Global Report on Tuberculosis Vaccines 2018

Executive Summary

AERAS

TBVI TuBerculosis Vaccine Initiative

EDCTP

Stop TB Partnership

Bill & Melinda Gates foundation

World Health Organization

Acknowledgements

The Global Report on Tuberculosis Vaccines 2018 is prepared at the request of the Global TB Vaccine Partnership (GTBVP) leadership group. The report will be completed following the 5th Global Forum on TB Vaccines to incorporate additional advances in the field, with complete references and full acknowledgements

The Report is co-authored by Lewis Schrager (lead writer); Ole Olesen, EDCTP; Johan Vekemans, WHO; David Lewinsohn, Stop TB Partnership; Jacqueline Shea, Aeras; Willem Hanekom, BMGF; Nick Drager, TBVI.

Funding for the Report has come from TBVI, Stop TB Partnership/USAID and WHO.

THE CASE FOR TUBERCULOSIS VACCINES

Tuberculosis is a major and deadly global epidemic. To end the epidemic, a $1.25 billion investment is needed to fund the development of the most efficient and most effective strategy to combat the spread of TB: a TB vaccine.

Ministers of the G20 have declared that developing interventions against tuberculosis (TB), including vaccines, represents a global health priority; the reasons are dramatic and straightforward. TB is the leading cause of death globally from a single infectious agent, killing approximately 1.67 million persons in 2016. In comparison, 1 million persons died of HIV/AIDS-related diseases and 445,000 died of malaria in 2016. At least one quarter of persons worldwide – approximately 1.7 billion people – are infected with *Mycobacterium tuberculosis* (Mtb), the bacterium that causes TB disease. Among these infected persons, approximately 10%, or 170 million persons globally, will be expected to develop TB during their lifetimes.

TB respects no international borders; Mtb spreads through the air and infection occurs simply by breathing. The vast majority of the global devastation resulting from TB, including its associated public health and economic damage, occurs in low- and middle-income countries, particularly in sub-Saharan Africa, China, India, Pakistan, and southeast Asia, including Indonesia. TB represents the single largest cause of morbidity and mortality in South Africa, causing 8.4% of deaths in that country as of 2014. India and China represent the countries with the world's highest burden of TB, due to an elevated incidence of TB disease and their populations of greater than 1 billion persons.

We Cannot Treat Our Way out of the TB Epidemic

Although a broad range of drugs currently are available to treat TB, their impact on the overall state of the global TB epidemic has stalled. Reasons for this blunting of the effect of TB drugs on global TB incidence include a rate of diagnosis of TB cases that is still disappointing despite recent improvements, the lack of uniform availability of TB drugs to those in need, the initiation of treatment not soon enough to prevent Mtb transmission, the financial burden of illness, and the complexity and duration of TB treatment regimens, which necessitate multiple drugs taken over 6 months, a situation that frequently results in patient non-compliance when time- and cost-intensive public health programs are limited.

The development and spread of drug-resistant strains of Mtb represents an additional factor blunting the effect of TB drugs, and a major public health crisis. While cases of drug-sensitive TB demonstrate a slow, worldwide decline, the incidence of Mtb strains resistant to more than one drug, including multidrug-resistant TB (MDR-TB)[i] and extensively drug-resistant TB (XDR-TB)[ii], has been increasing, and represents a significant threat to public health from the perspectives of both the well-being of the citizenry and the impact on funds required to maintain general public health services. Many of the countries with the highest rates of TB caused by Mtb strains resistant to multiple TB drugs exist in countries along Europe's eastern border.

Current treatment regimens for MDR-TB require a combination of five or more drugs be administered over nine months or longer—a difficult regimen to follow given the prolonged duration of treatment and the unpleasant and, in some cases, overtly dangerous toxicity of the drugs included in the regimen. Initial drug treatment cures only about 50% of MDR-TB patients, necessitating repeat regimens, often with more and/or different TB drugs, for a longer time period. Treating XDR-TB is even more problematic than treating MDR-TB, requiring that 5 or more drugs be administered for up to 3 years. Treatment success for XDR-TB is poor, with an estimated cure

i MDR-TB defined as Mtb isolates resistant to the two, first-line treatments for TB: rifampicin (RIF) and isoniazide (INH)

ii XDR-TB defined as Mtb isolates resistant to INH and RIF, as well as any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin or capreomycin)

rate of 26%. Additionally, the costs of treating patients with MDR-TB and XDR-TB are exorbitant. In Germany, for example, the total (direct and indirect) cost per MDR-TB/XDR-TB case has been estimated at between €82,000 and €109,000, with the potential for significant increases in the future if XDR-TB becomes a higher proportion of the reported number of drug-resistant cases.

The poor cure rates, high fatality rates, and extraordinary cost of treating patients with highly drug-resistant Mtb strains make the spread of these strains a danger both to public health and the health of national economies. Vaccines capable of preventing TB caused by drug sensitive strains, however, are likely to be effective against drug-resistant TB, given that the molecular mechanisms that confer Mtb drug resistance should not change the immunological characteristics of the organism against which an effective, vaccine-induced immune response is targeted. Accordingly, developing new and effective vaccines for TB represent critical components of efforts to control the TB epidemic, including the spread of drug-resistant strains. To achieve success, however, TB vaccine development efforts must be accelerated.

A Vaccine to Prevent TB is Feasible

Evidence of the state of natural human defenses against TB strongly suggests that a vaccine that could prevent TB is possible. Fully 90% of the approximately 1.7 billion people infected with Mtb are able to control the infection without ever manifesting disease. In studies from the pre-antibiotic era it has been shown that harboring latent Mtb infection provides some protection against TB disease developing from new exposure to the pathogen. Additionally, some individuals never acquire Mtb infection despite documented, long-term and close exposure to persons with active pulmonary TB, such as household contacts; some may even clear their infection naturally, raising the possibility of innate resistance. There is also direct evidence that vaccines would work: newborn BCG is effective in preventing TB disease in early childhood, while experimental evidence in the non-human primate suggests that novel vaccination approaches may be effective – such as protection induced by a CMV-vectored vaccine. The reality of the TB epidemic, and its human and economic cost, illustrate the importance of developing vaccines to improve upon natural immunity, and to protect those persons incapable of generating immune control of Mtb infection on their own.

A TB Vaccine is a Cost-Effective Means of Controlling the TB Epidemic and Protecting Global and National Health Security

TB costs the global economy approximately $21 billion in U.S. dollars annually: $1 billion in lost productivity from wage-earners too sick to work; $11 billion from the nearly 2 million deaths caused by TB, with an average loss of 15 years' income; and an estimated $9.2 billion global cost of caring for TB patients. The future cost of TB to the world's poorest countries is estimated at between $1 trillion and $3 trillion over the next 10 years. If no impactful intervention is introduced by 2050, MDR-TB alone could cost the world $16.7 trillion, reduce global GDP by 0.63 per cent.

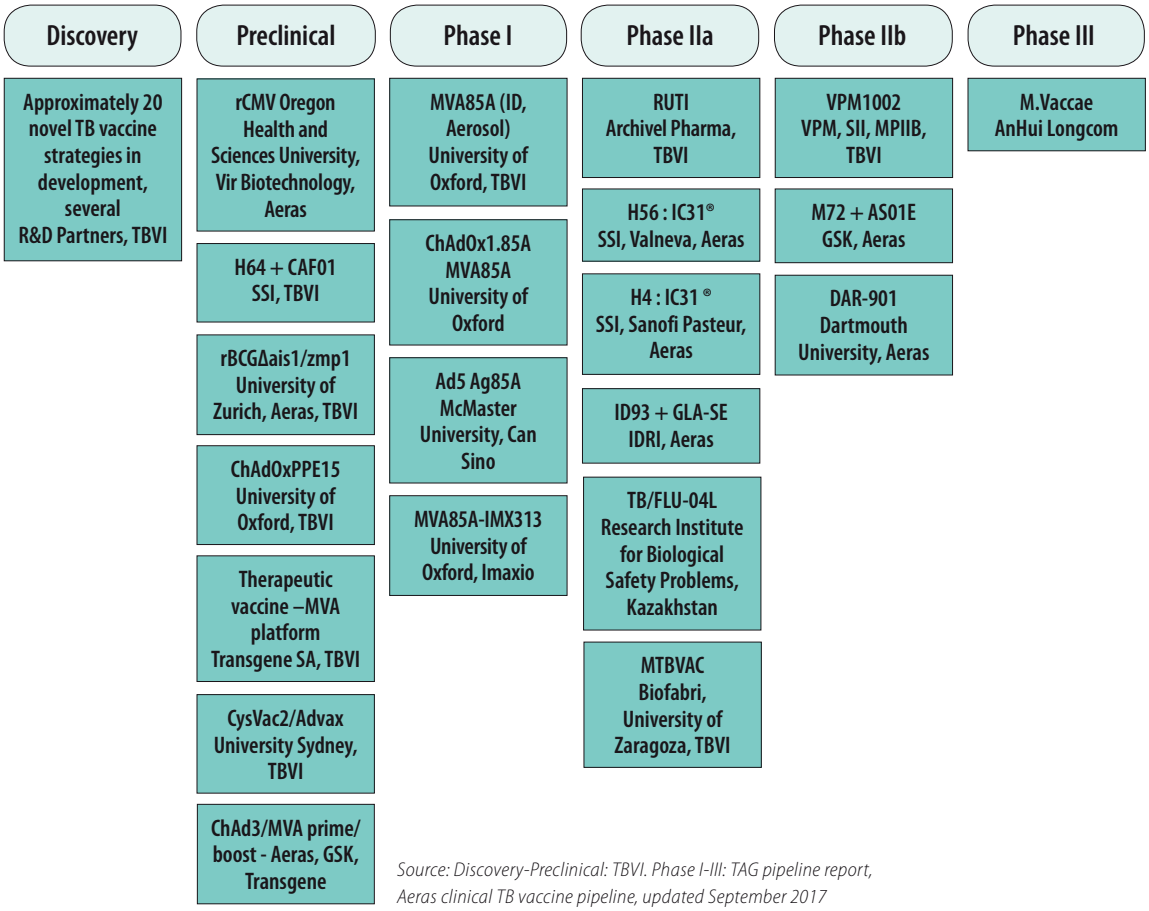
The security benefits of vaccines also merit emphasis. When addressing public health threats, governments often prioritize the allocation of resources into three areas: 1) protecting the safety of the population; 2) securing the organizations charged with responding to the biological threats; and 3) maintaining the stability of the government in the face of the threat, both by assuring the existence of a healthy and robust population that can assure the continued functioning of society in an ordered and predictable manner, and to control unanticipated costs associated with long-term disability, hospitalization and death resulting from the disease. Vaccines represent a critically important tool in meeting the needs in all three strategic areas of response. TB represents precisely the type of communicable disease requiring a robust response, given that it is a respiratory pathogen that can infect massive numbers of citizens. It is critically important for governments, in addition to allocating the appropriate level of resources, to motivate private industry to invest in TB vaccines through sharing the costs of vaccine discovery, engaging in additional "de-risking" efforts

as a vaccine candidate is developed, and assuring eventual purchase, particularly considering the benefits that governments, industry and society as a whole will derive from the development and implementation of safe and effective TB vaccines. By any of these metrics, the world cannot afford to bypass investments in TB vaccines.

THE CURRENT STATE OF TB VACCINE DEVELOPMENT

Fourteen TB vaccine candidates currently are in clinical trials (Figure 1). Only one vaccine, the Chinese candidate, Vaccae™, has entered phase 3 testing. Three vaccines are in late phase 2 testing while the others are in earlier stages of assessment. It will be imperative to continue assessing vaccine candidates in clinical trials, conducted in parallel with efforts to improve basic knowledge of TB pathogenesis and mechanisms of immunological control of Mtb infection. Only in this way can the critical tools and information needed for further Mtb vaccine development, including correlates of immune protection and animal models predictive of vaccine-induced protection, be developed.

Figure 1. Clinical and preclinical TB vaccine pipeline[iii]



Source: Discovery-Preclinical: TBVI. Phase I-III: TAG pipeline report, Aeras clinical TB vaccine pipeline, updated September 2017

iii Based on information provided by TBVI, Aeras and TAG

A number of vaccine candidates and concepts have advanced to the stage of preclinical testing (Figure 1). Additional support for early stage TB vaccine research and discovery is critically needed to fully assess the vaccine concepts in pre-clinical development, and to ensure that additional concepts transition into the pre-clinical and clinical pipeline.

The world needs new, more effective vaccines that protect against all forms of TB in all age groups, including persons with comorbidities such as HIV infection or diabetes mellitus. Modeling suggests that a TB vaccine capable of preventing TB disease in adolescents and adults would allow effective reduction of the spread of Mtb. This, in turn, would have greatest impact on the TB pandemic over the shortest period of time. A major challenge to testing vaccine efficacy to prevent TB disease is the requirement of phase 3 clinical trials, involving tens of thousands of participants who have to be followed for years: a very costly proposition. In light of this challenge, organizations central to global TB vaccine development have come together to suggest stage gate criteria needed to rationally advance TB vaccine candidates during stages of preclinical and clinical development. These criteria are intended to increase the efficiency of TB vaccine development efforts while decreasing the risk of candidate failure in expensive, later-stage clinical trials. The WHO is developing preferred product characteristics for TB vaccines that will provide additional guidance regarding optimal characteristics and efficacy targets for a TB vaccine.

ACCELERATING TB VACCINE DEVELOPMENT: A NEW TB VACCINE BY 2025

Ambitious goals for ending the global epidemic of TB disease and vastly reducing TB mortality on or before the year 2035 have been set by the UN within its Sustainable Development Goals, the WHO End TB Strategy, and the End TB Goals of the Stop TB Partnership (Table 1). None of these ambitious goals, however, can be met without the development of new and better drug treatments for TB, better point-of-care TB diagnostics, and the implementation of an effective TB vaccine.

Table 1: Goals for Ending the Global TB Epidemic

	Targets			
	Milestones		SDG*	END TB**
	2020	2025	2030	2035
Reduction in number of TB deaths (compared with 2015)	35%	75%	90%	95%
Reduction in TB incidence rate (compared with 2015)	20%	50%	80%	90%
TB-affecting families facing catastrophic costs due to TB	0%	0%	0%	0%

United Nations Sustainable Development Goals, Goal 3

***World Health Organisation, Global TB Programme End TB Goals/Stop TB Partnership Global Plan to End TB*

Future Directions in TB Vaccine Development

This is an exciting time in TB vaccine development. New information concerning the molecular nature and mechanisms of disease-producing activity of Mtb, the immunological responses to Mtb infection, the basic pathogenesis of TB disease in humans and animal models, and the efficacy or lack thereof demonstrated for a variety of preclinical and clinical TB vaccine candidates, point the way to a number of critically important and interrelated directions for future TB vaccine research and development. A key theme emerging in future efforts to develop TB vaccines is *diversification*: of vaccine platforms, of the nature of the immune responses induced, of the Mtb antigens to be included in future vaccines, and of vaccine administration routes. Developing better tools for testing vaccines, including improved animal challenge models and a controlled human infection model, also represent important goals. Additionally, increased attention is being paid to the potential need for developing new vaccine strategies that generate lung-based immune responses capable of responding to Mtb infection much more quickly than the immune responses generated by the current generation of TB vaccine candidates.

Funding Requirements Necessary to Support Future Directions in TB Vaccine Development

Developing new TB vaccines capable of preventing TB disease would represent the strategy with the greatest impact in controlling the TB epidemic. Recent estimates indicate that $1.250 billion will be necessary between 2016 and 2020 to support six critical TB vaccine development objectives cited by the Global Plan to End TB 2016-2020. This funding includes $537 million for advancing the TB vaccine clinical pipeline, $220 million for experimental medicine initiatives, $200 million for early-stage research and discovery, $150 million for improving animal models, $71 million for improving preclinical and clinical readouts, and $72 million for laying the groundwork for adolescent and adult vaccine campaigns. Recent funding trends have demonstrated a significant gap between investments in vaccine research and development and funds required to advance and accelerate the TB vaccine pipeline. This shortfall imperils the prospects of developing effective TB vaccines. Failure to develop a safe and effective TB vaccine will result in extraordinary costs to society, measured by the humanitarian costs of lives lost and ruined, the economic costs stemming from diminished productivity and the need to divert scarce resources to the treatment and care of the sick and dying, and to the overall security of those states hardest hit by the tuberculosis epidemic and the spread of drug-resistant TB. Clearly, this represents a shortsighted outcome that global leaders would certainly attempt to avoid once they fully appreciated the risk.

CONCLUSION

TB vaccine development is a difficult, high-risk endeavor, but the humanitarian, economic and health security risks of an ongoing TB epidemic, involving both drug-sensitive and drug-resistant Mtb strains, makes this an essential investment. This is both an exciting and challenging time for TB vaccine development; exciting, as research is successfully addressing the knowledge gaps required to develop better vaccine strategies, and challenging, as the current level of funding support for TB vaccine development is only a fraction of the need.

It would be a tragic mistake to consider TB a disease consigned to history. TB is still very much with us. The disease kills more people, globally, than any other infectious disease. The potential for TB—particularly in its evolving and spreading multidrug-resistant forms—to wreak $16 trillion worth of damage to the global economy by 2050 should provide ample impetus to provide the $1.25 billion investment needed to fund critically needed TB vaccine development.