of development.

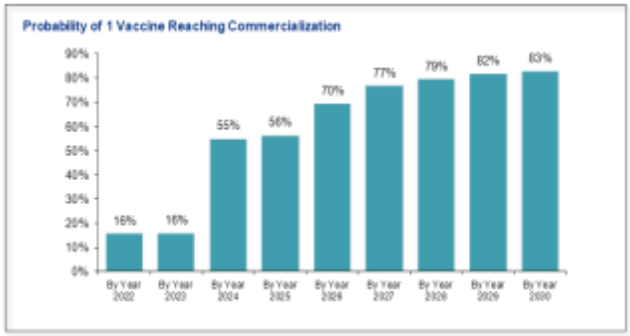
Given the broad portfolio of TB vaccines and the probabilities of success at each stage of vaccine development, there are numerous potential outcomes to the portfolio. For example, in a best case scenario, the one vaccine candidate currently in Phase 2B of development would have a successful outcome in Phase 2B and a successful outcome in Phase 3,

lowering the time needed to bring a vaccine to commercialization, and also limiting the overall development costs for the portfolio. On the other hand, it is possible that the current Phase 2B candidate does not reach commercialization, which means that the time to a successful commercialization is both further off and more costly. In order to better understand the vast set of potential outcomes, the model incorporates a Monte-Carlo simulation analysis tool that can further frame the range of possible outcomes and help assess the overall probability of success. Put simply, a Monte-Carlo analysis captures the data from numerous iterations of possible outcomes using randomly generated variables.

Figure 22: Hypothetical Overview of the Global TB Vaccine Portfolio Over Time

As illustrated in Figure 23, based on the assumptions and the current Global Portfolio, there is a 55% probability of having one vaccine commercialized by 2024 and a greater than 80% chance of having one vaccine commercialized by 2030.

Figure 23: Monte-Carlo Analysis – Probabilities of Successful Commercial Launch over Time



4.5 Analysis of Projected Portfolio Development Costs

As detailed in Figure 24 below, we estimate that the current global vaccine portfolio will require annual spending of approximately $15 to $25 million to enhance and sustain the discovery/pre-clinical stage 1 portfolio of leads. It is anticipated that this level of spending will continue for at least the next 8 years and then taper off as the portfolio advances. The estimated investment for pre-clinical Stage 2 (IND track) is approximately $1 to $2 million per vaccine to cover the costs of advancing that candidate into clinic. Once vaccine candidates progress to clinical trials, the development costs increase significantly, with the Phase 1/2A clinical trials stage of development costing $5 to $12 million per vaccine candidate and Phase 2B clinical trials costing $20 to $40 million per vaccine candidate. Clinical development costs per phase may

include more than one trial per phase. The most costly stage of development is Phase 3 clinical trials, which are estimated to be between $115 and $170 million per vaccine. The estimated development cost ranges for pre-clinical development and clinical trials were based on historical data generated by Aeras and TBVI as well as projected costs and benchmarking from industry standards.

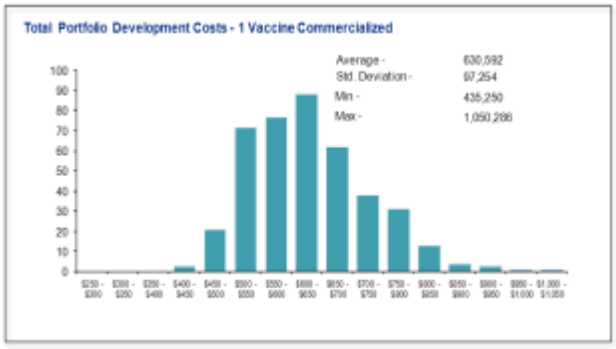
Figure 24: Vaccine Development Cost Assumptions

Development Costs ($ millions)	Discovery /Pre-Clinical Stage 1	Pre-Clinical Stage 2	Phase 1 / 2A Clinical Trials	Phase 2 B Clinical Trials	Phase 3 Clinical Trials	Total Clinical Trials
Range	$15 - $25 *Fixed Per Year*	$1 - $2 *Per Vaccine*	$5 - $12 *Per Vaccine*	$20 - $40 *Per Vaccine*	$115 - $170 *Per Vaccine*	$150 – $250 *Per Vaccine*
Base Assumption	$20 *Fixed Per Year*	$1.5 *Per Vaccine*	$10 *Per Vaccine*	$30 *Per Vaccine*	$150 *Per Vaccine*	$190 *Per Vaccine*

As detailed in Figure 24, we have used a base assumption for the discovery/pre-clinical Stage 1 of $20 million in annual development costs. It is further assumed that these development costs continue for 8 years, falling to $10 million annually and continuing at that level until one vaccine candidate from the portfolio reaches commercialization. The base assumption for development costs for the Pre-Clinical Stage 2 phase is $1.5 million per vaccine candidate. For the clinical trials stages, the base assumptions are $10 million per vaccine for Phase 1/2A clinical trials, $30 million per vaccine for Phase 2B clinical trials and $150 million per vaccine for Phase 3 clinical trials. The base assumptions on development costs are slightly higher than the midpoint of the range, particularly for the Phase 3 development cost assumptions.

As with the overall development timeline, there are numerous potential outcomes in terms of development costs. As would be expected, the total development costs are typically greater in iterations where there is a failure in Phase 3 Clinical Trials. Generally speaking, the minimum required development costs for the commercialization of one vaccine candidate is approximately $435 million, with total development costs being less than $800 million in approximately 35% of the potential outcomes and less than $1,050 million in approximately 85% of the potential outcomes. Thus, the estimated portfolio development cost for the commercialization of one vaccine out of the current portfolio is approximately $600 million to $800 million (Figure 25).

Figure 25: Monte-Carlo Analysis - Histogram of Potential Portfolio Development Costs

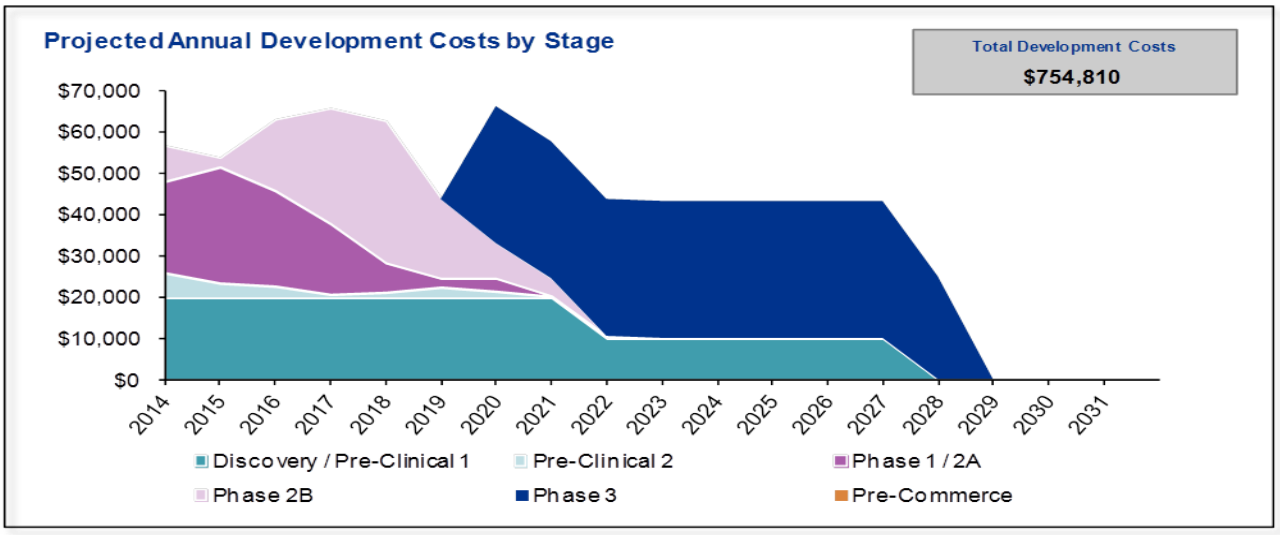


For illustration purposes, we have analyzed a potential development scenario that is from the higher end of the range for overall development costs, whereby one vaccine reaches commercialization by 2029. As shown in Figure 26, the total portfolio development costs are approximately $754 million, which is somewhat higher than the average portfolio development costs highlighted in the Monte-Carlo data presented in Figure 25. Figure 26 also highlights that the most significant investment is for Phase 3 clinical trials and that the Phase 3 investments are relatively close to the commercialization period.

There are also significant cumulative costs in Phase 1/2a and 2B in years 2014-2019 due to the number of

candidates in preclinical and early clinical testing today. Novel trial design including head-to-head comparison clinical studies could significantly reduce these costs, preserving scarce resources for candidates that outperform others with a similar design and immunological profile. When the portfolio is heavily weighted with candidates with similar characteristics (e.g. same antigens and immunological responses), in the same stage of development, portfolio management facilitates cost-efficiencies by forcing the down selection of products, versus the alternative of taking each candidate through expensive Phase 2B proof-of-concept trials.

Figure 26: Projected Annual Development Costs by Stage



5. Financing the Development of New TB Vaccines

5.1 Overview

Both the public and private sector have considerable incentives to pursue the development of new TB vaccines. Preventing new cases of TB, and mitigating the costs of treatment, death, disability and lost productivity for the public sector is significant as noted earlier in this document. As well, entire industries such as healthcare workers, military personnel, first responders, law enforcement, the international development community, prison personnel, those working in elderly care facilities and other high-risk professions who today have no protection, would benefit from vaccination. For example, in Romania healthcare workers have a ten-fold greater risk of getting TB than for the population (Study for Aeras, 2010). As well, an infectious individual on a US Navy amphibious ship, who went undiagnosed for nearly 3 months, spread TB on the ship resulting in 21 active cases of disease, and more than 700 individuals who tested positive for latent TB infection (Lamar, 2003). The impact and threat of X/MDR-TB makes it all the more urgent to pursue preventative strategies.

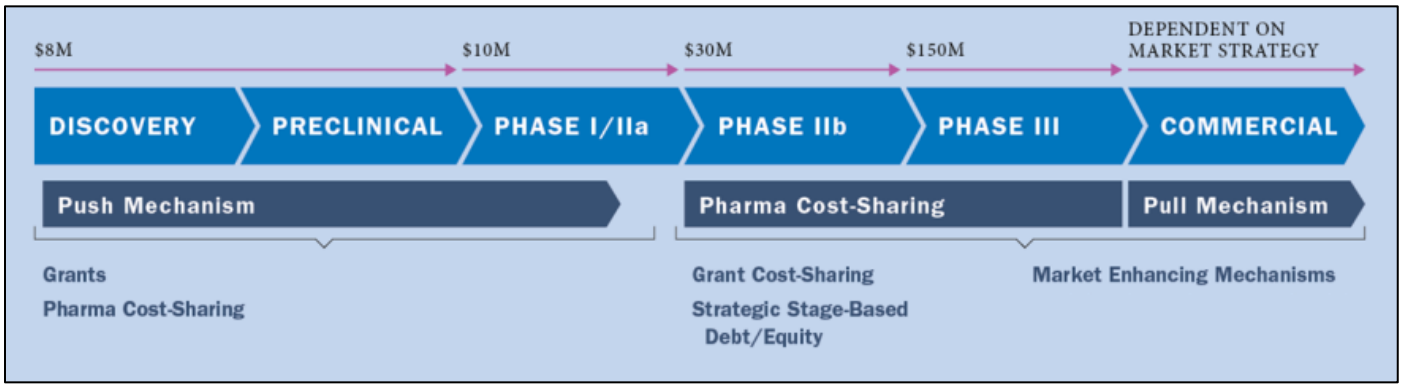
The potential commercial market, estimated to be $13-14 billion over 10 years, is an attractive draw for the pharmaceutical industry. However, significant scientific risks, with a low probability of success as noted earlier, prove to be a barrier for attracting priority interest from industry. To balance the risk and rewards between the public and private sector, the use of blended capital and the implementation of a rational portfolio management approach are being proposed. In this regard, public funds would be prioritized towards the highest risk development stages (discovery through phase 2a) through portfolio grant making mechanisms, and strategic pull

mechanisms would be deployed to enhance the commercial viability of new TB vaccines (Figure 27).

This model would ensure the most efficient use of public funds by catalyzing private sector investment to finance a portion of the most expensive phases of clinical development and by supporting a portfolio management approach that would ensure scarce resources were being deployed to advance only the most promising candidates. This stratification in the three funding principles presents the opportunity that Pharma and/or Equity/Debt could also (within certain limits) contribute to push mechanisms.

In return, we propose that industry partners cost-share utilizing their own resources or debt and/or equity mechanisms to fund the more expensive later stage clinical trials (phases 2b and 3). This strategic investment approach offers the maximum benefit to both stakeholder groups. Only the largest pharmaceutical companies have experience introducing and scaling up vaccines for the worldwide market, ensuring the highest international quality standards. Governments, in turn, are the largest customers for these new vaccines, representing 90% of the projected market. Governments will ultimately benefit from treatment cost-savings, and by protecting their workforce from a deadly, drug-resistant and contagious infectious disease. Governments may also have the opportunity to negotiate on price as a part of a well-structured pull mechanism.

Figure 27: Blended capital to advance the TB vaccine portfolio



5.2 Public and Private Sector Funding

The financial model enables us to evaluate a series of scenarios that blend public and private funds to evaluate the funding gap utilizing preferably their own resources, probably supported by debt and/or equity (Figure 28). Given that new TB vaccines will most likely take more than a decade to commercialize, utilizing debt at an estimated 2.5% p.a. (in the case of a strong guarantee support from highly rated institution) or an estimated rate of 5% p.a. (in the case of a partial guarantee support from a highly rated institution) to support the development of the entire preclinical and clinical portfolio today would be costly, imposing a high, and potentially unacceptable royalty payment on the first commercial manufacturer (Figure 28, Case 1), who might seek more cost-effective financing sources. [Interest rates mentioned in this business plan are purely indicative and presented for illustrative purposes] We do not believe this is in the best interest of the public sector since it would most likely increase the price of the vaccine to accommodate for the royalty payment, placing a financial burden on the public sector.

Debt, provided by multilateral development banks, could be utilized as part of a well-structured pull mechanism when a sufficient number of candidates enter late-stage clinical trials. Since the probability of success is high in Phase 3 (85%), and the development costs are nearly twice that of all the other stages combined, debt and/or equity mechanisms could be mobilized to support late-stage candidates through licensure with a minimal royalty payment (Figure 28, Case 2-5). However, given the projected evolution of the portfolio (Figure 26), this mechanism would not be applicable until 2019 at the earliest.

Given the status of the portfolio today, the vast majority of the funds needed over the next several years are best suited to come in grants (Figure 29, 30). However, if we are able to sufficiently incentivize industry with grant support from discovery through Phase 2a, and initiate various pull mechanisms, we envision that pharma would cover at least 50% of the Phase 2b/3 development costs. Given approximately $754,810 (illustrative model output) million would be required to support the global portfolio through the successful introduction of a new TB vaccine in 2027, $341 million, or 45%, of the total portfolio development costs would need to be covered by grants. Pharma's cost-sharing would be approximately $207 million, or 27% of the overall portfolio development costs. The remaining $207 million funding gap in Phase 2b/3 could be covered by grants, cost-sharing mechanisms such as EDCTP2, or with a combination of grants, debt or equity mechanisms. (Figure 28, Cases 2-5).

Figure 28. Blended capital approach to TB vaccine development

Case 1: 100% Debt for Entire Portfolio Development		
Total Funded with Debt ($000): $754,810		
Debt Interest Rate	**Required Royalty %**	**Total Debt Repayments**
2.5%	7.5.0%	$1,098,188
5.0%	11.0%	$1,589,784
Case 2: 100% Grants through 2a, 100% Debt 2b & 3		
Total Funded with Debt ($000): $413, 810		
Debt Interest Rate	**Required Royalty %**	**Total Debt Repayments**
2.5%	4.0%	$575,098
5.0%	5.5%	$798,409
Case 3: 100% Grants through 2a, 80% Grants/Pharma and 20% Debt for 2b & 3		
Total Funded with Debt ($000): $82,762		
Debt Interest Rate	**Required Royalty %**	**Total Debt Repayments**
2.5%	.8%	$115,023
5.0%	1.1%	$159,577
Case 4: 100% Grants through 2a, 80% Grants/Pharma and 20% EQUITY for 2b & 3		
Royalty Rate	**IRR on Equity**	
5.0%	17.2%	
10.0%	22.9%	
Case 5: 100% Grants through 2b, 80% Grants/Pharma and 20% Debt for 3		
Total Funded with Debt ($000): $58,333		
Debt Interest Rate	**Required Royalty %**	**Total Debt Repayments**
2.5%	.6%	$77,069
5.0%	.7%	$101,850

Figure 30. Illustrative 5-year incremental development costs ($M) and funding gap options

Phase of development	2014-2018	2019-2023	2023-2027
Discovery – Phase 2a	$211	$95	$50
Phase 2b/3	$90	$160	$165
Pharma (50%)	$45	$80	$82.5
Funding gap	$45	$80	$82.5
Total costs	$301	$255	$215
Gap funding options	grants/cost-offsets	grants, cost-offsets, debt or equity	grants, cost-offsets, debt or equity

5.3 Utilizing Push and Pull Mechanisms to Leverage Private Sector Investment

Push and pull mechanisms in R&D refer to economic incentives that facilitate the development of interventions that are perceived to be market failures, or in cases where there is commercial viability, the scientific risk and uncertainty is very high. Push mechanisms provide direct funding through grants, while pull mechanisms increase the monetary rewards for the development of an effective intervention. In more general terms, push mechanisms pay for research inputs and pull mechanisms pay for research outputs (Kremer, 1999).

Pull mechanisms are more important in the later stages of development, where the probability of success is higher. When governments agree to pay for results, it not only helps validate the market, but also increases the incentives for the biopharmaceutical industry to prioritize and accelerate R&D efforts for diseases that would otherwise not exist within their portfolio.

Purchase pre-commitments have an added advantage, because the potential for new vaccines is often difficult for those outside the field to assess (Kremer, 1999). In the case of vaccines, a government's willingness to purchase vaccines provides a strong economic incentive since the vaccine market is historically dominated by the public sector. The advantage to governments, in agreeing to these pre-commitments, would be to guarantee volume-based pricing.

Pre-commitment incentives serve three purposes; (1) To help pharmaceutical companies recoup R&D investments by mitigating the market risk (2) To leverage biopharma investment in the late-stage and costly phase 3 registration trials; and (3) To offer an opportunity for governments to secure an adequate supply of vaccines in the event that global demand outweighs supply. In the case of TB, this could very well be the case given the challenges and costs associated with X/MDR-TB.

To further validate the attractiveness of various pull and strategic stage-based funding mechanisms, a series of meetings with industry are underway. Once there is a better understanding of what pull

mechanisms would be considered most effective by industry, contacts with the health ministry officials will be made to explore their interest in pre-commitment incentives.

After sufficient consultation, a series of meetings will be scheduled with key Member States and high-disease burden, upper middle-income countries to assess their interest in collaborating on a pull mechanism that would aim to catalyze significant industry investment in TB vaccine R&D.

5.4 Portfolio Management

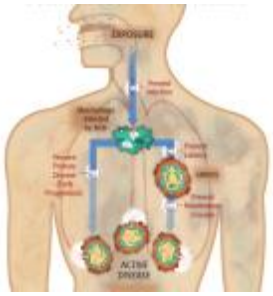
The overarching objective in portfolio management is to realize overall R&D cost efficiencies through effective decision-making regarding product/project expansion, redirection or termination. Decision-making is predicated on a comprehensive, strategic and well-defined portfolio development and diversification approach. Implementing portfolio management through tools and processes to introduce new ideas, to change strategic direction when supported by data, and to assess new alternatives will accelerate the learning curve and establish competencies that create a comparative advantage within the scientific field.

Portfolio management and TB vaccine development:

It is crucial that portfolio management incorporates both preclinical and clinical portfolios into the process to ensure a streamlined and adaptable approach to development, allowing data generated from animal studies and human clinical trials to inform on next generation vaccine candidates. This feedback loop helps facilitate the development of a diverse pipeline for future clinical testing building on knowledge generated in the field and the laboratory. Negative feedback from ongoing trials may result in elimination of candidates with similar immune responses, whereas positive feedback loops lead to improvements upon the existing candidates. The importance of feeding the results into the selection of candidates cannot be overstated.

It is also important to recognize that individuals representing project teams, which include the IP owners from industry, academia and other nonprofits, have strong biases towards their candidates. While an IP holder may presume a novel mechanism of action for their candidate, it must have a demonstrable preclinical or clinical comparative advantage over other similar candidates in the portfolio. In this regard, the portfolio manager plays a critical role as the steward of a broader set of stakeholder interests, including donors, and also ensures that development efforts are targeted toward the objective of maximizing the cost-effectiveness of new TB vaccines.

Figure 31. Multiple TB vaccine approaches



The scientific uncertainties, including our understanding of the mechanisms of protective immunity, the lack of robust animal models and the complexity of the bacterium itself, provide significant yet not insurmountable challenges for the TB R&D field, requiring a variety of development approaches. Today, research is being done on recombinant BCG, rationally attenuated *M. tuberculosis*, viral-vectored platforms, recombinant purified proteins, and novel adjuvants, as well as novel delivery systems such as RNA or DNA combined with electroporation (Annex 1). These platforms, discovery leads and vaccine candidates target a wide range of approaches, including differing immunological profiles, as part of our portfolio diversification strategy.

Establishing comprehensive, measurable and widely accepted criteria for selecting, assessing and advancing TB vaccine candidates is the cornerstone to effective portfolio management (Barker et al, 2012). As recently as two years ago, candidates in clinical trials were utilizing different endpoint definitions and immunological measures for analyzing outcomes, making it challenging to compare data across trials and implement a rational portfolio approach. Since that time, published stage gate criteria have been established and are being implemented to inform on each stage of vaccine development; these criteria include the vaccine targeted product profiles, manufacturing processes and feasibility, stability and delivery approach, immunogenicity and mechanism of action, efficacy in clinical testing, regulatory pathways, and business and marketing issues, including final cost at the point of delivery (Barker et al, 2012). A detailed list of stage gate criteria is provided in Annex 5a.

The establishment of a targeted product profile (TPP) is the cornerstone of portfolio management. The TPP offers a clear road map, informing on development efforts and portfolio priorities. Aeras' and TBVI's mission, to reduce the global TB disease burden through vaccination, naturally prioritizes candidates and vaccination approaches that aim to maximize the public health impact. Modeling data presented in this document, as well as in peer-reviewed articles, demonstrate that vaccines targeted toward adolescents and adults would have the greatest impact on the global TB epidemic (Tseng, 2011). For this reason, the adolescent/adult TPP is being prioritized for development within the portfolio.

As a second priority or with a lower priority, vaccine candidates targeted towards infants will be developed within the portfolio. Infant vaccine candidates, including a prime-boost strategy, could potentially be used in adults through mass vaccination campaigns and, vice versa, prophylactic adolescent and adult vaccines could be tested in infants as part of post-licensure strategy. Finally, prophylactic vaccines in the portfolio today have the potential to also be investigated as therapeutic vaccines. These various development approaches and regulatory pathways remain broad and flexible.

Perhaps the most attractive feature of portfolio management for donors is the realization of cost-efficiencies, through mechanisms that include the use of milestone-based finance linked to time-bound, agreed upon GO/NO GO criteria at each of the milestones, and utilization of innovative trial design and head-to-head comparison of preclinical and clinical studies to down select candidates with similar design and immunological profiles. When the portfolio is heavily weighted with candidates with similar characteristics (e.g. same antigens and immunological responses), in the same stage of development, portfolio management promotes cost-efficiencies by forcing the down selection of products, versus the alternative of taking each candidate through expensive clinical development up and through Phase 2B proof-of-concept trials.

Since Aeras adopted a more rational portfolio approach two years ago, more than 18 potential discovery leads and vaccine candidates have been evaluated, globally, for inclusion into the portfolio and were turned down. More than 5 clinical candidates were considered, and ultimately not included in the portfolio, for failing to meet stage gate criteria. In addition, four clinical programs have been halted or undergone major changes due to stage gating and clinical trial results. Plans are now underway to further down select among candidates currently in Phase 2a to ensure costly Phase 2b trials do not involve candidates with similar immunological profiles. Finally, to further realize cost-efficiencies, Aeras has worked with partners to re-design clinical studies with clear pre-defined milestones to be reached, with the objective of managing risk against the level of investment.

Challenges in conducting global TB vaccine portfolio management:

The 'Global Portfolio' today consists of candidates evaluated by Aeras and TBVI that have passed through the first stage gate. A pool of vaccine leads, and earlier stage preclinical candidates, is also being evaluated and tested for potential inclusion into the Global Portfolio. Key to developing a robust clinical pipeline is having a sufficient pool of preclinical candidates to ensure that 1-2 new vaccines enter the clinic each year. Failure to achieve this milestone is likely to create delays in the introduction of a new TB vaccine.

Basic research largely originates out of academia or small biotechnology companies. Researchers access funds primarily through grants provided by their local government. The amount of these funds is relatively small compared to what is required to support the more expensive translational studies. In addition, research methodologies specific to product development may be unknown to the academic researcher. In the absence of significant financial incentives to work with the portfolio management organization (Aeras and TBVI), projects may be confined to the lab for prolonged periods of time. Sufficient financial incentive is required to pull early stage technologies into a well-defined product development strategy for potential inclusion in the global portfolio.

Today, Areas receives the vast majority if its funds from the Bill & Melinda Gates Foundation to support the portfolio approach in addition to the UK and Dutch Governments as well. TBVI is the coordinator and steward of funds from the EC. However, funding for TBVI may cease in early 2014. It is unclear yet if the proposed EC funding platform, Horizon 2020, will

continue to support TB vaccine development through the existing TBVI coordinating structure. Given that there are only 5 major donors in the world supporting TB vaccine R&D, losing EC funding could have a catastrophic impact, pushing back the availability of new TB vaccines many years.

Regardless of the robustness of the preclinical and early stage clinical portfolio, PDPs, such as Aeras and TBVI, are not designed to commercialize and globally scale up new TB vaccines. There are only a handful of pharmaceutical companies or organizations in the world today (such as GlaxoSmithKline [GSK], Merck, Novartis, Sanofi Pasteur, and Pfizer) that have this capacity. These companies account for 80% of the worldwide vaccine market ("Shot in the arm," 2003). Because of the limited number of companies, vaccines are susceptible to large fluctuations in supply (Caplan, 2008). The relatively small number of multi-national vaccine manufacturers is related to market and financial considerations, including limited profits, costly R&D and manufacturing, and liability concerns related to the fact that vaccines historically have been developed for use in healthy infants and children. However, the market is growing as H1NI and fears of pandemic flu, as well as new 'blockbuster vaccines' such as Prevnar and Gardasil, have catalyzed renewed interest in vaccine R&D.

Making new TB vaccines available for the world will require the participation of the world's most experienced and capable pharmaceutical companies. Although manufacturers such as the Serum Institute of India (SII) produce hundreds of millions of doses of childhood vaccines a year, and distribute to 140 countries, they are currently building capacity and committing resources to work on the research, development, and clinical testing of new vaccines. Manufacturers such as SII, and China's National Biotech Group (CNBG), could play a major role in future R&D and global scale-up. In fact, both SII and CNBG have initiated work with international partners on new TB vaccines.

PDPs like Aeras, with significant experience in managing large-scale efficacy trials in high-disease burden countries, present industry with cost-sharing opportunity to manage risk. New IP, generated out of the robust preclinical portfolio facilitated by TBVI's large network, can be leveraged to potentially advance promising technologies into successful commercial ventures.

Understanding how to align interests, within the entire ecosystem of TB vaccine R&D, requires a wide array of incentive mechanisms that aim to pull the most promising technologies from the basic research and academic communities, and engage industry in the clinical testing and global introduction and scale-up of new TB vaccines. Without an ecosystem approach, the value chain risks becoming disjointed resulting in delays, increased costs and, in a worst case scenario, the failure to make new affordable TB vaccines available to the world.

Opportunities to enhance Global TB Vaccine Portfolio management:

Optimizing the organizational arrangements of TBVI and Aeras could have a transformative impact on global efforts to develop and make new TB vaccines available within the next decade.

Aeras operating model Founded in 1999, Aeras is a fully integrated nonprofit biotech with capabilities in

finance, portfolio management, and in-house capacity to conduct pilot manufacturing, immunology, assay development, clinical trials, regulatory affairs and policy, advocacy and resource mobilization. Aeras is uniquely qualified to serve as a critical translational bridge from research to clinical trials and from the lab to commercial manufacturing. Aeras has sponsored and conducted nearly 20 clinical vaccine trials, including those with thousands of subjects (Tameris, 2013), and is a key partner in 6 active clinical development programs. Aeras has approximately 160 employees, with offices in Rockville, Maryland, Cape Town, South Africa and Beijing, China.

In 2012, the Bill & Melinda Gates Foundation awarded Aeras up to $220 million over 5 years to advance the global portfolio. Aeras is now implementing a new 5-year strategy with 4 key objectives: (1) to advance 2-3 vaccine candidates with strong phase 2 data into phase 3 efficacy trials; (2) to increase the number of TB vaccine candidates in the preclinical portfolio to ensure a robust and diverse pipeline; (3) to establish and implement a rational vaccine discovery and development process, utilizing human and animal challenge models and systems biology to predict correlates of protection and innovative vaccine designs; and (4) to strengthen and diversify the funding base for TB vaccine R&D globally.

To effectively implement this strategy, Aeras uses an industry model of vaccine development, utilizing portfolio and milestone-based project management under independent external guidance of all critical activities. Aeras' Project Management System incorporates a matrix approach, led by product teams and a project leader. In addition, a new internal Portfolio Management Committee (PMC) and external Vaccine Advisory Committee (VAC) have been created to further facilitate transparent decision-making. The VAC is comprised of world-renowned experts in TB and vaccine development, and meets at least twice a year to evaluate the preclinical and clinical portfolios. Aeras has also initiated an external advisory Biomarker and Correlate Working Group that meets twice a year and reviews issues related to objective 3 above. Finally, Aeras recently launched a health economics working group, comprised of leading health economists, epidemiologists and modelers to build a robust evidence base to support advocacy and resource mobilization efforts and downstream vaccine access and financing.

Aeras collaborates with development and commercial partners under contractual agreements. Some of the key provisions governing these agreements include a cost-sharing split that varies based on the phase of development, global access provisions, transparency and publication, intellectual property management, regulatory filings, Institutional Review Board approval, care for human subjects research, use of animals in research and confidentiality. These contractual relationships are central to advancing products on a clear and legal basis.

TBVI's operating model:

TBVI's current structure is a function of prior EC funding Frameworks that require the existence of a coordinating entity to manage the program of work, administer the financial arrangements, and provide the communication channel between the partners and the EC. This coordinating entity has been restructured multiple times over the past decade resulting in what is today, i.e., TBVI – located in Lelystad, Netherlands,

as an independent legal entity. TBVI currently co-ordinates a consortium of 34 European partners and collaborators, with a third of the consortium working on technologies that are advanced enough to qualify for additional finance, and translational expertise that can be used to evaluate candidates' potential inclusion in a TB vaccine portfolio.

TBVI has played a key role in stabilizing and enhancing the existing scientific strengths of the European consortium. Without such a central coordinating entity, perceived as unbiased and trustworthy by the partners, the consortium structure and functionality may not be sustainable, threatening the scientific collaborative process and knowledge sharing, as well as the co-operation built over the past decade. TBVI's product and clinical development teams (PDT & CDT), and central coordinating and reporting structure, offer significant benefits to European researchers and have facilitated the development of the Global Portfolio. TBVI's advocacy efforts have also contributed to raising awareness and support for TB vaccines across the EU, by documenting and disseminating evidence based advocacy materials and through its convening power.

The EU TB research consortium has been recognized within the EC as one of their most successful funding initiatives, consistently delivering within budget and providing a rich resource of vaccine discovery, basic science and clinical development that has facilitated the Global Portfolio.

Discussions are now underway between Aeras and TBVI to assess how best to harmonize our technical expertise, scientific advisory committees and governance structures in order to enhance portfolio decision making and prioritization, transparency and knowledge sharing. Through pooled expertise it is anticipated that a more efficient and effective organizational arrangement can be achieved to maximize organizational synergies. Fundamental to our success will be the availability of sufficient funds to support the early preclinical and translational work underway across Europe.

6. Conclusion

In order to make new TB vaccines available for the world as soon as is feasibly possible and in the most cost-effective way, sustainable financing and the implementation of a streamlined, rational portfolio management approach is required. Four guiding principles need to be widely accepted:

- **First,** that sufficient grant funding is required to support and sustain the development of a robust preclinical pipeline for at least the next 8 years to ensure a critical mass of candidates enter the clinical pipeline;
- **Second**, that the major donors supporting TB vaccine R&D align around the principle that through focus and concentration of scarce resources, coupled with cumulative knowledge, the probability of achieving success is greatly enhanced;
- **Third** that the fundamental mechanism for efficient resource allocation is through an effective portfolio management approach;
- **Fourth,** that portfolio management, and the requisite technical expertise, does not have to exist within a single organization, but that there must be global governance mechanisms and decision making frameworks that support the flow of funds into the portfolio in a rational manner, with sufficient control over the use of those resources to ensure that stage gate decision processes are adopted and enforced as a prerequisite for funding. Without such alignment, disparate, independent programs and redundant scientific work will proliferate.

Strategic stage based funding mechanisms utilizing debt and/or equity, as part of a well-structured pull mechanism, could play a role in closing late-stage R&D funding gaps once a critical number of candidates are approaching Phase 2b/3 testing. Equally as important is the need to validate the market potential for new TB vaccines among various HIC/UMIC countries. Debt finance for the commercial manufacturing scale up and as a resource to support countries' comprehensive vaccination programs could also be an attractive 'pull' element for industry. Finally, there is a need to establish robust, evidence-based national health economic data to facilitate vaccine adoption and to garner buy-in from the WHO to support regulatory agencies.

Making new tuberculosis vaccines available to the world over the next 10-15 years is estimated to cost less than US $800 million utilizing a highly efficient portfolio management approach. These costs pale in comparison to the estimated US $8 billion a year required to provide tuberculosis treatment and care. Austerity measures demand that we invest in longer-term strategies that could ultimately save billions in treatment costs while protecting future generations from one of the longest lasting and deadliest epidemics of mankind.

It is only on the brink that people find the will to change. Only at the precipice do we resolve to act. This is the moment for tuberculosis.

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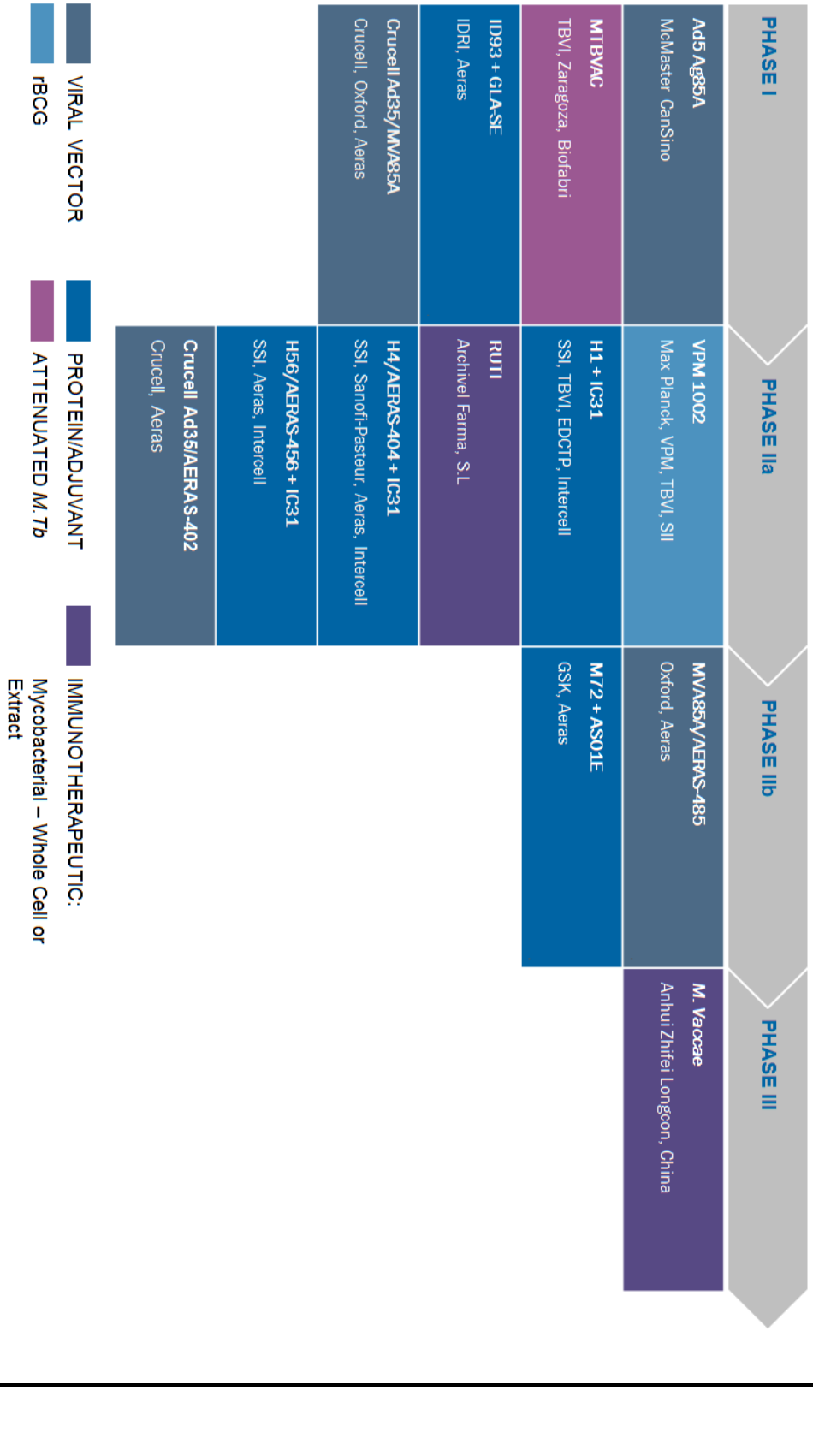
Annex 1: Global TB Vaccine Portfolio (as of December 2013)



Annex 2: Market Segmentation

55 High-Income Countries			
Aruba	Czech Republic	Japan	Saudi Arabia
Australia	Denmark	Korea, Rep.	Singapore
Austria	Equatorial Guinea	Kuwait	Slovakia
Bahamas	Estonia	Luxembourg	Slovenia
Bahrain	Finland	Malta	Spain
Barbados	France	Netherlands	Sweden
Belgium	French Polynesia	Netherlands Antilles	Switzerland
Brunei	Germany	New Caledonia	Trinidad & Tobago
Canada	Greece	New Zealand	United Arab Emirates
Channel Islands*	Hungary	Norway	United Kingdom
China, Hong Kong SAR	Iceland	Oman	United States of America (including Puerto Rico and Guam)
China, Macao SAR	Ireland	Poland	US Virgin Islands
Croatia	Israel	Portugal	
Cyprus	Italy	Qatar	
94 Middle-income Countries			
Albania	Egypt	Malaysia	Sao Tome and Principe
Algeria	El Salvador	Maldives	Senegal
Angola	Fiji	Mauritania	Serbia
Argentina	Gabon	Mauritius	Solomon Islands
Armenia	Georgia	Mexico	South Africa
Azerbaijan	Ghana	Micronesia	Sri Lanka
Belarus	Grenada	Moldova	Sudan
Bhutan	Guatemala	Mongolia	Swaziland
Bolivia	Guyana	Montenegro	Syria
Bosnia & Herzegovina	Honduras	Morocco	Thailand
Botswana	India	Namibia	Tonga
Brazil	Indonesia	Nicaragua	Tunisia
Bulgaria	Iran	Nigeria	Turkey
Cameroon	Iraq	Pakistan	Turkmenistan
Chile	Jamaica	Panama	Ukraine
China	Jordan	Papua New Guinea	Uruguay
Colombia	Kazakhstan	Paraguay	Uzbekistan
Congo	Kiribati	Peru	Vanuatu
Costa Rica	Lao, PDR	Philippines	Venezuela

Cote d'Ivoire	Latvia	Romania	Vietnam
Cuba	Lebanon	Russia	Yemen
Djibouti	Lesotho	Saint Lucia	Zambia
Dominican Republic	Lithuania	Saint Vincent and the Grenadines	
Ecuador	Macedonia	Samoa	
34 Low-income Countries			
Afghanistan	Eritrea	Liberia	Sierra Leone
Bangladesh	Ethiopia	Madagascar	Somalia
Benin	Gambia	Malawi	Tajikistan
Burkina Faso	Guinea	Mali	Tanzania
Burundi	Guinea-Bissau	Mozambique	Togi
Cambodia	Haiti	Myanmar	Uganda
Central African Republic	Kenya	Nepal	Zimbabwe
Chad	Korea, DPR	Niger	
Congo, Dem. Rep.	Kyrgyzstan	Rwanda	

[Based on 2011 World Bank Classification]

57 GAVI Countries 2012		
Afghanistan	Guinea Bissau	Pakistan
Bangladesh	Haiti	Papua New Guinea
Benin	India	Rwanda
Burkina Faso	Kenya	São Tomé e Príncipe
Burundi	Korea, DPR	Senegal
Cambodia	Kyrgyz Republic	Sierra Leone
Cameroon	Lao PDR	Solomon Islands
Central African Republic	Lesotho	Somalia
Chad	Liberia	Republic of Sudan
Comoros	Madagascar	South Sudan
Congo, Dem Republic of	Malawi	Tajikistan
Côte d'Ivoire	Mali	Tanzania
Djibouti	Mauritania	Togo
East-Timor	Mozambique	Uganda
Eritrea	Myanmar	Uzbekistan
Ethiopia	Nepal	Viet Nam
Gambia	Nicaragua	Yemen
Ghana	Niger	Zambia
Guinea	Nigeria	Zimbabwe

Annex 3: Selected Sources for Market Applied Strategies Data for High-risk Populations

- The Military Balance 2011, The International Institute For Strategic Studies; active forces include army, navy, air force and any other forces that are included under the active forces of that country
- Data of immigrants from all high disease burden countries (except Vietnam) present in the OECD countries extracted on 06 Dec 2011 from OECD.Stat
- Data for Vietnam extracted on 13 Dec 2011 from OECD.Stat; assumed 10% of the total immigrant population to be children of immigrants from high disease burden countries; regional proxies used for countries with missing data
- WHO Global Atlas accessed on 30 Nov 2011; regional proxies used for countries with missing data
- Tourism factbook of UNWTO website; assumed 10% of total travelers to HDB countries were children, 90% were adults (Aeras); regional proxy (EMR) used for Equatorial Guinea (missing data) did not include Macao & Hong Kong, China since ~99% of their travelers are to mainland China
- "High Risk Population_HIC_2010%_16Dec2011"
- "WHO TB data_Outcomes%_Sent to Tei_7Dec2011" and "WHO TB data_Outcomes%_High Risk Population_HIC_19Dec2011"
- Coverage rate data: Historical data from http://WHO.int/immunization_monitoring/en/global summary/timeseries/tswucoveragedtp3.htm
- HIV data: Country wise HIV prevalence_Low&Middle income_12Dec2011 & Country wise HIV prevalence_High income countries_28Dec2011

Annex 4: Year of Country TB Vaccine Introduction

Conservative Scenario		
	Year of Introduction	
Country	Adolescent/adult	Infant
Afghanistan	2040	2043
Albania	2034	2037
Algeria	2039	2042
Angola	2035	2038
Argentina	2040	2043
Armenia	2039	2042
Aruba	2040	2043
Australia	2030	2033
Austria	2031	2034
Azerbaijan	2040	2043
Bahamas	2042	2045
Bahrain	2035	2038
Bangladesh	2031	2034
Barbados	2042	2045
Belarus	2034	2037
Belgium	2034	2037
Belize		
Benin	2033	2036
Bhutan	2035	2038
Bolivia	2042	2045
Bosnia and Herzegovina	2039	2042
Botswana	2032	2035
Brazil	2032	2035
Brunei	2035	2038
Bulgaria	2036	2039
Burkina Faso	2036	2039
Burundi	2034	2037
Cambodia	2032	2035
Cameroon	2033	2036
Canada	2032	2035
Cape Verde		
Central African Republic	2036	2039
Chad	2036	2039
Channel Islands		
Chile	2039	2042
China	2032	2035
China, Hong Kong SAR	2032	2035
China, Macao SAR	2032	2035
Colombia	2042	2045
Comoros		
Congo	2035	2038
Congo, Dem. Rep.	2035	2038
Costa Rica	2040	2043
Cote d'Ivoire	2036	2039
Croatia	2031	2034
Cuba	2041	2044
Cyprus	2038	2041
Czech Republic	2034	2037
Denmark	2033	2036
Djibouti	2036	2039
Dominican Republic	2030	2033
Ecuador	2042	2045
Egypt	2036	2039

Conservative Scenario		
	Year of Introduction	
Country	Adolescent/adult	Infant
El Salvador	2039	2042
Equatorial Guinea	2031	2034
Eritrea	2038	2041
Estonia	2032	2035
Ethiopia	2039	2042
Fiji	2041	2044
Finland	2031	2034
France	2031	2034
French Guiana		
French Polynesia	2031	2034
Gabon	2031	2034
Gambia	2033	2036
Georgia	2039	2042
Germany	2035	2038
Ghana	2031	2034
Greece	2040	2043
Grenada	2041	2044
Guadeloupe		
Guam	2033	2036
Guatemala	2037	2040
Guinea	2037	2040
Guinea-Bissau	2038	2041
Guyana	2040	2043
Haiti	2038	2041
Honduras	2032	2035
Hungary	2032	2035
Iceland	2037	2040
India	2036	2039
Indonesia	2042	2045
Iran	2037	2040
Iraq	2038	2041
Ireland	2033	2036
Israel	2035	2038
Italy	2035	2038
Jamaica	2042	2045
Japan	2032	2035
Jordan	2041	2044
Kazakhstan	2035	2038
Kenya	2035	2038
Kiribati	2041	2044
Korea, DPR	2038	2041
Korea, Rep.	2037	2040
Kuwait	2035	2038
Kyrgyzstan	2035	2038
Lao, PDR	2038	2041
Latvia	2041	2044
Lebanon	2041	2044
Lesotho	2038	2041
Liberia	2039	2042
Libyan Arab Jamahiriya		
Lithuania	2040	2043
Luxembourg	2032	2035
Macedonia	2042	2045
Madagascar	2037	2040
Malawi	2037	2040

Conservative Scenario		
	Year of Introduction	
Country	Adolescent/adult	Infant
Malaysia	2033	2036
Maldives	2042	2045
Mali	2039	2042
Malta	2033	2036
Martinique		
Mauritania	2039	2042
Mauritius	2042	2045
Mayotte		
Mexico	2039	2042
Micronesia	2040	2043
Moldova	2039	2042
Mongolia	2040	2043
Montenegro	2042	2045
Morocco	2037	2040
Mozambique	2032	2035
Myanmar	2040	2043
Namibia	2034	2037
Nepal	2037	2040
Netherlands	2034	2037
Netherlands Antilles (Curacao, Sint Maarten)	2037	2040
New Caledonia	2034	2037
New Zealand	2033	2036
Nicaragua	2038	2041
Niger	2040	2043
Nigeria	2040	2043
Norway	2033	2036
Occupied Palestinian Territory (West Bank & Gaza)		
Oman	2037	2040
Pakistan	2040	2043
Panama	2042	2045
Papua New Guinea	2033	2036
Paraguay	2040	2043
Peru	2040	2043
Philippines	2033	2036
Poland	2035	2038
Portugal	2040	2043
Puerto Rico	2033	2036
Qatar	2037	2040
Réunion		
Romania	2038	2041
Russia	2034	2037
Rwanda	2036	2039
Saint Lucia	2042	2045
Saint Vincent and the Grenadines	2042	2045
Samoa	2042	2045
Sao Tome and Principe	2042	2045
Saudi Arabia	2036	2039
Senegal	2035	2038
Serbia	2041	2044
Sierra Leone	2037	2040
Singapore	2030	2033
Slovakia	2037	2040
Slovenia	2038	2041
Solomon Islands	2041	2044
Somalia	2040	2043

Conservative Scenario		
	Year of Introduction	
Country	Adolescent/adult	Infant
South Africa	2030	2033
Spain	2040	2043
Sri Lanka	2038	2041
Sudan	2040	2043
Suriname		
Swaziland	2033	2036
Sweden	2034	2037
Switzerland	2034	2037
Syria	2041	2044
Tajikistan	2037	2040
Tanzania	2034	2037
Thailand	2036	2039
Timor-Leste		
Togo	2036	2039
Tonga	2042	2045
Trinidad and Tobago	2035	2038
Tunisia	2041	2044
Turkey	2034	2037
Turkmenistan	2041	2044
Uganda	2036	2039
Ukraine	2038	2041
United Arab Emirates	2035	2038
United Kingdom	2030	2033
United States of America	2031	2034
United States Virgin Islands	2036	2039
Uruguay	2041	2044
Uzbekistan	2036	2039
Vanuatu	2042	2045
Venezuela	2038	2041
Viet Nam	2036	2039
Western Sahara		
Yemen	2040	2043
Zambia	2040	2043
Zimbabwe	2040	2043

Annex 5: Gating Strategy (as of December 2013)

Portfolio and Candidate management is undertaken through the application of a development process making use of a stage specific Gating Strategy. An overview of the strategy is tabled below.

Gateway Point	Gate 1	Gate 2.1	Gate 2.2	Gate 3.1	Gate 3.2	Gate 4
Purpose	To identify and select candidates from R&D (Discovery) for product development and PoC animal studies	To identify and select candidates from Product Development portfolio for clinical development and Phase I Safety Studies	To review and confirm data, dossier and IND submission are complete and robust for candidate/s selected through Gate 2.1	To identify and select candidates from Phase I study portfolio for clinical development and Phase IIa Safety/Immunology Studies	To identify and select candidates from Phase II study portfolio for clinical development and Phase IIB PoC, Safety/Immunology Studies	To review and assess date from PoC study, to decide on pivotal Phase III licensure study

For each of these Gates or stages, a series of specific criteria have been developed which cover the critical processes and data needed to reach a decision from both a portfolio management perspective as well as individual product development plan.

As the Gates or stages are reviewed for a specific candidate vaccine, the detail and quality of the data required to pass the gate is increased, to properly reflect the investment and product development risks. For example, for the Parameter relating to Product Characterization and Quality starts at the level of laboratory preparation with the requirements tightening to ensure that at each stage of development the product quality matches the development stage, manufacturing capability and regulatory requirements.

Annex 5a: Detailed Gating Strategy (as of December 2013)

GATE 1: Advancing a Vaccine Candidate from Discovery to Preclinical Development		
Characteristics	**Objectives**	**Criteria to pass**
Production process	Define process • Establish seed lot • Establish lab scale production • (estimate of COGs)	• **Process feasible at lab scale** • **History of seed documented** • **Plan for lab scale production established** • **Acceptability of cell lines and other microbial aspects**
Product Characterization & Quality	Characterize substance / product • Prove antigen expression and purity (proteins) • Document genetic stability	• **Genetic stability established; no reversions, R gene removal feasible;** • **Candidates / formulation(s) selected for animal testing;** • **Characterization tests defined**
Safety	Define safety • Identify safety elements relevant to candidate	• **Criteria for safety identified**
Immunogenicity	Define immunity / potency • Describe proposed mechanism of action; • Test immunogenicity in at least one animal species	• **Evidence of (T and/or B cell) immunogenicity to vaccine antigens in at least one animal species** • **Significant responses to vaccine antigens**
Protection / efficacy	Define protection • Test protection vs. Mtb challenge in mouse model or equivalent	• **Protection vs. Mtb challenge demonstrated in mouse model or equivalent** • **Protection statistically better than BCG**
Clinical	Plan for Clinic • Describe proposed target population • Have a Clinical Development Plan	• **Primary target population and clinical development path acceptable, feasible (including route of delivery) and addresses unmet medical or public health need**
Regulatory	Identify RA pathway • Assess possible regulatory barriers	• **Key Regulatory elements assessed and no major roadblocks identified**
Business	Analyze business aspects • Describe IP status • Describe partnership(s) for development • Provide budget for pre-clinical development	• **No IP obstacles identified** • **Viable partnership(s) are identified** • **MTA and other cooperative agreements established** • **Cost estimate/budget for pre-clinical development stages are acceptable** • **Resource plan outlined for next gate**

GATE 2. Advancing a Vaccine Candidate from Preclinical Development to Early Clinical Stage (Phase I/IIa)		
Production process	Prepare manufacturing • Improve process up to pilot scale • Improve formulation • Remove R marker • Demonstrate reproducibility of process	• **Feasibility at pilot scale;** • **Satisfactory yield for phase I material** • **Reproducibility acceptable;** • **Process development done and pilot lots**
Product Quality	Prepare release • Characterize substance • Selected criteria for purity, stability, potency • Develop QC methods	• **Lots released for formulation(s) ready for Phase 1 testing.** • **All QC tests done and specifications met** • **Potency assay under development** • **Stability data satisfactory**
Safety	Document safety • Define pre-clinical package • Conduct RA required General Safety	• **General Safety passed** • **Safer than BCG and/or equivalent acceptable.** • **Biodistribution, persistence specifications (BL2 facility) and GMO requirements met** • **Plan for autoimmune potential clear**
Immunogenicity	Same for immunogenicity • Repeat immunogenicity (Th1, prime-boost, etc) • Confirm immune responses vs. expressed antigens in an appropriate animal model to support proposed mechanism; • Evaluate assays feasibility for human trial	• **Significant immune responses vs. expressed antigens (equivalent or "superior" to BCG).** • **Immune mechanism explored.** • **Satisfactory assay/s for clinical trial established**
Protection / Efficacy	Evaluate or confirm protection • Test protection vs. Mtb challenge in 2 standardized animal models. Confirm or establish PoC	• **Protection vs. Mtb challenge is statistically better than BCG in 2 animal models. (eg mice & gps) as demonstrated by a read-out with high statistical power for the group size, typically 0.5 log statistically significant decrease in CFU.**
Clinical	Plan pathway to clinic • Prepare or revise Clinical Development Plan • Draft synopsis of Ph 1	• **CDP drafted** • **Synopsis drafted**
Regulatory	Prepare RA / EC file • Prepare RA path • Obtain early RA input, e.g., pre-IND meeting; scientific advice.	• **Pre-IND and/or scientific advice obtained from RA indicates no major roadblocks to non-clinical and clinical development.**

GATE 3. Advancing a Vaccine Candidate from phase I/IIA to Phase 2B (Proof of Concept / Initial Clinical Efficacy Trial)		
Production process	• Define scale up process suitable for commercial level • Validate facilities & equipment	• **Consistency lots successfully manufactured under GMP as for Phase 3 and can be scaled up** • **Full process development for commercialization finalized**
Product Quality	Optimization based on earlier trials: • Characterization of substance: • Stability studies • Validate QA and QC processes	• **Product passes all established final product QC and release assays required for licensure**
Safety	• Analyze all safety data from earlier trials	• **Acceptable safety profile of selected doses regimen in the target population**
Immunogenicity	• Analyze all immunogenicity data from earlier trials • Ensure immunoassays used in CT are standardized • Consider interferences with other vaccines used concomitantly • Consider differentiation plan for comparator purposes	• **Immune responses above baseline at one or more data points for at least one cytokine that exhibits a dose-response** • **Percentage of responders is at least (70?)% for those who receive the vaccine** • **Interference studies started / protocol approved**
Protection / Efficacy	• Define relevant endpoints for efficacy assessment and case ascertainment methods • Develop epidemiology plan based on the TPP at various geographical sites	• **Clinical / immunological endpoints validated** • **Relevant epidemiology data available in the target population**
Clinical	• Develop CDP and design protocols for initial phase 2B and phase 3 efficacy trials • Identify study sites and PIs • Develop monitoring process • Update TPP	• **Phase 2B synopsis completed** • **DSMB and other relevant independent committees identified** • **Study sites identified, monitoring process ready to be implemented according to GCPs** • **Laboratory support identified** • **TPP updated, including draft core data sheet (CDS)**
Regulatory	• Update regulatory strategy; obtain scientific advice from RA and submit required docs to RA • Prepare strategy for timely review of clinical data	• **Scientific advice obtained** • **Regulatory strategy for review process accepted**
Business	• Analyze / update of IP • Analyze market environment on acceptability and cost (part of TPP) • Update partnership agreement (s) if needed • Establish budget and financial resources to complete phase 2B • Work with WHO 5SAGE) and other national / international bodies to prepare introduction of the vaccine (in a broadest sense)	• **IP status satisfactory** • **Market analysis supports target population to be tested in phase 2B** • **Partnership agreement updated** • **Adequate resources in place to complete phase 2B** • **Introduction strategy in progress**

GATE 4. Advancing a Vaccine from Phase 2B to Phase 3 pivotal efficacy trial		
Production process	• Scale up to commercial level	• **Final process successfully scaled up to commercial level** • **Consistency lots made under GMP**
Product Quality	• Define final formulation • Continue stability testing • Define final QC processes, batch and final product release tests	• **Final formulation defined** • **Consistency lots pass final QC, batch and final product release tests**
Safety	• Analyze all safety data from earlier trials, including phase 2B • Draft risk management plan (RMP)	• **Safety studies in phase 2 studies completed at all sites** • **Safety profile satisfactory in final target population** • **RMP designed for updating active surveillance in phase 3**
Immunogenicity	• Analyze all immunogenicity data from earlier trials, including phase 2B • Complete interferences with other vaccines used concomitantly • Analyze phase 2B data for correlates of protection	• **Immune responses in target population acceptable in phase 2B and consistent with previous trials** • **No interference with immune responses when co-administered with other vaccines given in the same target population** • **Correlates of protection embedded in phase 3 protocol**
Protection / Efficacy	• Establish clinical proof of concept	• **Phase 2B demonstrated clinical PoC validated by independent review board (IRB)** (to be more precisely defined according to the candidate vaccine and the target population)
Clinical	• Analyze efficacy data from phase 2B to adapt design of phase 3 efficacy trial • Prepare monitoring procedures according to GCPs • Finalize TPP	• **Phase 3 study design (adaptive?) validated and approved by IRB** • **DSMB and other relevant independent committees in place** • **Study sites satisfactorily audited** • **Monitoring and data management plans defined and validated** • **TPP finalized**
Regulatory	• Ensure regulatory process is in place	• **Registration strategy determined, including for prequalification by WHO** • **Successful phase 2B meeting with RA and phase 3 protocol acceptable**
Business	• Analyze / update of IP and market environment • Update partnership agreement (s) if needed • Establish budget and financial resources to complete phase 3 • Extend collaboration with WHO (SAGE) and other national / international bodies to prepare introduction of the vaccine • Anticipate requirements for recommendation by health authorities	• **Cost of goods (CoG) acceptable** • **Strong industrial partnership in place and action plan defined** • **Market analysis supports the introduction of the vaccine if efficacy satisfactory** • **Supportive PI/KOL community** • **Adequate resources in place to complete phase 3**