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TUBERCULOSIS VACCINES

A Strategic Blueprint
for the Next Decade

March 2012

Special Issue containing the TB Vaccine Blueprint, Editorials and Opinion Pieces

Co-Editors
Michael J. Brennan & Jelle Thole
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A New TB Vaccine Blueprint

This special Supplement to *Tuberculosis* is distinguished by the presentation of the important document *Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade*. This roadmap for the future of vaccine development against tuberculosis was preceded by the former *Blueprint for Tuberculosis Vaccine Development* arising from a workshop held in the Washington DC area under the chairmanship of Dr. Barry Bloom in 1998 and *A Framework for the Development, Clinical Study and Introduction of Improved TB Vaccines for the Global Community*, developed by the Global Forum on TB Vaccines Research and Development at WHO Headquarters, Geneva, June 2001 organized by Dr. Uli Fruth and Dr. Michael Brennan. More recently, Dr. Brennan now at Aeras and Dr. Jelle Thole of the TuBerculosis Vaccine Initiative convened the Second Global Forum on TB Vaccines in Tallinn, Estonia, September 2010. Out of this meeting arose this *Blueprint for Tuberculosis Vaccine Development*. However, as Dr. Brennan and Dr. Thole describe, other key meetings on the subject of TB vaccine development before and after the Tallinn assembly helped to shape the framework. In the document itself they rightly acknowledge the sources of funds that facilitated the convening of the Tallinn meeting and the subsequent shaping of the document, and also those others who contributed to its final structure. In this supplement the *Blueprint* itself is complemented by several key papers that capture the outcomes of discussions from Workshops held at the Tallinn forum.

I attended the Second Global Forum on TB Vaccines in Tallinn, and it was a most memorable meeting in all respects. Although with a documented history dated from 1050, Tallinn came into prominence in 1285 as the northernmost member of the Hanseatic League. Its Old Town, which is the actual Hanseatic town, is the most remarkable of an otherwise modern, prosperous city. The meeting itself was distinguished by the exceptional prior preparation and organization. Most important were the pre-conference surveys distributed to the relevant community – researchers, clinicians, pharmaceutical companies, government and non-government agencies, donors and other stakeholders involved in the global TB vaccine development efforts. Out of these efforts arose a consensus definition of the priority areas, the essentials for progress, the critical research and discovery activities to be followed, and the hallmark decision points in selection of TB vaccine candidates for clinical trials. All of these aspects provide the framework of this *Blueprint*, a document in itself is a model in clarity, decisiveness and presentation.

I would like to thank Dr. Michael Brennan and Dr. Jelle Thole and their colleagues from the research community and the Stop TB Partnership Working Group on New TB Vaccines for their year-long effort to assemble this historical consensus document. I would also like to thank their benefactors, the Bill & Melinda Gates Foundation, Aeras, TuBerculosis Vaccine Initiative, European Commission FP 7 Framework Programme, and other organizations that sponsored the Global Forums, as well as Eva Nagtegaal of Elsevier for facilitating the publication of *Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade* as a supplement to *Tuberculosis*.

Patrick J. Brennan,
Co-Editor in Chief, *Tuberculosis*
The 2012 Strategic Blueprint for tuberculosis (TB) vaccines presents a cogent vision for developing and introducing safe and effective TB vaccines within a decade. This document offers a valuable reappraisal of how we can best move this critical area of research forward to help achieve our ultimate goal of eliminating tuberculosis worldwide. The new Blueprint builds on more than 10 years of exceptional progress in TB science and product development since the 2000 publication of the first Blueprint, which resulted from a workshop organized by the U.S. National Institutes of Health (NIH). For a research field that began to receive serious attention and commitment of substantial resources only in the mid-1990s, remarkable gains have been achieved. The framework laid out in the original Blueprint for creating a sustainable infrastructure for the clinical development of candidate TB vaccines is updated in the current plan to reflect new knowledge gained from studying multiple vaccine candidates in preclinical studies and human clinical trials. This update will enable us to refine our approach and define research gaps that must be filled if we are to make licensure of new TB vaccines a reality. The NIH welcomes the publication of the 2012 Blueprint, and we look forward to continuing to work with the many committed scientists and our public and private partners in the global effort to control and ultimately end the global TB pandemic.

TB control programs have led to a recent worldwide decline in the number of people falling ill and dying from TB. However, as noted in the 2011 Global Plan to Stop TB, novel drugs, rapid diagnostics, and, importantly, an effective vaccine are all needed to accelerate the decline of TB cases worldwide and drive TB toward elimination. Multifaceted global efforts will be required to reach this goal. As part of the international team dedicated to TB elimination, NIH will sustain and accelerate our support of the basic and clinical research that plays a critical role in developing medical countermeasures for TB, primarily through research supported by the National Institute of Allergy and Infectious Diseases (NIAID). NIAID’s strategic goals for the developing new TB vaccines are well complemented by and reflected in the new Blueprint.

In U.S.-based research and collaborations conducted in more than 100 countries, NIAID-supported scientists are contributing important data delineating the natural course and dynamics of TB disease, information critical to creating new vaccines candidates. Key questions under investigation include why only some people infected with Mycobacterium tuberculosis (M. tb) develop active disease, while most harbor latent infections; how the current licensed vaccine, BCG, protects children while remaining ineffective in preventing pulmonary disease in adults; and what antigenic factors are needed to trigger protective and long-lasting immune responses to TB vaccines. These studies highlight the immense complexity of TB and underscore why we must continuously rethink how to optimize the design of candidate TB vaccines. Equally important, this and other research will guide us in deploying licensed TB vaccines for the purpose of maximizing declines in the global incidence and prevalence of TB.

Using knowledge gained from clinical studies of human TB disease and the evaluation of candidate vaccines, and our deeper understanding of the immune response to M. tb, we now can transform our approach to TB prevention. To move TB science into the 21st century, NIAID is working to bridge basic and clinical research by applying innovations in systems biology; genomics and bioinformatics; animal modeling; and contemporary immunologic and molecular tools to the outstanding questions concerning human immunity to TB. We now have an unprecedented opportunity to learn from the successes and failures of several TB vaccine candidates currently in or soon entering clinical trials. A transformation in our understanding of protective immunity against TB in humans can become a reality through the inclusion of systematic and targeted biomedical studies in TB vaccine trials conducted worldwide. Such research will be aided by the comprehensive clinical trials infrastructure and the engagement of the scientific communities that NIAID and other agencies support in TB-endemic countries.

Getting the first new TB vaccine expeditiously into the hands of health care workers can be accomplished only through continued and close collaboration among all stakeholders. The new Blueprint provides a roadmap for this coordination and for scientists to address practical and relevant fundamental and translational questions, and for funders to maximize resources in the current economic climate.

NIAID is a long-standing and proud partner in the global fight against TB, and we remain committed to supporting fundamental research and the translation of scientific knowledge into new candidate TB vaccines consistent with the objectives set out in the Blueprint. We are confident that our efforts, together with those of
our many partners, will bring TB vaccine research squarely into the 21st century and accelerate our common goal of eliminating this ancient scourge.

**Conflicts of interest**

The authors have no conflicts of interest to declare.
A central dogma in the tubercular realm is that a vaccine that prevents adolescents and adults from developing infectious tuberculosis would be the single greatest advance in the global fight against the disease. In 1998, Barry Bloom chaired an NIH-led effort to draft a plan to develop such a vaccine. The resulting plan acknowledged the fundamental “catch 22” that one can’t rationally develop an effective vaccine if one does not understand the nature of protective immunity while one can’t determine the nature of protective immunity without an effective vaccine\(^1\). In order to address this fundamental conundrum a number of consultative meetings, including one held at the Gates Foundation in 2002, prioritized rapidly moving the most clinically advanced candidates into human testing.

And yet, at that time TB vaccine development was a moribund field, mired in a vicious cycle of futility. Simply stated, the prospect of obtaining data to show the ability of a TB vaccine to protect humans was grim. There were no credible vaccine candidates that had been developed such that they merited overcoming the financial and logistical barriers of advancing into clinical trials. This was in part because these barriers were enormous – a lack of clinical trials capacity meant that advancing into a regulatory quality proof of concept trial included the financial brunt of building trial site capacity. In the absence of impending trials there was no justification for public or private investment in developing trial capacity. In the absence of resources, industry style vaccine development programs and experienced vaccine developers had no interest in tuberculosis. Finally, in the absence of programs and developers there were no credible candidates that merited clinical trials. And this vicious cycle repeated itself on and on and on...

However, following the publication of the 1998 blueprint and in the context of increased focus on global health and vaccines, a cascade of events ensued that began to chip away at every challenge that perpetuated that vicious cycle. A few candidates underwent industry style preclinical development. Some of these entered into early phase human trials. Importantly, significant investments were made – largely based on the fundamental belief that vaccines could be developed. These investments attracted experienced vaccine developers who built strong clinical development programs that yielded increasingly credible candidates and the ecosystem of TB vaccine development began to change.

Because the majority of these activities were focused on the strategic goal of rapidly generating human protection data they primarily included two constrained sets of activities. Firstly, because there was no rational reason to prioritize one candidate over another, the vaccine candidates were selected to move into humans primarily based on which were furthest along in the preclinical development process. Secondly, clinical vaccine testing capacity was developed at centers selected for relatively high rates of TB in populations that were felt to be the most easily studied.

In aggregate, these activities comprise a decade of previously unimaginable progress. An infusion of greater than 600 million USD between 2005 and 2010\(^2\) has allowed more that fifteen vaccines to be tested in more than 50 human trials\(^3\). In addition, it has created a pipeline with five candidate vaccines in serious preclinical development programs and additional 33 novel candidates are in early pre-clinical development. In the process clinical trial capacity has been developed in the US, Europe, Africa, and Asia. And serious TB vaccine development programs exist in the private (GSK, Sanofi Aventis and Oxford/Emergent) and the public sectors (Aeras, TBVI, IDRI).

However, as we realize the dream of the last blueprint and start to see regulatory quality human protection data on candidates that could be rapidly manufactured at scale, we face critical challenges – many of which are an inevitable downside to the strategic choices made a decade ago. Because the field prioritized candidates primarily on proximity to the clinic, human data will be available for a group of vaccines that were not optimized for diversity. Moving forward we will need to rapidly push more innovative and heterogeneous candidates through the pipeline. In order to get fast results, Phase IIb studies were conducted in highly selected populations. Moving forward, difficult decisions will need to be made about how to move these candidates into populations in which the vaccine will have the most epidemiologic impact. A focus on clinical development has been associated with a dearth of investment in and collaboration with fundamental researchers and it is not clear that we are fully prepared to learn all that can be deduced from human samples to understand the nature of protective immunity. Moving forward, we need to engage the best fundamental and quantitative scientists in deconvoluting these clinical trials. Fortunately, with the persistent NIH investment in fundamental immunology and their, and others’, increased investment in clinical trials capacity, the future looks promising. And finally, as we anticipate product development success, it becomes increasingly clear how much we have yet to learn about vaccine adoption and dissemination pathways.

Coordination and collaboration are the key elements needed in...
In order to address these challenges and minimize new ones going forward. These elements underline the importance of the current blueprint which outlines a plan for the coming years. This plan includes issues related to R&D, correlates of protection, clinical trial design, vaccine selection and advocacy. It should serve as a blueprint for increased resource mobilization – clearly articulating specific opportunities that play to the comparative advantage of different donors to enable TB vaccine development in the coming decade.

Indeed, there are innumerable reasons why the field of tuberculosis is so well positioned to make unprecedented progress as we move into the Decade of Vaccines. But the most important, is that we have moved from a moribund vicious cycle to a vibrant virtuous one. We embark upon the Decade of Vaccines in an ecosystem in which the dream of having the best and the brightest individuals, institutions, companies and countries working together on this blueprint to deliver an improved lifesaving TB vaccine can be realized.

Conflicts of interest

The author has no conflicts of interest to declare.

References

Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade

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1. Purpose of TB Vaccine Blueprint

The Purpose of the “Blueprint” is to provide a meaningful and creative detailed plan that outlines a comprehensive strategy for developing and introducing safe and effective TB vaccines over the next decade.

Tuberculosis (TB) remains an urgent global health problem with about 9 million new cases and 1.4 million deaths each year. An estimated one third of the world population is latently infected with Mycobacterium tuberculosis, and at risk of developing TB. The dual pandemic of TB and HIV/AIDS and the increasing emergence of (multi) drug-resistant strains severely aggravate the problem and hamper current control strategies. The present decline in incidence is insufficient to reach the global target of elimination of TB in 2050 and new more effective tools, including new vaccines, are urgently required.

The current vaccine strains M. bovis Bacille Calmette-Guérin (BCG) protect against severe progressive TB in children but are inconsistent in protecting against the predominant adolescent or adult form of TB, notably pulmonary or lung-TB. This is the contagious transmittable form of the disease. Furthermore, BCG has recently been shown to be unsafe in HIV-infected infants and its use in this population is no longer recommended by WHO. New vaccines are needed that are safe in HIV infected infants as well as in other immuno-compromised individuals, and effective against all forms of TB in all age groups and in all global populations. The ability of the new vaccines to reduce TB transmission needs to be specifically addressed.

In the last decade, much progress has been made: a rich pipeline of new vaccine candidates has emerged; fifteen candidate TB vaccines have entered clinical trials; promising activities for development of new biomarkers have emerged; capacity for vaccine production and carrying out (large-scale) clinical trials is present and being developed in endemic countries; basic information on safety and immune responses to a variety of first generation TB
antigens is now available. The effectiveness of these vaccines in controlling TB will be revealed over the next several years and plans for regulatory approval, delivery and access of effective vaccines, including combination vaccines, are being established.

Despite this progress, we still have a profound lack of understanding of what constitutes protective immunity in different age groups and populations against TB. In addition, there is no correlate or surrogate endpoint of protective immunity, so the success of new TB vaccines cannot be predicted or identified in experimental animal models or early clinical trials, thus necessitating evaluation of efficacy against clinical endpoints in long, protracted and costly clinical trials. Moreover, it is unlikely that the current TB vaccine pipeline will be able to cover all target profiles required for the needed global TB vaccination strategy. Thus, research on TB vaccines and TB biomarkers needs to be intensified and adequately supported. New animal and human challenge models and objective criteria for down selecting vaccines for the various target profiles are urgently needed, especially vaccines preventing reactivation of latent 

\[ \text{Mycobacterium tuberculosis} \] (Mtbc) infection (a target population of over 2 billion worldwide). To mobilize increased resource at all levels, effective advocacy, communication and fundraising strategies will be essential.

**Vision:** To introduce the safest and most effective TB vaccines that reduce tuberculosis worldwide through partnerships, innovative strategies and creative mechanisms.

Over the past year, the TB vaccine community identified a need to develop a detailed plan or Blueprint that could provide scientists, clinicians, vaccine manufacturers, global health policy makers and donors with:

- a clear picture of the current status of TB vaccine development,
- an outline of the major scientific challenges faced by the TB vaccine community,
- a list of key areas where efforts should be prioritized to enhance the successful advancement of TB vaccines over the next decade.

Discussions on the Blueprint began at the Second Global Forum on TB Vaccines (September 22–24, 2010, Tallinn, Estonia) and have continued with input from various vaccine developers, stakeholders and the scientific community. The process has been coordinated through the StopTB Working Group on Vaccines with support and contributions from the WHO, Bill & Melinda Gates Foundation, Aeras, TuBerculosis Vaccine Initiative (TBVI), the US National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases, and other organizations recognize the importance of TB vaccines. Priority areas have been selected based on surveys of researchers, clinicians, pharmaceutical companies, governmental and non-governmental organizations, donors and other stakeholders familiar with TB vaccine development. The Blueprint has also benefited from discussions held at specific meetings and conferences including the “out-of-the-box” meeting held in Annecy France in September 2010 (organized by the Task Force on New Approaches to TB Vaccine Development of the STOP TB Working Group on New TB vaccines), the Keystone Symposium on Tuberculosis in Vancouver, Canada (January 2011), the TBVI Symposium preceding the NEWTBVAC meeting in Les Diablerets (February 2011), and Clinical Research Issues and Advocacy, Communication and Social Mobilization task forces of the STOP Working Group on new TB vaccines (summer of 2011). The critical priorities and major activities appearing in the Blueprint have been assembled from the thoughtful contributions of many during this year long process.

We also want to recognize that this current effort stands on the shoulders of the first “Blueprint for Tuberculosis Vaccine Development” developed at a Workshop sponsored by the National Institute of Allergy and Infectious Diseases, held in 1998 and chaired by Barry Bloom that recognized the need to jump-start the TB vaccine field by encouraging human clinical studies of the best candidates available at the time. A statement from this document describes well why new TB vaccines are critical to the control of global tuberculosis:

“One of the historic ironies of tuberculosis research is that it has always been assumed that the current interventions would eliminate this disease as a major public health problem. BCG, an attenuated bovine tuberculosis strain was discovered in 1908, and was thought to be the vaccine for tuberculosis. Streptomycin in the 1940s was hailed as the wonder drug for tuberculosis. Yet even with better antibiotics, tuberculosis remains a major global health problem. Concomitant with these historically shortsighted miscalculations were reductions in support for research on new tools and strategies, based on the assumption that with existing interventions the disease would disappear. It has not.”

In *Tuberculosis vaccines: A strategic blueprint for the next decade*, we recommend a renewed, intensified and well integrated international effort to develop TB vaccines that will have a significant global impact on tuberculosis and five key priority areas have been identified for advancing TB vaccines over the next decade.

**Five keys to progress**

- Creativity in research and discovery.
- Correlates of immunity and biomarkers for TB vaccines.
- Clinical trials: harmonization & cooperation.
- Rational selection of TB vaccine candidates.
- The critical need for advocacy, community acceptance and funding.

Each of these “Keys to progress” is discussed in detail below. Critical activities for each of the priority areas are described and are provided as action items and as areas where interested parties should focus their efforts (see Appendix 1). Key questions that arose during the many meetings and discussions are also grouped under the five keys to progress topics (see Section 3). We hope this document demonstrates to donors the commitment of the TB vaccine community to this crucial endeavour and encourages additional creative ideas to help us reach our goal of having safe and effective TB vaccines to prevent and control this devastating disease.

2. Tuberculosis vaccines: a strategic blueprint for the next decade

**2.1. Creativity in research and discovery**

To date, the approach to TB vaccine development has been mostly empirical following a common pattern of using a scientific rationale for antigen or live vaccine selection, screening using available TB animal models, selection of a delivery approach as a live recombinant vaccine (BCG or attenuated Mtbc), adjuvanted protein or viral-vectored vaccine and partnering with a manufacturer who can produce GMP lots of vaccine for human testing. Twelve of these TB vaccine candidates are in clinical trials in 2011 and efficacy data from the most advanced candidates will be available in the next few years (see Appendix 2). Until that time it will be unclear if these vaccines will be successful and address the many forms of TB disease. Since there is a lack of knowledge in key areas of TB immunology, microbiology, pathology, molecular biology and vaccinology, innovative research approaches are needed to address these critical areas in TB vaccine research. There is a crucial need at this time for scientists and clinicians with various expertise supported by generous research institutes to address the critical gaps in our understanding of tuberculosis disease and the *Mycobacterium tuberculosis* pathogen.
Three critical activities in research and discovery

1. Use out-of-the-box approaches and advanced technologies to identify mechanisms of protective immunity for tuberculosis.

2. Expand the antigenic vaccine repertoire and introduce new antigen combinations to prevent infection and provide sterilizing immunity.

3. Facilitate translational research, comparative preclinical studies and animal models that mimic human TB disease.

The critical activities are discussed in detail below.

2.1. Use out-of-the-box approaches and advanced technologies to describe mechanisms of protective immunity for tuberculosis

We know surprisingly little about what exactly constitutes protective immunity in humans. Most persons infected with the Mtb pathogen control the disease and are “latently” infected and show none of the hallmarks of active disease. The immune mechanisms responsible for this “resistance” to disease remain elusive. In addition, in contrast to other infectious diseases there is no evidence that people who recover from TB disease or who are latently infected with Mtb are protected from subsequent reinfection. There is an urgent need to reveal the true nature of the immune mechanisms responsible for natural resistance to disease and to design a vaccine that elicits a response that is superior to natural immunity induced by infection with Mtb. A thorough understanding of the very earliest events of infection with Mtb and their consequences is needed.

The T cell mediated response is thought to be a central feature of protective immunity and most empirical approaches have focused on the ability of a vaccine to induce a dominant T cell mediated immune response. The contribution of regulatory immune pathways, the innate immune response and antibody mediated mechanisms to protection has remained largely unexplored. While vaccine approaches focus on reduction of pathology or bacterial replication it may also be useful to focus on reduction of transmission. Antibody-mediated mechanisms may be particularly important for such transmission blocking vaccines and should be further explored in this context.

2.1.2. Improve the antigenic vaccine repertoire to prevent infection and provide sterilizing immunity

No TB vaccine to date has provided clear evidence from animal models that it can block lung infection, provide sterilizing immunity or reduce transmission within populations. In addition, the current subunit vaccines mostly include antigens that are representative of those expressed during early stages of infection and there is an under representation of antigens expressed during late and latent stages of infection. In contrast to the protein antigen repertoire, the glycolipid and polysaccharide repertoire of Mtb has largely remained unexplored in vaccines and provides a unique opportunity to extend the repertoire for TB vaccine development. In addition to their antigenic properties, lipids often have intrinsic adjuvant properties which may make these molecules especially suitable for vaccine applications. Subdominant antigens or antigenic epitopes may, in general, be undetectable in the immune responses found in infected individuals or TB patients, but may be uncovered when dominant epitopes or antigens are not present in the vaccine repertoire. The use of non-conserved, sequence variable antigens of Mtb which could prove to be conformationally conserved, and a better understanding of antigens involved in Mtb host immune evasion mechanisms should also help in the design of vaccines, particularly live whole cell vaccines. Lastly, there is an urgent need for collaborative efforts to advance the use of novel adjuvants for TB vaccines. The antigenic repertoire currently used for TB vaccine development could well be suboptimal and the use of stage specific, less dominant, and more sequence variable antigens recruiting novel populations of immune cells should be vigorously explored.

2.1.3. Facilitate translational research, comparative preclinical studies and animal models that mimic human TB disease

Animal challenge models for tuberculosis including mice, guinea pig, non-human primates, and other models for certain targets such as latency and models that mimic immuno-suppression have an important role in TB vaccine development but there is considerable room for improvement in both how these models measure protection and how well they mimic human TB disease. New or better animal models that enable assessment of protective responses for specific human target populations (including natural infection) and for defining correlates of protection are urgently needed. There is an urgent need for standardization of existing models and for the development of new promising models such as cattle and pig transmission models. New technologies for measuring vaccine responses in animal models such as modern imaging technologies should also be explored.

Coordination of TB research efforts by the European NEWTB-VAC consortium and within the U.S. National Institutes of Health contract laboratories would help standardize animal models and expedite the selection of new TB vaccine candidates. Comparative studies using the lead TB vaccine candidate in a vaccine category are very important for selecting new candidates to enter into the vaccine pipeline (see Section 2.4). There is also growing evidence that Mtb strains can differ both genotypically and phenotypically; therefore, there is a need to use circulating human clinical isolates as challenge strains in preclinical models. Since preclinical data is critical for entry into early clinical trials, it is very important that models be developed and adapted for use for vaccine submissions to regulatory agencies to address issues of safety, immunogenicity and effectiveness required for regulatory approvals. There is a belief in the TB vaccine community that much can be learned from experimental failures therefore this data should be published or made available through information sharing mechanisms. Also, TB vaccine development can benefit from the successes and failures of others especially those researching malaria, HIV and cancer vaccines.

2.2. Correlates of immunity and biomarkers for TB vaccines

Next to the identification of safe and effective TB vaccines, no issue is more critical to the success of testing and introducing new TB vaccines than the discovery of biomarkers that predict vaccine efficacy, that serve as useful markers of vaccine success or that correlate with natural protection and susceptibility. Correlates and biomarkers can significantly reduce the subject numbers and timelines of clinical trials of new vaccines, and can serve as the basis of human immunoassays to measure the biological potency of vaccines and the stability of manufactured vaccines at an early stage. Substantial efforts to identify an immuno-biological marker for TB vaccines have led to a small number of signatures that continue to be evaluated (e.g. http://www.biomarkers-for-th.net/). However, most of these efforts have not been successful and new innovative approaches are required to determine correlates of immune protection for TB vaccines, as well as markers that correlate with disease risk following infection. This is an area where new technologies and the willingness to create innovative partnerships across scientific fields will likely yield the most benefit.

IFN-γ is widely believed to be important in protective immunity to Mtb, yet it appears not to be a useful biomarker (surrogate end point) of protection. Genome-wide host gene expression profiling studies are providing new information, pointing to novel host biomarker signatures of both protective immunity and disease activity. These results may help in identifying potential correlates of protection, and also unravel cellular pathways involved in the pathogenesis of and resistance to Mtb. Recent studies have
described new biomarker signatures correlating with and possibly predicting the outcome of infection.

Such "omic" approaches, including functional genomics and immunology, will be important in obtaining new insights, and should be supported to decipher the pathways responsible for TB resistance and susceptibility. An alternative approach to developing clinically relevant biomarkers would be to focus on markers that are associated with disease progression or remission. Longitudinal assessment of a range of clinical markers can provide a sensitive and specific indicator of vaccine effects through modulation of the disease state. These markers can also be useful for measuring specific vaccine uptake in clinical vaccine trials.

Three critical activities in correlates of immunity and biomarkers
1. Explore novel (high risk) approaches using immunological, transcriptional and other biological state-of-the-art technologies to identify correlates of immunity for tuberculosis.
2. Introduce novel assays into vaccine trials to establish a surrogate of protective immunity.
3. Identify signatures of efficacy that can be used as readouts for induction of protective responses in TB vaccine studies.

2.3. Clinical trials: harmonization & cooperation

Clinical testing of new TB vaccines is complicated not only by the difficulties and expense of performing clinical trials in regions where tuberculosis is endemic but also by the nature and variability of the novel candidate vaccines being tested, which include viral vectored, protein subunit with adjuvant and live recombinant vaccines. Unlike other vaccines which have recently been introduced first in industrialized nations, such as pneumococcal, rotavirus and HPV, TB vaccine formulations are being tested for the first time in large human populations in emerging economies and developing countries and this presents investigators with significant scientific and logistical challenges. Challenging aspects of clinical studies beyond Phase I include disease endpoint definition, immunological assays, safety profile assessments, immunization regimens and laboratory capabilities and these will need to be implemented in large samples sizes that will be required, these are inadequate. Trial sites developed for other types of vaccines are now being drawn into the TB vaccine arena but it should be kept in mind that specific laboratory and clinical expertise is also needed for TB vaccine trials. But, even if vaccine developers work together on sharing trial sites (already happening to some extent, and greatly facilitated by bodies such as the European and Developing Countries Clinical Trials Partnership, NIH, TBVI and Aeras), there is still the question of how many vaccine candidates can reasonably be tested in a single location. There is already a clear realization that for a really large-scale Phase III efficacy trial, perhaps not many more than two of the strongest candidates could be accommodated. A reasonable approach might be to define large, global networks that would aim to conduct specific types of trials for promising vaccine candidates.

2.3.2. Design clinical trials with appropriate endpoints for determining an acceptable efficacy for TB vaccines

An ideal trial design requires a population with a high incidence of TB and a competent immune system where specific endpoints are easily determined. The absence of an immune correlate of protection means that it will be critical to carefully define clinical endpoints that are versatile; that is, specific but broad enough to maximize endpoint accrual in an efficacy trial. There is consensus that microbiological endpoints are likely to be the mainstay of primary endpoints for trials in HIV negative and positive adults and adolescents. It is important to discuss endpoints with regulatory authorities who may prefer less complex endpoints that give clear case definitions for clinical trial analysis.

What has become clear is that clinical endpoints for infant clinical trials will be particularly challenging. This is because TB is a pauci-bacillary disease in infants so microbiological confirmation of disease is rare. Thus, evidence of exposure to Mtb in combination with symptoms and radiological features have been proposed as an endpoint for this target group. However, these features
may lack specificity even in combination and there is a risk of undermining efficacy measures when specificity is in doubt. This will be a key area for further attention. Infants are a priority target for replacement and prime-boost vaccines as well as accurate assessment of efficacy in this group is essential.

An adaptive trial design that can drop ineffective or reactogenic candidates, or modify group sizes based on predefined criteria could accelerate the clinical development of a vaccine. However, the robustness of the statistical analysis will be changed by eliminating groups that were originally planned for analysis or revising group numbers. Another challenge for adaptive trial design is that because of the chronic nature and subacute course of TB disease, clinical endpoint trends only occur late during trial conduct, making early changes to enrolment distribution amongst different sites difficult. Such effects need to be considered when introducing adaptive trial design into a trial protocol.

Given the low reproductive number for TB, an efficacy level of 60% may have a major public health impact on the TB epidemic. Since we are in the early stages of finding vaccines that would improve on BCG, modest efficacy goals may be appropriate and in concert with the malaria vaccine field. A trial that identifies even a partially effective vaccine would generate specimens that could help identify correlates of immune protection to guide future vaccine design and development.

### 2.3.3. Address regulatory and ethics issues and plan for post-licensure sustainability

The regulatory and ethics expertise in endemic countries needed for approving TB vaccine clinical trials is limited. Developing creative strategies for obtaining timely regulatory approvals while assuring the quality of the review and protecting clinical subjects is an important part of the TB vaccine development process. It is important to engage regulatory authorities early in the development process so that sponsors can receive advice from regulators on clinical trial design, endpoints and ethical issues. Working with regional regulatory harmonization initiatives such as the African Vaccines Regulators Forum (AVAREF), a pan-African regulatory body coordinated by the WHO, can be very valuable for discussing regional clinical vaccine issues and also serves as a capacity building activity for less experienced regulatory agencies. Plans for global recommendations, vaccine qualification and distribution of new TB vaccines will require coordination with programs administered by the World Health Organization.

Given where we are with TB vaccine development, not only do we need to plan for Phase III vaccine trials, but there is also a need to look beyond to the post-licensure aspects of vaccine implementation. Postmarketing surveillance is critical for assessing the potential for rare adverse events and there is a need to establish mechanisms for assuring the sustained quality of TB vaccines following marketing authorization and distribution.

### 2.4. Rational selection of TB vaccine candidates

Potentially as important as scientific challenges, establishing comprehensive, measurable and globally acceptable criteria for selecting, assessing and advancing the best vaccine candidates that are in the pipeline is one of the most crucial issues in the TB vaccine community. Unless vaccine candidates fail safety or immunogenicity testing in early trials or are studied in comparative clinical studies, it will be difficult to determine which are likely to be the safest and most effective. Likewise, identifying acceptable specific criteria that can select the most promising candidates from among a large portfolio of preclinical research candidates for human clinical studies is a significant challenge. Perhaps just as challenging is obtaining general consensus for the use of these criteria within the TB vaccine community.

The general development pathway for vaccines can be considered as a series of phases or stages with assessment and selection occurring at a gate between each stage using multiple criteria to determine if candidate products proceed to the next stage (see Fig. 1).

A key factor for sponsors, who are managing significant portfolios of products, is the difficulty, given the current understanding of immunology and protective immunity in tuberculosis, to be able to select the best candidates from a number of possible candidates. Experience to date has indicated that current preclinical (or non-clinical) testing methods may have difficulty distinguishing or recognizing superiority among candidates of a similar vaccine strategy. For the purposes of selecting specific candidates to advance from discovery to early preclinical development, clear criteria for acceptable test data in the areas of production, product characterization, target product profile, safety, immunogenicity, efficacy, clinical, regulatory, business and health impact are needed. If a candidate can meet all or most of the criteria, even if not fully developed, then there is a case to be made for including the candidate within a rigorous product development portfolio. This would provide an opportunity to further develop the product and work towards a more robust data package that can provide support for development through pre-clinical development to early (Phase I/IIa) studies in humans. At present the “gates for vaccine development” provide specific points at which a decision to invest significant funds is a requirement to advance the product to the next stage. Head to head comparisons within agreed upon model systems can help determine if a product meets the characteristics mentioned above. Use of standardized assays among laboratories evaluating clinical specimens or use of a centralized laboratory, would also enable comparison among different candidates. Limitations on resources, both financial and clinical, apart from formidable ethical considerations, demand a structured and transparent “rational selection” process for advancing TB vaccine candidate in the modern world.

**Two critical activities in rational selection of TB vaccine candidates**

1. Establish comprehensive measurable and globally acceptable criteria for selecting, assessing and advancing vaccine candidates through preclinical and clinical phases of development.
2. Obtain consensus within the TB community on stage-specific criteria for moving new candidates through various stages of development from research to preclinical and through subsequent phases of clinical trial testing.

![Figure 1](image-url)
2.5. Building support through advocacy, communications and resource mobilization

Modeling studies show that more effective vaccines are essential if we are to reach the global target of eliminating TB. However, there continues to be a lack of adequate global awareness about both the urgent need for new TB vaccines and the tremendous progress that has been made toward that goal. There is a need to increase the profile of TB vaccine research at global, national and community levels in order to generate support and political will, to increase investment in TB vaccine research, to create an enabling and supportive environment for clinical trials, and to lay the groundwork for acceptance and adoption of new TB vaccines once licensed. To effectively accomplish this, we must prioritize advocacy, communications and resource mobilization.

Three critical activities in advocacy, communications and resource mobilization

1. Expand financing to provide sufficient resources to advance and sustain research on TB vaccines.
2. Continue and expand on efforts to raise awareness of the role of new TB vaccines as part of a comprehensive response to the global TB epidemic, and build support at all levels.
3. Broaden the base of advocates, allies and champions for TB and vaccine R&D.

The critical activities are discussed in detail below.

2.5.1. Expand financing to provide sufficient resources to advance and sustain research on TB vaccines

There are many challenges to mobilizing resources and support for TB research. Apart from the generous support of the Bill & Melinda Gates Foundation, the majority of funding for TB vaccine research and development is provided through the US National Health Institutes, the EC Framework Programmes and other governments and governmental organizations. The global economic crisis has made securing additional funding from these and other sources more difficult, and there is increasing pressure on research and donor agencies to demonstrate the value of their investments. Because the benefits of a new TB vaccine will take years to be realized, it can be difficult for funders to balance the immediate need to diagnose and treat those who are already sick with investing in long-term solutions.

Traditional funding sources are critical, but will not be sufficient to cover the full costs of global TB vaccine development. New funders need to be identified; partnerships and collaborations need to be supported; opportunities for cost-sharing across sectors and utilization of existing resources need to be sought; and new innovative financing models should be explored. Emerging economies, and particularly the “BRICS” countries (Brazil, Russia, India, China and South Africa), will play an increasingly important role in global health and will be important partners in global efforts to develop new TB vaccines. These countries – and particularly India, China and South Africa – have both a high burden of TB and the infrastructure and resources to be part of the solution for their countries and for the world. These opportunities should be tapped and integrated into current global efforts to develop new TB vaccines.

2.5.2. Continue and expand on efforts to raise awareness of the role of new TB vaccines as part of a comprehensive response to the global TB epidemic and build support at all levels

A greater understanding of the complexities of global control of TB, as well as the shortcomings of the currently available BCG vaccine are necessary to stimulate demand for new TB vaccines from communities, national level policymakers, decision makers and international leaders who help set global health priorities and action. In order to build public and political support for new TB vaccines and to secure the funding required to advance the field, it will be important to provide donors, policymakers, health care providers, civil society and other key stakeholders with information and evidence to support investment in TB vaccines. Recent public health impact modeling should be more broadly communicated and disseminated, and cost-effectiveness modeling should be expanded upon. Linkages between TB and other global health and development issues, such as HIV/AIDS and maternal and child health, the threat of MDR and XDR-TB and the contributions that new TB vaccines could make to advance the global health and development agenda should be more fully explored.

By necessity, large-scale clinical trials of new TB vaccines will be conducted in endemic countries. As with all research, there is the potential for controversy, misinterpretation or misinformation regarding clinical trials of new TB vaccines. Therefore, it is critically important to inform and engage the media, government officials, NGOs, affected communities and other key stakeholders at the community, regional and country level about the value of TB vaccine development efforts and clinical trials in order to ensure transparency, generate a supportive environment and reduce the probability of misinformation or negative public response to clinical trials.

2.5.3. Broaden the base of advocates, allies and champions for TB vaccine R&D

In order to be successful in mobilizing resources and support for TB vaccine R&D, it will be imperative to expand the base of advocates, allies and champions that support this goal and ensure that TB vaccine research is included in the global dialogue. We must look beyond the TB community and engage with the broader global health community, emphasizing the alignment between TB research and global health and development. We need to better utilize existing champions and seek new ones.

It will also be critical to link the advocacy and research communities, which have too often operated independently of each other. Researchers can play a very important role in advocacy by translating research findings and providing the scientific evidence to support key messages, and lending credibility to research advocacy efforts. As national budgets across the globe are being cut and difficult decisions on spending are being made, researchers and advocates for the vaccines must work together to promote the need for continued and expanded investment in global health research.

As has been observed for other successful global vaccine programs such as the introduction of pneumococcal and meningococcal vaccines, the efforts of all parties including scientists, global organizations, public health agencies, pharmaceutical companies and community advocates working together with support from donors are critical to accelerate the development and introduction of new TB vaccines.

3. Implementation

Numerous discussions and surveys of the TB vaccine community were used to identify the priorities outlined in this Blueprint. In addition, important questions that need to be addressed were highlighted during these discussions and some are organized here under the Five Priority areas.

It is clear that to address these challenging questions and to implement the critical activities outlined in the Blueprint a consortium of partners will be needed. Much as the Product Development Partnerships initiated by the Bill and Melinda Gates Foundation are successful because they coordinate and facilitate partnerships among academics, pharmaceutical and biotech companies, governmental and non-governmental organizations; implementation of the recommendations offered in the Blueprint will also require an
active and sustainable consortium of partners responsible for the
various tasks outlined in the document. Leadership will also be
crucial to the implementation and success of the Blueprint ideas.

Vehicles to enhance communication and exchange information
among partners is a vital activity needed to ensure the continued
engagement required to solve the questions raised in the Blueprint.

Establishment of trusted global organizations or consortia that can
broker partnerships, need to be funded so they can coordinate
meetings, establish useful websites and offer venues that solve
problems in a timely manner. Also, critical for success is the estab-
ishment of links to organizations developing similar products for
neglected global diseases other than TB so that lessons learned and
solutions to common problems can be effectively communicated to
the TB community. The organizations developing new diagnostics
and drugs for TB should work closely together with the vaccine
community to effectively reduce TB disease in at risk communities.
Introduction of new safe and effective TB vaccines will not be
successful without the assistance and acceptance of the populations
targeted for new TB vaccines. Their willingness to participate in
investigational clinical studies and to help introduce effective vac-
cines into their communities is perhaps the most important need of
all. It is clear that the global problem of tuberculosis requires global
solutions.

Appendix 1. A summary of the critical activities outlined in the
Blueprint

Recommended critical activities for TB vaccine development

Research and discovery
1. Use out-of-the-box approaches and advanced technologies
to identify mechanisms of protective immunity for
tuberculosis.
2. Expand the antigenic vaccine repertoire and introduce new
antigen combinations to prevent infection and provide
sterilizing immunity.
3. Facilitate translational research, comparative preclinical
studies and animal models that mimic human TB disease.
Correlates of immunity and biomarkers
4. Explore novel (high risk) approaches using immunological,
transcriptional and other biological state-of-the-art
technologies to identify correlates of immunity for
tuberculosis.
5. Introduce novel assays into vaccine trials to establish a
surrogate of protective immunity.
6. Identify signatures of efficacy that can be used as readouts
for induction of protective responses in TB vaccine studies.
Clinical trials
7. Determine TB prevalence and incidence, select trial sites
and choose target populations for TB vaccines that result in
the greatest reduction in disease.
8. Design clinical trials with appropriate endpoints for
determining an acceptable efficacy for TB vaccines in
different target populations.
9. Address regulatory and ethics issues and plan for
post-licensure sustainability.
Rational selection
10. Establish comprehensive measurable and globally
acceptable criteria for selecting, assessing and advancing
vaccine candidates in human clinical studies.
11. Obtain consensus within the TB community on
stage-specific criteria for moving new candidates through
various stages of development from research to preclinical
and through subsequent phases of clinical trial testing.
Advocacy, partnerships and funding
12. Expand financing to provide sufficient resources to advance
and sustain research on TB vaccines.
13. Continue and expand on efforts to raise awareness of the
role of new TB vaccines as part of a comprehensive response
to the global TB epidemic, and build support at all levels.
14. Broaden the base of advocates, allies and champions for TB
and vaccine R&D.

Key questions for TB vaccine development

Research and discovery
• Why are certain Mtb infected individuals resistant to TB
disease?
• Can vaccines prevent infection and provide sterilizing
immunity?
• Will investigators cooperate to combine new Mtb antigens
with novel adjuvants to develop the best TB vaccines?

Correlates of immunity and biomarkers
• Are there new approaches for identifying correlates of
immunity for TB vaccines?
• What are the key cells and effector pathways that control
host protective immunity to M. tuberculosis?
• Can more relevant models of human TB disease be
developed?
• Are antibody responses to TB vaccines relevant to
protection?
• Is it possible to develop a useful human challenge model for
TB?
• How can specimens from TB vaccine trials best be utilized to
learn about correlates and guide future vaccine design and
evaluation?

Clinical trials
• What are the best clinical strategies for showing that
vaccines can effectively prevent the reactivation of latent TB
disease?
• Can vaccines effectively reduce transmission of Mtb?
• How can organizations performing clinical studies in areas
endemic for infectious diseases best share trial site
infrastructure to expedite clinical trials of vaccines?
• What are the best strategies for studying therapeutic TB
vaccines?

Rational selection
• Will all vaccine developers agree to use a standardized
criteria approach for selection and development of novel TB
vaccines?
• Will vaccine developers participate in comparative
preclinical and clinical vaccine studies if their vaccine is in
clinical trials?
• Can creative approaches be implemented that are acceptable
to regulatory agencies that shorten timelines without
compromising quality?
• What are the best criteria for measuring the public health
impact of vaccines?

Advocacy, partnerships and funding
• What innovative approaches can be used to mobilize
resources for TB vaccines?
• How do we best prepare communities for the acceptance of
a new TB vaccine?
## Appendix 2. The twelve TB vaccines currently in clinical trials (circa 2011)

<table>
<thead>
<tr>
<th>Global TB Vaccine Pipeline</th>
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<tbody>
<tr>
<td><strong>Phase I</strong></td>
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<td>AERAS-422</td>
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<td>Oxford-Emergent</td>
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<td>Tuberculosis Consortium</td>
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### Viral-vectored: MVA525A, AERAS-422, AdAg85A

### Protein/Adjuvant: M72, Hybrid-1, MVA525A, H56, rBCG, VPM 1002, AERAS-422

### Killed WC or Extract: Mw, RUTI

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Creativity in tuberculosis research and discovery

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ABSTRACT

The remarkable advances in TB vaccinology over the last decade have been driven by a pragmatic approach to moving candidates along the development pipeline to clinical trials, fuelled by encouraging data on protection in animal models. Efficacy data from Phase IIb trials of the first generation of new candidates are anticipated over the next 1–2 years. As outlined in the TB Vaccines Strategic Blueprint, to exploit this information and to inspire design of next generation candidates, it is important that this empirical approach is complemented by progress in understanding of fundamental immune mechanisms and improved translational modalities. Current trends towards improved experimental and computational approaches for studying biological complexity will be an important element in the developing science of TB vaccinology.

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1. Natural or supernatural immunity

Classical approaches to vaccination are based on the observation that recovery from initial infection is associated with markedly enhanced immunity to reinfection. This phenomenon is only weakly evident in the case of TB. While the initial phase of bacterial replication is truncated during a second infection in experimental animals, this results only in a relative reduction in pathogen load and not in the induction of sterilising immunity. In humans, neither prior latent infection nor recovery from active TB confers reliable protection against reinfection or reactivation disease. It can be argued therefore, that in contrast to classical “vaccine-preventable” diseases, an effective vaccine against TB will have to elicit a response that is superior to natural immunity.

A rationale to account for the weak or ineffective recall response upon natural exposure needs to be sought in the complexity of the host–pathogen relationship which largely remains unresolved for TB so far. Knowledge gaps exist in understanding the mechanisms of natural protective immunity and immunopathogenesis, as well as vaccine induced protective mechanisms. Protective efficacy is notoriously variable depending on the population that is targeted by M. bovis BCG vaccination. Well able to protect the young from meningeal TB, it most prominently fails against pulmonary disease later in life (the stage which drives the spread of the disease, see below). Immune maturation and immuno-senescence are active research areas awaiting to be integrated into our TB and vaccine research activities. These areas may benefit from new TB models like pigs which present a life cycle that is intermediate between that of mice and primates, making such maturation and senescence studies relevant and feasible.

Based on epidemiology and animal experiments it has long been suggested that pre-exposure to (non-pathogenic) mycobacteria compromises the effect of live BCG vaccination, but the immune mechanism behind this remains elusive so far. Current efforts to elucidate the influence of gut microbiome on immune regulation may stimulate novel relevant research opportunities. To improve our mechanistic understanding comprehensive clinical and preclinical research efforts should investigate vaccine failure as well as successful immunisation events. Although some level of BCG efficacy seems required as a comparative control in TB models, maybe a bolder approach of actively modelling BCG vaccine failure is necessary to generate the relevant contrast to learn about correlates that reflect protective mechanisms (biomarkers) rather than epiphenomena, and that promote rationalised vaccine improvement beyond the level of BCG.

An alternative perspective to explain the interaction of the host with the M. tuberculosis pathogen is that modern humans may have co-evolved with M. tuberculosis in the form of a relatively benign infection, with the current aggressive disease manifestations emerging as a consequence of recent increases in human population densities. It may be that our natural immune response is programmed to treat M. tuberculosis as a commensal organism requiring containment rather than elimination. This model is consistent with the evolutionary perspective emerging from mycobacterial genome analysis, and with the observed sequence conservation of dominant antigens that is in contrast to the antigenic diversity predicted to arise in genes that are under selective pressure from the immune system. This line of reasoning has interesting practical implications for selection of novel vaccine...
antigens. Rather than focusing on antigens that are dominant in the natural response – as indicated by strong recall responses during latent infection, for example – it may be preferable to try and displace the equilibrium of the natural response by recruiting novel populations of T cells that recognise sub-dominant or cryptic epitopes. Perhaps we should select the antigen repertoire for vaccination rather than relying on those that M. tuberculosis would like us to see. The restricted subset of antigen-encoding genes that do show evidence of genetic diversity – PE-PGRS proteins and some members of the Esx secretion family – may be interesting to explore in this context.11

A related hypothesis is that pathogenic strains of M. tuberculosis that are associated with aggressive disease have acquired the ability to subvert the natural immune response, for example by suppressing or delaying pro-inflammatory signalling. Many molecular cascades of innate host immunity and overlapping homeostatic signalling have been unravelled in recent years, and at the same time mycobacterial compounds like glycolipids and polysaccharides have been identified as agonists of such receptor-signalling systems.12,13 In the tradition of vaccination addressing adaptive immunity compounds such as sulfoglycolipids, may prove excellent vaccine targets for classical and non-classical (e.g. CD1b restricted) effector populations.14 Alternatively, such compounds may have a profound role in immune modulation possibly contributing to immune evasion.15 Incorporation of this latter concept into the rational design of attenuated mycobacterial vaccines suggests that, rather than the conventional approach of engineering vaccines to make them resemble the pathogen as closely as possible without causing disease, there may be positive immunological advantages in deliberately stripping away some of the characteristic attributes of M. tuberculosis.16,17

2. Blocking transmission

The power of vaccines as a public health intervention lies in their ability to reduce onward transmission of disease as much as in their ability to protect vaccinated individuals; a feature generally referred to as “herd immunity”. While BCG clearly provides a degree of protection to individuals, saving the lives of around 50 thousand children every year, wider public health benefit has been precluded by the absence of any measurable impact on TB transmission. There is a danger that new vaccine strategies that build directly on the BCG model may similarly fail to interrupt transmission, and it is important to consider whether blocking of transmission could be introduced as a potential endpoint in an early phase of vaccine assessment.

Transmission of M. tuberculosis is largely dependent on remodelling of human lungs to act as aerosol generators, and is contingent on a combination of bacterial replication together with immune-mediated pathology.18 While smear-positive sputum represents an approximate surrogate for infectivity, it is likely that the degree of infectiousness varies considerably over time and between individuals. Experimental models of vaccine efficacy tend to rely primarily on pathogen load in tissues as an indicator of effectiveness, though it is conceivable that some forms of immune-mediated reduction in bacterial numbers could actually result in enhanced pathology and transmission. In primate models, however, clinical parameters and systemic markers of inflammation have been shown to correlate with severity of lung disease by post-mortem pathology and (to a lesser extent) bacterial counts. Validation of such longitudinal surrogates of severe pulmonary TB in preclinical research would substantially improve upon quantitative statistically valid readouts as well as head-to-head or multi-centre evaluations of new vaccine candidates. While we lack tools to measure pathogen load in humans, it could be argued that a vaccine that was able to divert bacteria from pulmonary TB to extrapulmonary disease would represent an important benefit to public health, though with obviously limited appeal to individual patients.

Progressive pathology can be induced in a wide range of lower vertebrate animals by experimental infection with M. tuberculosis, but this rarely results in onward transmission of disease at a population level. In contrast, non-human primate species are naturally susceptible and upon infection present pulmonary disease (including coughing) reminiscent of transmissible “open TB” in man. Cases of transmission in closed populations have been reported. While old world monkeys, e.g. cynomolgus and rhesus macaques, may pose limitations regarding feasibility and affordability of study design, developing a TB model in social groups of smaller new world monkeys (e.g. marmosets) may prove a valuable investment towards meaningful transmission studies.

Also, animal-adapted forms of M. tuberculosis – the various sub-divisions of M. bovis – establish sustainable infections in cattle and other mammalian hosts such as badgers and possums. While bearing in mind the underlying species differences affecting both microbes and host immune mechanisms, it is attractive to consider whether these natural infection models could be used for proof-of-concept studies to assess the impact of vaccines on transmission.19 Conventional laboratory containment approaches involving negative pressure and continuous air changes reduce levels of natural transmission and this line of investigation requires design of alternative facilities, or reliance on “field studies” conducted in the less constrained environment of actual fields. More distant relatives such as M. marinum might offer the possibility of carrying out field studies of transmission under water.

While current clinical trials of new TB vaccines focus specifically on the primary endpoint of a reduction in disease incidence between vaccinated and unvaccinated individuals, it may also be useful to consider the potential design of trials with transmission endpoints. By exploiting rapid advances in genome sequence technologies, it may become possible to use changes in bacterial population structure as a marker of a successful intervention, supporting wide-scale evaluation of vaccine impact at a population level.

3. Systems vaccinology

An important trend in current immunology research is to move away from simple linear cause-and-effect models towards an appreciation of the importance of interacting networks of cells and molecules.20 This trend fits well with the consideration of TB as a multi-factorial and/or spectral disease that is affected by intrinsic host and pathogen factors as well as a microbial environment that modulates response profiles. While measurement of a single cytokine such as IFN-$\gamma$ might previously have been regarded as an indication of a “good” or a “bad” response, it is now recognised that the local environment of cells and cytokines is critical in determining the biological impact of an individual molecule. The emerging discipline of “systems vaccinology” places emphasis on quantitation of multiple molecular determinants and their inter-relations over time and in space.21,22 The initial effect of this approach is to generate vast datasets that require substantial mathematical input for analysis and interpretation, but it can be anticipated that patterns will progressively emerge from these clouds of data, and that these will generate a platform that will support a new science of truly “rational” vaccinology. An important aspect of this approach is that it provides a formal structure by which information from clinical trials can be fed back into fundamental research, completing a virtuous cycle in which discovery research and clinical observation are integrated into a programme of progressive vaccine improvement.23

Given the complexity already apparent in our understanding of the immune response, it is likely that TB vaccinology will have much
to gain from systems biology approaches and it is important that this thinking is incorporated both into the fundamental discovery phase and into the analysis of clinical trials.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

Ten challenges for TB biomarkers

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ABSTRACT
The availability of tuberculosis (TB) biomarkers of protection (or: “surrogate endpoints of protection against active TB” (Biomarkers Definitions Working Group, 2001)) would greatly facilitate and accelerate TB vaccine development and increase the likelihood of success. TB biomarkers of protection could determine which vaccines in clinical trials are the most efficacious; which vaccine candidates and strategies are the most promising in early stages in the preclinical development pipeline (including relevant antigens, antigen delivery, live vaccines); and which combination vaccines (prime/boost) would be the most effective. Here we discuss ten major challenges for biomarker identification and validation in TB. Current major roadblocks and critical limitations in understanding TB pathogenesis are highlighted, and new solutions and strategies proposed.

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1. Introduction
This special issue of Tuberculosis with “Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade” highlights the importance of identifying correlates and biomarkers for TB vaccines. An important aspect of developing and testing new tuberculosis (TB) vaccines is the ability to assess, at an early stage, whether a vaccine can induce protection against developing active TB disease. To assess this in preclinical studies and in clinical trials, biomarkers of protective vaccine efficacy against TB are needed. Currently, however, no biomarkers of protective vaccine efficacy, or of protection against natural infection exist. Most individuals infected with Mycobacterium tuberculosis (Mtb) are able to control Mtb infection in a latent state and do not develop any clinical symptoms of active TB disease. The host defense mechanisms responsible for this human “resistance” phenotype(s), however, remain largely elusive. Further, resistance may wane over time or with intercurrent immunosuppression caused by HIV infection or other co-morbidities, such as by immune deviation due to helminth co-infections. This may result in reactivation of the latent focus and in active TB disease. The basis for the loss of protection leading to active TB is equally unknown.

Currently, the only way to determine a vaccine’s protective potential is to compare it to BCG in the context of large-scale, long-term phase III efficacy studies. Such studies not only consume sizeable fractions of the globally available budgets for TB vaccine research, they also heavily engage available clinical field sites and thereby hamper the rapid evaluation of other vaccines. Further, the absence of early clinical data providing evidence that a vaccine induces protective immunity, increases the uncertainty and the risk of failure of initial trials, which would be a major set back to the field. The availability of true TB biomarkers of protection (Figure 1), more accurately termed “surrogate endpoints of protection against active TB”5–7 thus would greatly facilitate and accelerate TB vaccine development and importantly increase the likelihood of success. Surrogate endpoints could also be used to determine which of the vaccines currently in clinical trials – which were often developed relatively early in the new TB vaccine era – will prove to be the most efficacious. The availability of TB biomarkers of protection will allow more rapid and rationalized down selection of the best candidates and strategies at an earlier stage in the development pipeline, which may include selection of the most relevant antigens, delivery systems and routing, live vaccines, vaccine dosing and timing. Finally, such biomarkers could help in the decision process for combination vaccination, combining the best prime candidate(s) with the most appropriate boost candidate(s).

There have been a substantial number of reviews on TB biomarkers recently.2–6 Here we highlight and briefly discuss ten major challenges and questions that we envisage for the rational development of better TB vaccines and biomarkers in the next decade.

2. Ten challenges for TB biomarkers

Challenge 1: There is a lack of understanding of what constitutes protective immunity against TB. This creates a roadblock to improved TB vaccine development and the identification of correlates of protection.

Despite increasing knowledge on the crucial role of individual cell types, genes and molecules in protective host defense against
Mtb e.g. CD4+ Th1 and CD8+ cytotoxic T-cell pathways), we lack a true understanding of what exactly constitutes protection and protective immunity against TB. This creates a readblock for improved TB vaccine development and the identification of TB biomarkers of protection. We need a better understanding of the innate and adaptive immune responses that control infection with virulent Mtb; to understand why these fail in TB-susceptible (but otherwise immunocompetent) individuals; and how this failure results in either progressive primary, reactivation and/or re-infection TB, each of which may involve different impairments of host defense. What are the current priorities and considerations?

1. We need better insight into which host immune pathways need to be targeted for optimal protection in order to achieve better vaccine efficacy.

2. We need to identify the proper tools, such as vaccines, to optimally stimulate the most relevant pathways of protective host defense.

3. We need to identify TB biomarker signatures that can be used as read-outs for induction of protective responses in vaccine trials.

4. It should be recognized that biomarkers of vaccine-induced protection may differ from biomarkers of natural resistance against developing TB.

5. It may be that different immune mechanisms are essential for the prevention of infection versus prevention of active disease.

6. It may be that different immune mechanisms are essential for the prevention of infection/disease in naïve versus Mtb-infected individuals.

Challenge 2: Two types of TB biomarkers, which would have the largest impact in TB, need to be identified: (1) biomarkers of early TB disease development, and (2) biomarkers of vaccine-induced protection against TB.

1. Biomarkers of early TB disease development.

These primarily diagnostic biomarkers should identify those that are susceptible to, and/or those that have progressed to the subclinical phase of developing active TB. These diagnostic biomarkers will help target (preventive) Mtb eradication strategies (drugs or vaccines which clear infection) at an early stage, ideally before transmission of infection has occurred. Current diagnostic tools are deficient in identifying such individuals, and in discriminating them from Mtb-exposed-/infected individuals with chronic “stable” or latent infection, including those that might have cleared viable Mtb organisms. Such diagnostic tools will also be important in diagnosing “paucibacillary” extra-pulmonary TB and culture-negative forms of TB. The recently developed and powerful GeneXpert MTB/RIF test can diagnose TB (and rifampicin resistance), but mostly in active pulmonary TB cases; it is as yet lacking sensitivity in extrapulmonary TB, particularly meningeal TB, and in smear-negative pulmonary TB in HIV-infected individuals.

2. Biomarkers of vaccine-induced protection against TB.

Biomarkers/biosignatures able to predict clinical endpoints of protection would be critical tools to facilitate:

- **Pre-clinical vaccine research**, by allowing early-stage selection of relevant antigens, adjuvants, viable vaccines, routes of administration, selection of optimal (likely heterologous) prime–boost regimens in preclinical models, including animal challenge models and refined human in vitro models. An important caveat is that mechanisms and markers may differ between animals and humans.

- **Clinical vaccine research**, by reducing size, costs and length of otherwise long and protracted trials; and by providing a rational basis for selection of dose, schedule, choice of proper adjuvant, vaccine carrier as well as prime–boost regimes.

- **Head-to-head comparative evaluation of different vaccine candidates.** It is currently virtually impossible to compare different vaccines that are in the clinical evaluation pipeline. Nevertheless, this will become an important issue when down selecting the best possible vaccines and vaccination strategies, including prime-boost regimens.

Challenge 3: Different vaccines will require the usage of different sets of optimized biomarkers depending on the vaccine context.

Biomarkers of vaccine-induced protection may differ according to the type of vaccine used (subunit vs. live attenuated vs. non-replicating vector-based vaccines). For example, when specific Mtb antigen-induced immune responses are considered, in the case of a subunit vaccine with this given antigen, the specific Mtb antigen-induced immune responses can be measured as a biomarker of vaccine-induced immune responses. Alternatively, if the antigen is not part of the vaccine, these antigen-induced immune responses could instead serve as a potential biomarker of infection or disease severity post-vaccination. In addition, in the case of a live vaccine (e.g. recBCG, attenuated recMtb or modified atypical mycobacteria), this same antigen could be used as a biomarker of vaccine-induced immunity when it is present in the live vaccine, but of infection or disease activity post-vaccination if it does not exist in the live vaccine.

Another consideration is that sets of biomarkers might be different when vaccines are used for primary prevention as opposed to “booster” vaccines, depending on the specific prime or boost setting. Thus, biomarkers of TB vaccine-induced immunity can serve different purposes depending on the specific vaccination context. This implies that for each clinical trial that uses a different vaccine, optimal sets of biomarkers will have to be selected.

Challenge 4: Before biomarkers can be used as substitutes for vaccine-induced protection (or other clinical endpoints), they have to be validated against these same clinical endpoints in clinical trials (vaccine or relevant other studies).

Biomarker validation or “biomarker efficacy” studies need to proceed along a clinical evaluation path that is highly similar, if not identical to clinical vaccine evaluation studies. This will need to include objective criteria for down-selection/gating, head-to-head comparative evaluation, and also account for the specific vaccine context in which the prospective biomarkers are studied (see Challenge #3). It will be important to derive and bank relevant high quality clinical specimens for biomarker studies (see also Challenge #9).

Challenge 5: Since current tools and approaches in TB have had limited impact on identifying relevant biomarkers in TB, innovative approaches and strategies need to be used to remove this readblock.

TB is no exception to the rule of limited biomarker availability, and the same obstacles apply to many other complex human diseases, including auto-immune/inflammatory diseases and various forms of cancer. To remove this roadblock, innovative technologies and approaches should be harnessed and promoted, for example, systems biology and integrational “biomic” screening approaches. More attention should be given to assessing pulmonary innate and adaptive immune responses where the critical decisions are made as to whether infection will be controlled or allowed to progress toward active disease at a later time point. This includes both the lung tissue and the draining lymph nodes classically defined as the Ghon complex. It is possible that early innate signatures can already provide indications as to how the adaptive immune response is oriented and instructed to develop.
Challenge 6: Is it possible to derive TB-specific signatures of protection and/or disease?

This question asks what distinguishes TB from other chronic infectious, or non-infectious granulomatous diseases, and if it is possible to derive completely TB-specific signatures. In a recent study, among the TB disease-associated signature of 393 differentially expressed human genes, a core set of 86 genes was found to be relatively TB-specific. Nevertheless, a biosignature characteristic for sarcoidosis, another granulomatous disease mostly affecting the human lung, showed significant overlap with TB disease. If it is not possible to identify a set of TB-specific human gene expression biomarker profiles, complementary diagnostic biomarkers, for example, Mtb-derived components, might be sufficient to allow differential diagnosis.

Challenge 7: TB biomarker signatures of protection and/or early disease development need to be validated across geographically and ethnically diverse populations; as well as across populations affected by co-infections, including malaria, helminths and HIV.

Recent studies have suggested that there are at least six specific Mtb lineages that have co-evolved with and adapted to human populations. These Mtb lineages may have shaped mechanisms of host resistance in specific human populations, such that different biomarkers may be discriminatory in different population settings, depending on the underlying Mtb epidemiology. Similarly, population-based differences in baseline immune reactivity may impact on biomarker signatures emerging in the local TB setting, such as immune deviation induced by helminth co-infection, which compromises BCG vaccine efficacy.

Challenge 8: There is an imminent shortage in high quality TB clinical trial sites where phase IIb and III vaccine efficacy trials can be conducted.

In the absence of reliable biomarkers of protection, only phase III efficacy trials will provide true answers regarding the protective efficacy of TB vaccines. Therefore, investments need to be made in developing such sites, preferably in geographically and ethnically diverse settings with solid baseline information on infection and host-status epidemiology (see also Challenge #7). It should be noted that these trials will be equally important for the discovery and validation of relevant biomarker signatures of protection (see also Challenge #4).

Challenge 9: Better investments need to be made in large high quality sample biobanks.

This effort will allow biomarker identification and validation across geographically and environmentally different human populations, including the impact of co-infections (see also Challenges #4, 7 and 8). It is particularly important that appropriate specimens are banked in the context of phase III trials of vaccine candidates that may provide a link to clinical efficacy.

Challenge 10: The TB community should search for a relevant in vivo human challenge model.

Several potential human challenge models can be envisaged, of which we mention three:

First, intradermal injection of live M. bovis BCG would be the easiest model. It would provide information on vaccine-mediated immune inhibition of replication of an attenuated mycobacterium at a local tissue site. However, as BCG does not fully recapitulate the infection cycle of Mtb, this model may offer significant yet somewhat limited information.

A second alternative is the use of live-attenuated Mtb. However, in addition to potential regulatory issues, its genetic attenuation may compromise its ability to fully recapitulate all relevant steps of the Mtb infection cycle in humans. Nevertheless, this model could provide useful information of vaccine-mediated immune inhibition of replication of an attenuated Mtb derivative at a local tissue site.

And third, the most informative of these models would be a live Mtb challenge, akin to Plasmodium falicuprum challenge models in humans. However, because Mtb may not be completely eradicated by antibiotic treatment, an inducible Mtb suicide gene should probably be incorporated in the challenge strain.

In all cases, establishing a good human challenge model will prove difficult. Implementation of these models, particularly the live Mtb challenge model, will require extremely careful weighing of critical information gained and possible risks imposed on study participants, and will involve approval of ethical committees from the very beginning.

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Conflicts of interest

TO is co-inventor of an *Mtb* latency antigen patent, which is owned by LUMC. SHEK is co-inventor of the rBCGΔUreC:Hly vaccine candidate and of the vaccine antigen Rv3407, and member of the Scientific Advisory Boards of Intercell, Vienna, and Vakzine Projekt Management (VPM), Hannover.

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Clinical trials of TB vaccines: Harmonization and cooperation
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ABSTRACT

A new efficacious tuberculosis (TB) vaccine has the potential to dramatically assist control efforts for the global TB epidemic. Good progress has been made with the clinical development of new TB vaccine candidates with twelve being actively tested in clinical trials. However, there are many challenges that need to be addressed before a new vaccine is licensed for public use. The diversity of risk in populations needs to be factored into clinical development plans, specific but feasible clinical endpoints need to be agreed upon, and TB vaccines need to be effective in both uninfected and infected populations. An achievable efficacy target needs to be set while standardisation of trial outcomes and critical choices based on the vaccine development pipeline need to be made. Alternative routes of vaccine administration should be thoroughly explored, sufficient adequately prepared trial sites for performing TB vaccine assessments are required and creative use of study designs should be used to expedite progress towards licensure while at the same time containing costs. Lastly, there needs to be sufficient funding to support TB vaccine development. These challenges can be met through commitment by all role-players within the TB vaccine arena and with support from external stakeholders.

1. Introduction

Directly Observed Treatment Short-course (DOTS) is currently implemented in the 184 countries where, in 2006, 99% of all estimated TB cases occurred and 93% of the world population lived; yet global TB incidence remains two orders of magnitude above the Stop TB Partnership goal to eliminate TB as a public health problem, defined as <1 case per million population per year by 2050. Against this background, Abu-Raddad and colleagues 1 recently argued that combining a potent new regimen of TB drugs with at least a good neonatal pre-exposure vaccine and a highly efficient molecular-based diagnostic test in a global intervention strategy can reduce annual TB incidence in 2050 by 94%, over current rates. Epidemiologically, this would set the scene for elimination of TB. Other models have suggested similar strategies for achieving elimination. 2

2. The TB vaccine pipeline

There is reason for optimism about the prospects for a new TB vaccine that is more effective than the current BCG. Fifteen new TB vaccines have been evaluated in clinical trials to date, many in high burden settings, and 12 are actively being tested currently. 3, 4 Of these, at least 4 have entered or completed Phase IIb or Phase III testing. The development of new TB vaccines has thus progressed well, with definitive clinical assessment of different types of candidates underway. In an excellent recent review of vaccines in clinical trials, Rowland and McShane 5 describe the trial approaches and status of live mycobacterial vaccines designed to replace BCG as a primary vaccination, subunit vaccines designed to enhance the effectiveness of BCG, and post-exposure therapeutic vaccines.

However, trialists face challenges. Until very recently, the collective experience with anti-TB vaccine assessment has largely been lodged in observational cohort or case-control studies of BCG with tuberculin skin test responses as a surrogate for immunogenicity, assuming protective efficacy, or of TB morbidity and mortality monitored over extended periods of time in large cohorts as an indicator of vaccine efficacy. Experiences with double-blind, randomized controlled trials to assess protective efficacy are almost non-existent, with the notable exception of the well-known Chingleput trial in India in the 1970s. 6 Furthermore, regulatory experience with licensing/registration of a vaccine for tuberculosis is limited, and almost entirely focused on BCG product manufacturing and quality, and a demonstration of adequate tuberculin skin test responses as per WHO guidelines. Clearly, study designs and outcome criteria as per the BCG experience are inadequate for direct application in the assessment and selection of current candidates. However, the experience that is gradually building in the advanced clinical stage assessment of the candidates mentioned above is consider-
able and provides a valuable opportunity for defining standardized approaches to clinical trial design, and for establishing criteria for advancing candidates from early to final clinical phase testing. In this context, Barker, Hessel and Walker have proposed specific stage-gating criteria elsewhere. Nevertheless, certain other challenges relevant to the clinical development of new vaccine candidates remain, and are briefly considered below.

3. Diversity in risk of TB infection and disease

Diversity in the risk of TB infection and disease and in the protective efficacy of BCG has been observed over many decades. Specific population-associated features might result in marked differences in immune responses to the same vaccine in similar age cohorts from different parts of the world. Clearly, the clinical assessment of TB vaccines needs to take into account geographic, epidemiological variables and genetic diversity. Even smaller Phase II proof-of-concept trials may need a multi-center approach to factor in the impact of this diversity. More specifically, these factors include concomitant diseases with high prevalences (particularly HIV and parasitic infections), exposure to environmental mycobacteria, pre-disposing environmental conditions, socio-economic factors and population demographics.

It is known that in the absence of an underlying HIV co-infection, the greatest proportion of TB incidence is generally driven by recent TB infections (within two years). There are exceptions: in young children up to the age of 2 years, and in adolescents, the progression to disease is sometimes continuous following infection, while in pre-adolescent years, latency is mostly maintained. Furthermore, there has been an almost universally observed higher rate of disease in males than in females in high prevalence settings in pre-HIV times; now, high rates of disease occur in co-infected females in their reproductive years. Moving forward, there is a need to re-define the clinical pathway for assessment of vaccine efficacy and the dynamic of latency and progression to disease needs to be understood for every population where vaccine trials are being run. Multi-country epidemiological cohort studies in different target age-groups are required for two important reasons: (a) To establish an adequate understanding of the epidemiology of disease pathogenesis in the absence of a new preventive intervention; and (b) To enable the design of a scientifically sound schedule for mass vaccination campaigns.

4. Clinical endpoints

Because of the current lack of an immune correlate of protection, efficacy trials will be dependent on clinical endpoints. These will be particularly challenging in infants because the disease is paucibacillary. From a vaccine development point of view, a hard endpoint such as bacteriological confirmation of disease is likely to be favoured by trialists, even in very young children. The proportion of sick children with bacteriologically detectable disease would be low, however, and clinical algorithms to indicate high probability for TB might be required until suitable biomarkers could be validated. It is also not possible to ignore symptoms compatible with TB in the absence of bacteriological proof, and to defer treatment. Thus, even if bacteriological proof of disease might be desired, medical interference with the development of this stage of the disease would defeat its utility as an endpoint. These special challenges for setting hard immunogenicity or vaccine efficacy targets for paediatric cohorts, indicate a need for more concerted research into what constitutes a protected or a diseased child.

In adults and adolescents, microbiological confirmation is more feasible so endpoints can more easily be defined for these groups. Nevertheless, there needs to be consensus on the definition of these endpoints in terms of the microbiological assay to be used, and the interpretation of results. Also, in the post-marketing phase, these endpoint definitions need to be such that outcomes could reasonably be observed and documented by TB control programme staff and primary health care service providers. The development and integration of modern molecular diagnostic procedures for the detection of the pathogen, and of any relevant assays to detect enhanced immunogenicity, is necessary especially as part of a pre-defined set of tests to be used as part of ongoing vaccine safety and efficacy assessments.

5. What level of efficacy will be acceptable for a new TB vaccine?

A range of protective efficiencies between 60% and 90% have been proposed in an opinion survey conducted amongst TB vaccine experts (as part of the development of the TB Vaccine Blueprint) as necessary for licensure of a TB vaccine. The lack of consensus highlights the importance of this issue, and might have implications for the mass introduction of a vaccine in populations where the benefits are potentially great. Lessons can be learned from the malaria field, where the acceptance of efficacy levels of 53–65% in phase II trials for a malaria vaccine were regarded as sufficient for moving forward into a phase III trial. A number of factors will influence discussions about an acceptable level of efficacy for TB vaccines, however. One factor is the variable efficacy of BCG against pulmonary TB, making it difficult to set a value for relative efficacy of a new vaccine versus BCG, and might require an absolute level to be stated. Another key question is what level of efficacy has both a significant public health impact and a compelling cost/benefit ratio. Mathematical modeling may help to answer these questions and to determine the impact of vaccination in selected populations. Modelling data suggest that a 60% level of efficacy is likely to have a substantial public health impact. TB is a massive public health problem and the impact of fairly modest gains in efficacy over BCG by next generation vaccine candidates should not be underestimated.

6. Standardisation

Standardization of parameters and definitions to be used in the safety assessment of all TB vaccine candidates is a high priority. In this regard, the work of groups such as the Brighton collaboration (https://brightoncollaboration.org/public) may be useful. Likewise, standardization of the criteria to be met in the clinical development pathway, is essential. Some vaccines have gone through a gradual age de-escalation path from adults to adolescents to children to infants whilst others have been able to move directly from adult to infant studies. This partly reflects an evolution in regulatory requirements among different regulatory authorities. Not all vaccines in Phase Iib proof-of-concept trials have undergone interference assessments with other childhood vaccines, for example. This is an important step in planning towards implementation where in all likelihood a licensed efficacious vaccine would best be given with other vaccines. Safety in the HIV-infected community (adults and exposed infants) is crucial, and all vaccines should be required to be tested for safety in this group, given the high prevalence HIV in a number of high TB burden countries.

7. Alternative routes of vaccination

Preparedness for clinical assessment of vaccines delivered by alternative routes (e.g pulmonary, nasal, oral) might also be required, given recent developments in this context. The lung is the primary, if not the sole, portal of entry for mycobacteria that cause TB, and it has been of interest since the 1950s to deliver certain key drugs and the TB vaccine, BCG, by the same route.
Because of technical difficulties, also for pharmaceutical reasons, most of these early studies were abandoned despite encouraging results. In recent years, however, a renewed interest in formulating vaccines for pulmonary delivery emerged, for reasons that remain significant. Targeting the lung mucosa for immunisation against TB potentially offers advantages over current injection approaches, with advanced studies in primates with new subunit candidates and BCG, showing promising results.16 Such an approach might be particularly suitable for live recombinant or attenuated vaccine candidates. The nasal route of administration has been investigated for flu vaccines and might offer lessons for TB vaccine development, in particular for adjuvanted or viral vectored candidates. Several recent investigations involving room-temperature stable oral microparticle preparations of BCG showed promising results in bovine models, and this route of delivery might hold promise for application in humans as well.5,17 Although not yet having been explored in the context of TB vaccines, skin patches containing microneedles coated with dried solutions of various other vaccines, including influenza vaccines, also hold promise as needle-free options. These are early developments worthy of further investigation.

The emphasis for changing the route of delivery would be on developing needle-free, room temperature stable vaccine products that would be easy and cheap to administer, and would enhance a protective immune response by targeted delivery to appropriate immunological compartments. Recent publications suggest that such technologies are within reach, and would be affordable and pharmaceutically scalable.18

8. Trial sites

Given the fact that BCG has in some populations and age cohorts managed to reach a protective efficacy of around 80%, there is little scope for any vaccine to do much better in similar target groups, and large numbers of subjects would need to be enrolled in order to demonstrate better efficacy. In such situations, prime-boost studies with the objective of showing significantly better long-term protection, rather than BCG-replacement studies, might be the objective.

Populations with the highest prevalence of disease would be chosen for establishing vaccine trial sites, and such efforts are currently being widely pursued in areas like sub-Saharan Africa where TB rates are fuelled by the high prevalence of HIV co-infection. Trial capacities would need to be integrated (but not necessarily merged) in a targeted way, in order to access large populations at risk of disease so that small margins of improved vaccine efficacy could be detected. Accurate estimates of incidence rates are key to planning efficacy trials. This may be challenging in certain areas where only routine data are available. In this regard, routinely collected TB control programme data often underestimate true incidence, in particular as far as case definitions compatible with clinical trial endpoints are concerned. Data from specially-conducted epidemiological studies might be required.

Another reasonable approach might be to define large, global networks that would aim to conduct only specific types of studies. There are essentially three arenas for Phase II/III trials: (A) Live mycobacterial vaccines designed for replacing BCG; (B) Subunit vaccines designed to boost BCG; and (C) Therapeutic vaccines designed as an adjunct to chemotherapy. For A, strong capability in paediatric TB research and health service delivery is essential. Target cohorts would be infants and young children, including babies born from HIV-infected mothers. Trialists, including vaccine developers, would need to gain consensus on which endpoints to use and would likely have the need for access to specialised clinical laboratory and radiological infrastructure.

For B, access to adolescent and adult populations is important. This is likely to be the largest but also most challenging population for the immediate future (those requiring HPV vaccination are similarly challenging). Significant networking across diverse geographical areas are beginning to be utilized for certain advanced TB vaccine candidates, but may not be accessible to later vaccines candidates now transitioning into Phase II studies. A very comprehensive networking effort is called for in order to allow for sufficiently powered studies to be conducted. In these cohorts, disease as detected microbiologically, is a reasonable indicator of vaccine efficacy, and a rapid diagnostic infrastructure to detect the pathogen is essential. Populations with substantial prevalences of latent TB infection would be needed since proposed mass campaigns currently being proposed as a strategy with a successful vaccine would be done in individuals with and without latent infection.

For C the aim will be to provide access to special risk groups with high rates of TB, and where the risk of disease progression from an underlying TB infection would be high. A history of BCG vaccination in these groups is typically remote. Subjects for recruitment might include TB patients on treatment, or TB-HIV co-infected adults on preventive isoniazid therapy. A close interaction with TB drug research groups might be useful.

9. Target groups

Although clinical development to date has shown that the candidate TB vaccines are by and large safe (in the groups tested) and provoke a range of immune responses, there is, as yet, no unequivocal indication of vaccine efficacy, although some candidates clearly have demonstrated promise in phase II and III trials. Phase IIb trials are in progress in infants and HIV positive adults with efficacy objectives. However, given the challenges of demonstrating efficacy in these two target groups, sponsors of vaccines at an earlier stage of development, may follow an approach of doing efficacy trials in HIV negative adolescents/adults to confidently assess vaccine efficacy. Vaccine candidates thus achieving measured efficacy may then be subsequently introduced to infant and HIV positive cohorts for vaccine efficacy assessments. The discovery of immune correlates of protection would help expedite the length and costs of such trials.

Vaccines targeted at adolescents/adults need to be versatile and be able to prevent infection as well as reactivate in latently infected individuals. In particular, safety and efficacy in HIV co-infected individuals will be important. Currently, such trials are being conducted in high co-infection prevalence settings in South Africa, which should guide the way for trial designs appropriate to other candidates. It is anticipated that subunit vaccines or non-replicating whole-cell constructs would be eligible vaccine candidates in this context.

10. Study designs and trial costs

Some degree of creativity in designing Phase III trials for assessing vaccine efficacy is clearly required, with the key points to keep in mind being as follows:

- The role of BCG in enhancing or inhibiting protective immune responses is unknown – it is assumed to be enhancing. Evidence of efficacy will be needed in order to develop immunological correlates (surrogates) of protection that can be used to determine immune-protection rates and level of immunity in vaccinees.
- From a regulatory point of view, the concept of a “Phase IIb/III” type trial needs to be explored with regulatory authorities who may find such an approach challenging.

Clinical trial applications that intend to permit amendments to the protocol should prospectively include a description of the intended change points, the arrangements for independent interim analysis that will drive such changes, and the mechanisms that
will ensure statistical validity of the results. Oversight by Data and Safety Monitoring Boards (DSMBs), or similar independent safety committees, will be required.

Head-to-head comparisons of new TB vaccines have not occurred to date in human trials, but have occurred with other vaccines such as pertussis, and can serve as a model for similar trials with different TB candidates. The benefits of head-to-head comparisons include, firstly, the reduction of costs of clinical trials if a single protocol tests a number of vaccines simultaneously at a single site. There is no reason why early phase trials cannot be conducted in this way. Secondly, this may be an important step for deciding which vaccine or vaccines proceed to the next stage of development. Thirdly, this will clearly be one way in which issues of standardization may be addressed. However, vaccine developers may be resistant to this idea for various reasons such as protection of their intellectual property. Therefore, contractual arrangements with multiple partners may be complex. Also, if these trials are performed at early phases, one would be dependent on immunogenicity measurements as a proxy to determine potential efficacy and there is not enough scientific evidence to support such an approach. The fact that new TB vaccines are at different stages of development will also make head to head comparisons difficult.

Moving towards efficacy trials which require larger subject numbers and are therefore more expensive, there is recognition of the fact that funding for such trials will be limited. There would need to be a rational approach for selecting candidates for efficacy trials, as clearly, there will not be enough funding for all candidates to undergo such trials. [see also Barker et al in this series] On the other hand, there should be an exploration of reducing the costs of such trials. One suggestion is to utilize existing trial site networks such as the HIV Vaccines Trial Network (HVTN) and IMPAACT to mitigate the costs of setting up suitable trial sites. Another way of reducing costs is through creative trial designs. Simplifying follow-up or using existing infra-structure such as demographic surveillance sites or routine health care services are options that should be considered. However, trial designs need to factor in meeting the required regulatory standards while trying to deal with costs constraints. Partnering with large pharmaceutical companies will be critical in addressing some of the cost constraint issues. Others may be adaptive trial designs, where multiple candidates are studied simultaneously and the expected failure of some vaccines which do not meet the stage-gate criteria, should also be evaluated as cost-saving options. Another cost-saving approach is to use a stepped-wedge design in Phase III studies where one vaccine (e.g. BCG) is replaced by the new vaccine in different arms at different time-points. This approach has been successfully used in a hepatitis intervention study in the Gambia and might offer a model for vaccine candidates proposed to replace BCG.

### 11. Conclusion

In conclusion, good progress has been made in the clinical development of new TB vaccines. There are many challenging areas that need to be addressed such as trial designs, funding, alternative routes of vaccination, TB epidemiology and standardization of outcome measures and clinical pathways. However, with the commitment of resources to TB vaccines, a promising avenue for global TB control may achieve substantial success.

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### Conflicts of interest

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A rational process is clearly needed and can be extremely helpful for selection, assessing and advancing TB vaccine candidates from entry into preclinical and clinical development and for advancing candidates from early safety and immunogenicity clinical trials to proof-of-concept and pivotal efficacy trials. A joint effort between Aeras and the Tuberculosis Vaccine Initiative has focused on the development of objective criteria for a number of key general vaccine characteristics which can be assessed at critical stages of development. In order to maximize development efficiency, increase likelihood of success, and optimize use of scarce resources, this process includes establishment of gates for moving TB vaccine candidates through progressive development stages based on meeting the established criteria for specific vaccine candidates.

Establishing comprehensive, measurable and widely acceptable criteria for selecting, assessing and advancing vaccine candidates that are in the product development pipeline is one of the most crucial issues facing the TB vaccine development community. Currently more than ten vaccine candidates are being tested in clinical studies in individual clinical trials often using different endpoints and immunological measures for analyzing outcomes. Many more vaccine candidates and concepts are in the discovery phases and a number of these have or will enter preclinical development, with the expectation that some will enter future clinical development.

Accordingly, identifying acceptable criteria that can help with selecting and advancing the most promising candidates to move forward in human clinical studies from among those now in the clinic, and to move into initial clinical studies from the larger portfolio of preclinical vaccine candidates, is a significant challenge in the TB vaccine field. It is critical that specific and measurable selection criteria be established based on vaccine type, target population and product profile, manufacturing process and feasibility, stability and delivery approach, immunogenicity and mechanism of action, efficacy in clinical testing, regulatory pathway, and business and marketing issues, including final cost at the point of delivery. Obtaining a general consensus for the use of these criteria within the TB vaccine community will also be challenging.

Product development typically uses a stage-gating approach (Fig. 1) to provide structure, discipline, and a rational decision-making framework to the process that moves from innovation through new product development to the market. This framework best operates at two levels: first, in a linear pathway for each specific product to determine if there is sufficient and robust evidence to allow further development of that specific product, and second, in a matrix fashion, comparing similar products in a portfolio, to determine the most promising candidate from a range of very similar candidates.

The linear development pathway for a specific vaccine can be considered as a series of stages from Discovery to Preclinical development to Phase 1–3 Clinical trials to Marketing Application (MA) and Market, with assessment and selection occurring at a gate between each stage, using multiple criteria to determine if candidate products proceed through the gate to the next stage (Figure 1). Certain specified criteria must be met to pass through gates and move into the next phase of product development. Application of this approach can also help with prioritization of multiple products that are competing for development resource commitments. The needed resources expand considerably as successful products move from the discovery and preclinical phase to early clinical testing, to advanced, large pivotal Phase III trials, marketing application (MA) and marketing.

A key factor for vaccine candidate sponsors, who are managing significant portfolios of products, is the difficulty, given current understanding of immunology and protective immunity in tuberculosis, to be able to apply meaningful criteria to the selection of the better or best candidate from a number of likely possible candidates. Experience to date has indicated that current preclinical (or non-clinical) testing methods can have difficulty distinguishing or allowing a clear recognition of superiority between candidates with a similar vaccine strategy. Also requirements such as formulation complexity can differ between the development strategies

Keywords: Tuberculosis Vaccines Stage-gates
for specific products, whereas in portfolio management of multiple candidates such considerations are potentially similar.

For the purposes of selecting specific candidates to advance from discovery to support for early pre-clinical development, clear criteria for acceptable laboratory and development background data are needed and a potential list of such desired product characteristics can be seen in Table 1. Table 1 also includes examples of specific criteria to be met that need to be tailored to specific types of candidates. This can best be done initially in partnership between sponsors and scientists proposing to advance their candidates.

If a candidate can meet all or most of the criteria in Table 1, even if not fully developed, then there is a case to be made for including the candidate within a product development portfolio. This would provide an opportunity to further develop the product and work towards a more robust data package that can provide support for making a case for development through Pre-Clinical Development to early (Phase I/IIa) studies in humans (Table 2).

At present the so called gates for vaccine development are positioned at specific points in the development process at which a decision to invest significant funds is a requirement to advance the product to the next stage. For example, the point at which a decision is made to advance a candidate into initial human trials (Phase I/IIa), requiring cGMP manufacture and including formal toxicology and safety studies, is one at which a significant increase in investment is required to move forward. Here a series of more stringent criteria, building upon those set out in Table 1 should be applied, requiring a greater burden of proof of concept, manufacturing scale up capability, safety and preclinical efficacy data to support further investment – see other examples of characteristics in Table 2.

As noted earlier, these decisions can be linear (with regard to a single candidate and its development pathway), or more of a matrix if portfolio management is required in the face of multiple similar products. Head to head comparisons within agreed animal model systems can help decision-making, as can robust critical assessment of manufacturing, regulatory issues and intended target product profile. It must be noted that animal models of disease and vaccination remain just that – models – and therefore there

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**Table 1**

Criteria for advancing past Gate 1 from discovery into pre-clinical development

<table>
<thead>
<tr>
<th>Candidate characteristics</th>
<th>General criteria</th>
<th>Examples of potential product-specific specifications to be provided by developers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product quality</td>
<td>• Antigen expression/purity</td>
<td>• SDS-PAGE/Westerns/Abs needed</td>
</tr>
<tr>
<td></td>
<td>• Stable construct or protein</td>
<td>• Genetic stability established, no reversions, resistance gene removal is feasible</td>
</tr>
<tr>
<td></td>
<td>• Vaccine carrier evaluated</td>
<td>• Specific characterization studies defined and criteria met for viral vector; adjuvant; live bacterial vector, DNA or other carrier</td>
</tr>
<tr>
<td>Safety</td>
<td>• Lack of gross toxicity in vitro and in vivo</td>
<td>• No gross toxicity in animals</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>• Describe proposed mechanism of action</td>
<td>• Immunization of animals elicits IFN-γ, CD4+CD8, etc.</td>
</tr>
<tr>
<td></td>
<td>• Evidence of T and B cell immune responses in animals to vaccine antigens</td>
<td>• Significant responses to vaccine antigens</td>
</tr>
<tr>
<td>Efficacy</td>
<td>• Protection in mouse model or equivalent vs. Mtb challenge</td>
<td>• Measure colony forming units (CFUs) and/or disease and survival compared with BCG</td>
</tr>
<tr>
<td>Clinical</td>
<td>• Target population and indication identified</td>
<td>• Primary target population and clinical development path acceptable, feasible and address unmet medical or public health need</td>
</tr>
<tr>
<td></td>
<td>• Feasible clinical development path</td>
<td>• Documented history of seed strains</td>
</tr>
<tr>
<td>Production process</td>
<td>• Establish seed lot</td>
<td>• Plans for pilot lot production</td>
</tr>
<tr>
<td></td>
<td>• Good Laboratory Practice (GLP) production established</td>
<td>• Possible regulatory barriers assessed and no major roadblocks identified</td>
</tr>
<tr>
<td>Regulatory strategy</td>
<td>• No obvious product or clinical development barriers for regulators</td>
<td>• No IP obstacles identified</td>
</tr>
<tr>
<td>Business</td>
<td>• Intellectual Property (IP) status identified</td>
<td>• Viable partnerships identified</td>
</tr>
<tr>
<td></td>
<td>• Describe development partnerships</td>
<td>• Material Transfer Agreements (MTAs) and other cooperative agreements established</td>
</tr>
<tr>
<td></td>
<td>• Resource plan outlined</td>
<td>• Cost estimate/budget for preclinical development stages are acceptable</td>
</tr>
<tr>
<td>Health impact/Novelty/Other</td>
<td>e.g. Novel concept</td>
<td>• Resource plan to next gate outlined</td>
</tr>
<tr>
<td></td>
<td>Novel antigens</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Novel adjuvant in formulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feasibility</td>
<td></td>
</tr>
</tbody>
</table>

---

Figure 1. Typical development in phases (stages) and gates from Discovery to Market.
is a necessary acceptance that the information obtained from these models may not necessarily reflect the outcome that will be seen during testing in human trials. Having said that, it must be recognized that established animal models have been shown to resemble a variety of aspects of human tuberculosis. It follows therefore that proper and due deliberation of the questions being

Table 2
Criteria for advancing past Gate 2 from preclinical development to early clinical development (Phase I trials)

<table>
<thead>
<tr>
<th>Candidate characteristics</th>
<th>General criteria</th>
<th>Examples of potential product-specific specifications to be provided by developers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product quality</strong></td>
<td>• Pure</td>
<td>• Purity/identity assay</td>
</tr>
<tr>
<td></td>
<td>• Stable</td>
<td>• Stability data</td>
</tr>
<tr>
<td></td>
<td>• Potent</td>
<td>• Potency assay under development</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>• General safety established</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Safety in immunocompromised model</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Toxicology or equivalent study</td>
<td></td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>• Equivalent or superior to lead candidate</td>
<td>Measure T cell, cytokine and Ab responses in comparative study</td>
</tr>
<tr>
<td></td>
<td>• Evaluated in a “prime-boost” model</td>
<td>Significant responses to specific Mtib antigens</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Statistically superior to BCG in two animal models</td>
<td>Measure CFUs and survival</td>
</tr>
<tr>
<td></td>
<td>• Evaluated in a “prime-boost” model</td>
<td>Superior protection in model with boost vaccine</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>• Feasibility of a pilot clinical plan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Target Product Profile (TPP) established</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Human immunoassay available</td>
<td></td>
</tr>
<tr>
<td><strong>Production process</strong></td>
<td>• Good Manufacturing Practices (GMP) production consistency</td>
<td>Lot release data</td>
</tr>
<tr>
<td></td>
<td>• Satisfactory yield</td>
<td></td>
</tr>
<tr>
<td><strong>Regulatory strategy</strong></td>
<td>• Evaluate Regulatory barriers for product and clinical approach</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pre-IND advice obtained</td>
<td></td>
</tr>
<tr>
<td><strong>Business</strong></td>
<td>• IP &amp; freedom to operate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Established partnerships</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Resource plan</td>
<td></td>
</tr>
<tr>
<td><strong>Health impact/Novelty/Other</strong></td>
<td>e.g.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Superior in comparative studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Novel antigen and adjuvant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mechanism of immunity established in animal model</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Feasibility</td>
<td></td>
</tr>
</tbody>
</table>

Table 3
Criteria for advancing past Gate 3 from Phase I to enter Phase II/IIB proof-of-concept testing

<table>
<thead>
<tr>
<th>Candidate characteristics</th>
<th>General criteria</th>
<th>Examples of potential product-specific specifications to be provided by developers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product quality</strong></td>
<td>• Continue evaluation of GMP product</td>
<td>• Accumulate stability data</td>
</tr>
<tr>
<td></td>
<td>• Validate Quality Control &amp; Quality Assurance (QC/QA) for product</td>
<td>• Do comparative testing of scaled up product</td>
</tr>
<tr>
<td></td>
<td>• Continue development of potency assay</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>• Establish safety of product in human clinical trials</td>
<td>• Conduct Phase I studies in appropriate target populations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Analyze Adverse Event (AE) data</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>• Evaluate candidate immuno-assays in clinical studies</td>
<td>• Develop assays in human studies to establish correlates of immunity and risk</td>
</tr>
<tr>
<td></td>
<td>• Use one standardized immuno-assay in clinical trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Continue to evaluate product in animal models</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>• Develop protocols for acquiring effectiveness data in Phase II/IIB trials</td>
<td>• Evaluate epidemiology at varied geographical sites for TB incidence</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>• Conduct clinical trials in varied target populations</td>
<td>• Analyze safety and immunogenicity data</td>
</tr>
<tr>
<td></td>
<td>• Establish safety and immunogenicity profile</td>
<td>• Store human specimens for assay development</td>
</tr>
<tr>
<td></td>
<td>• Study human immunoassays</td>
<td></td>
</tr>
<tr>
<td><strong>Production process</strong></td>
<td>• Confirm manufacturers for scale-up procedures</td>
<td>• Continued evaluation of GMP product</td>
</tr>
<tr>
<td></td>
<td>• Validate facilities &amp; equipment</td>
<td>• Final formulation defined</td>
</tr>
<tr>
<td></td>
<td>• Initiate production of consistency lots</td>
<td></td>
</tr>
<tr>
<td><strong>Regulatory strategy</strong></td>
<td>• Meet with relevant regulatory authorities</td>
<td>• Implement strategies for timely review of clinical protocols in target countries</td>
</tr>
<tr>
<td></td>
<td>• Provide documents and responses through submissions to Regulatory Authorities (RAs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Work with World Health Organization (WHO) and other international bodies to prepare for global introduction</td>
<td></td>
</tr>
<tr>
<td><strong>Business</strong></td>
<td>• Maintain sustainable partnerships for manufacturing and clinical development</td>
<td>• Develop partnerships for performing multisite Phase II/IIB and III trials</td>
</tr>
<tr>
<td></td>
<td>• Resource plan</td>
<td>• Resource mobilization for large scale clinical trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Conduct marketing analysis on acceptability and costs</td>
</tr>
<tr>
<td><strong>Health Impact/Novelty/Other</strong></td>
<td>e.g.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vaccine safe and immunogenic in various target populations including Mtib infected and HIV+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acceptability by endemic populations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Correlate of risk or immunity established</td>
<td></td>
</tr>
</tbody>
</table>
asked of the model systems used be undertaken, along with a critical and clear appraisal of the data derived from such studies. Within this discussion on decision-making strategies for investment in vaccine candidates, there will be a number of circumstances where candidates of a similar nature (recombinant BCGs, for example) are effectively indistinguishable with regard to the gating criteria available (see Tables 1 and 2) and therefore, in order to facilitate an orderly decision-making process, the data from animal model studies may become critical. The merits of a centralized animal testing paradigm to assess candidates of a similar vaccination strategy, using an agreed upon model with uniform challenge and positive control material and outcome parameters, lie in the capacity to provide data on direct head-to-head comparisons. This reduces the problem of inherent variability between preclinical studies and study sites, and uses common reference materials providing benchmarks for comparison. For example, the TB vaccine research community might establish as a positive control either a single lot of a licensed BCG vaccine, or standardized comparison against the most advanced vaccine candidate of a similar nature in the clinical pipeline. A robust critical appraisal of the animal model and data outputs can provide the basis for developing algorithms for use of these model systems and defining a range of sensitivities for detection of functional differences in vaccine effects, thereby allowing for both discrimination of function and evidence-based support for specific ongoing development selection decisions among similar candidates.

Even more critical points for decision-making and portfolio management occur after Phase I and II safety studies in humans have shown no major safety issues and consideration is being given to the next step – Phase IIb targeted efficacy testing for clinical proof of concept (Table 3), and, subsequently, the possibility of Phase III full safety/efficacy studies (Table 4 – note Specifications for specific products in this table are incomplete at this time). Here the resource requirement implications escalate substantially and the highest level of stringency must be applied to the selection of candidates for advanced clinical and safety aspects of large scale trials in at risk populations.

As noted, the most advanced stages of product development become the most difficult in terms of developing a rational strategy if one is faced with multiple similar candidates. The linear model of application of these gating strategies provides a formalized structure for proceeding with development of individual vaccine candidates, assessed individually, measuring actual achievement against desired outcomes, before further investment. However beyond Phase I studies, this process becomes more complex and subtle; since investment and cohort (field site) capacity are

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Criteria for advancing past Gate 4 from Phase II/IIB proof-of-concept into Phase III pivotal efficacy trials</th>
</tr>
</thead>
</table>
| Candidate characteristics | General criteria | Examples of potential product-specific specifications to be provided by developers (to be developed) *
| Product quality | • Final formulation defined  
• Consistency lots pass final QC, batch and final product | • Satisfactory final testing results of scaled up GMP product
| Safety | • Safety studies in Phase II completed at all sites  
• Safety profile satisfactory in final target populations  
• Risk management plan designed for updating active surveillance in Phase III |  |
| Immunogenicity | • Immune responses in target populations acceptable in Phase IIIB  
• No interference with immune responses to other vaccines when given to target population  
• Correlates of protection evaluation embedded in Phase III protocol |  |
| Efficacy | • Clinical efficacy proof of concept demonstrated in Phase IIIB |  |
| Clinical | • Phase III study design validated and approved by Institutional Review Boards/Ethics Committees (IRBs/ECs)  
• Data Safety Monitoring Board (DSMB) and other relevant committees in place  
• Satisfactory audits of study sites  
• Monitoring and data management plans defined and validated  
• TPP finalized |  |
| Production process | • Final process successfully scaled up to commercial level  
• Consistency lots made under cGMP | • GMP product meets all specifications
| Regulatory strategy | • Registration strategy determined, including for prequalification by WHO  
• Successful End of Phase IIIB meeting with RA and Phase III protocol acceptable |  |
| Business | • Budget and financial resources to complete Phase III established  
• Cost of goods acceptable  
• Strong industrial partnership in place and action plan defined  
• Market analysis supports introduction of vaccine if efficacy is satisfactory  
• Satisfactory IP status |  |
| Health impact/Novelty/Other | e.g.  
- Vaccine safe and immunogenic in various target populations  
- Acceptability by endemic populations  
- Correlate of risk or immunity established |  |

* The product-specific specifications for Gate 4 are still under development at this time.
resource-limited, it is likely that a single or very few candidates will have to be selected from a number of possibilities, for advancement.

Herein lies the complex and difficult process of portfolio management, where sponsors and developers must focus limited resources onto one or a very small number of selected candidates. Clearly, without a defined and validated correlate of protection, other measurable criteria for selection are required. The strategy for gating and selection proposed here is an attempt to formalize and rationalize what has, in the past, been a somewhat more ad-hoc and subjective process. It should be recognized that given current levels of scientific understanding and assay limitations, there is a risk, not definable, that potentially important candidates may not be selected. That said, limitations on resources, both financial and clinical, apart from formidable ethical considerations, demand a structured and transparent process for advancing TB vaccine candidates in the modern world.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

Bridging the gap: Engaging researchers and advocates to build support for TB vaccine research and development

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Civil society
Community engagement
Resource mobilization

ABSTRACT

The success of global efforts to develop new TB vaccines will rely on both addressing the scientific challenges identified throughout this Blueprint and mobilizing sufficient support and resources to sustain and advance the TB vaccine pipeline. As outlined in the TB Vaccine Blueprint, activities over the next decade will include expanding financing to provide sufficient resources, raising awareness of the need for new TB vaccines, and broadening the base of advocates, allies and champions for TB vaccine R&D. These activities will only be successful if advocates and researchers – including scientists, clinicians and product developers – work together. Researchers and advocates play an essential role in promoting the advancement of TB vaccine research and development (R&D), but have too often operated independently of each other, with researchers focusing on the science and advocates and civil society focused on advocacy, communications and resource mobilization. As we look toward the next decade of TB vaccine development, it will be critical for the research and advocacy communities to work more closely together to support the common goal of developing new, more effective TB vaccines.

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1. Engaging in TB vaccine R&D advocacy

Researchers and advocates both play an important role in building support and mobilizing resources for TB vaccine R&D. Researchers provide the scientific evidence to support key messages and lend credibility to advocacy efforts; advocates can help to translate R&D findings for a lay audience and serve as a link between researchers, other advocacy groups, donors, policymakers, and the communities their research is intended to serve. Establishing a stronger relationship between these two groups can serve to better leverage the contributions of each and strengthen R&D advocacy efforts overall.

Researchers can be very powerful advocates and it is in their self-interest to be involved in research advocacy efforts, which often seek to increase – or at least maintain – agency budgets that could support their work. The global economic crisis has led to an increasingly difficult budget climate, making it more important than ever for the TB vaccine research community to be engaged with advocates as they seek to prevent cuts to research and global health funding in national budgets. Budget decisions, as well as other legislative decisions that could impact R&D, are being made by policy makers who are not experts in the field, and it is the job of researchers and advocates together to educate them about the critical need for new TB vaccines and to make the case for increased support and investment in TB vaccine R&D.

Advocates serve a vital function in developing key messages to build support for TB vaccine R&D, maintaining a consistent flow of communication and providing a basis of information and understanding to policy and decision makers. However, advocates can also be dismissed as “just another lobbyist.” It is less likely that policymakers will dismiss a distinguished doctor or researcher working specifically in the field, particularly if that person is from the district or area they represent. Researchers working in the field lend credibility to advocacy efforts, and are ideally situated to convey the progress and potential of scientific advances based on their experience. Researchers can also demonstrate the positive domestic impact of global health research by providing information on funding received, jobs created and other economic stimulation that research funding has provided in districts and communities, which helps policymakers to justify funding decisions.

The relationship between researchers and advocates is mutually beneficial. Researchers provide the data that drive advocacy efforts and support evidence-based policy, and advocates provide the platforms and vehicles for disseminating this information beyond the R&D community. Advocates are aware of key target audiences and the best mechanisms to reach them, be it through: media outreach; social and new media platforms; dissemination through networks, briefings, or one-on-one meetings; or other means of information distribution.

Just as advocates and researchers have unique but corresponding roles to play in advocacy at home, they also must work with
2. Engaging civil society in field research

Civil society organizations – which can include non-governmental organizations, faith-based organizations, community organizations, formal and informal networks, and other groups centered on a topic or interest – can play an important role in the conduct and support for R&D, particularly clinical research, by serving as a link between researchers, advocates and the community. Many of these organizations have extensive experience in working with affected communities and have established relationships and a basis of trust within the community. They can tailor messages and information in ways that are easily understood by community members and often have broad networks through which information can be disseminated.

Civil society organizations can help create a dialogue between researchers and the community and can also assist in the dissemination of study results to participants and the community. When this is done, participants are further motivated, they feel ownership of the results, and they actively continue to support the research trial. In disseminating study results, it is important to make sure that participants and community members truly understand them, and civil society organizations can help translate the results into understandable language.

Civil society organizations are also often well-versed in national policies and politics, and can be an important ally in efforts to engage national policy makers and incorporate TB vaccine research into national action plans and policies. They are able to identify key decision makers and influencers in the region, and develop messages that will resonate with these constituencies. Civil society organizations and researchers can partner together to invite national policy makers to clinical trial sites or research facilities to showcase the work that is being conducted, and to demonstrate the positive impact that TB vaccine R&D can have in the country. In turn, researchers can provide civil society with the data, facts and information they need to be able to more effectively discuss the progress that is being made in TB vaccine R&D and opportunities for national governments to support R&D efforts.

Building support at the local and national level for TB vaccine R&D can also be beneficial when new vaccines are moved into the implementation stage. Communities and countries will already be familiar with the concept of new TB vaccines, and may be more open to adoption and acceptance of new vaccines once licensed.

3. Bridging the gap – recommendations for working together

The benefits of bridging researchers, advocates and civil society are clear. The following are recommendations on how to more effectively engage these constituencies to advocate for greater support and investment in TB vaccine research and development:

- **Use national and international forums to learn and to keep each other informed.** Researchers should participate in advocacy conferences to share the latest data, advances and progress in TB vaccine R&D to inform advocacy efforts and to ensure that advocates are disseminating the latest data and information. Advocates should also participate in research meetings to stay abreast of the latest advances in the field. By doing this, researchers and advocates can develop common messages, and also build relationships to underpin future advocacy efforts.

- **Identify opportunities for researchers to share their knowledge and findings.** TB vaccine advocates should identify ways for researchers to participate in advocacy. This could include identifying key opportunities for them to engage with their Member of Congress or Parliament, to write a letter to the editor or an Op-Ed, to participate in community meetings, to sign-on to joint letters, statements or calls to action, or to present at an advocacy-related conference or event.

- **Share information and develop a common language and messages.** Researchers and advocates tend to communicate in different ways (see Fig. 1). For example, advocates focus on having a compelling factual argument while researchers focus on staying objective and unbiased; and advocates strive to keep the message simple while researchers may be compelled to explain findings in great detail. Researchers add value to the messages put forth by advocates by ensuring that they are accurate, and advocates can ensure that the messages deployed by researchers are straightforward, convincing and tailored to the target audience. Understanding how each group communicates will help researchers and advocates to identify common ground and ensure that key messages are accurate and factual, while also appropriate for those to whom the messages are directed.

![Figure 1. Differences between advocacy and research communication.](source: Image)
- Engage civil society in clinical research.
Researchers conducting clinical trials of new TB vaccines should seek ways to engage civil society and affected communities. Some opportunities include forming community advisory boards to provide input on various aspects of clinical research, convening or participating in community meetings to share information about a potential or ongoing trial, and engaging in advocacy efforts targeted at local, regional and national governments to create a supportive and enabling environment for clinical research.

4. Conclusion
Researchers have the knowledge and data to make a huge impact, and their voices are credible and influential. Advocacy is crucial in global health, where the stakes are life and death. As we move into the next decade of TB vaccine R&D, it is more important than ever for researchers and advocates to work together in securing sufficient support and resources to achieve the ultimate goal of developing new, more effective TB vaccines.

Acknowledgements
This opinion piece was informed by interviews with and feedback from individuals that have experience in engaging researchers and advocates to advance research goals. Our thanks to those who contributed their knowledge and experiences, including David Bryden, Stop TB Partnership Officer at RESULTS; Alexandra Cordts, Research!America; Lucy Ghati, National Empowerment Network of People Living with HIV/AIDS in Kenya (NEPHAK); Christine Lubinski, Center for Global Health Policy at the Infectious Diseases Society of America; Stephanie Seidel, Global Alliance for TB Drug Development; Mandy Slutsker, RESULTS; and Dr. Jeffrey Starke, Texas Children’s Hospital.

Conflicts of interest
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References
The blueprint for vaccine research & development: Walking the path for better TB vaccines

Christian Lienhardt, Uli Fruth, Michel Greco

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ABSTRACT

Much progress has been made in TB vaccine research over the past ten years, and a series of new live genetically altered mycobacterial vaccines, viral-vectorized vaccines and sub-unit vaccines composed of recombinant antigens are presently in clinical development phases. A series of challenges remain, however, to be addressed in order to develop new and better candidate TB vaccines, especially an expansion of our knowledge of what constitutes protective immunity in TB, the identification of the most suitable vaccination strategies, the capacity and infrastructure to conduct large-scale trials in endemic countries, the investment in vaccine manufacturing capacity, and the development of effective regulatory pathways that shorten review timelines. In this brief paper, we review how the Vaccine Blueprint places itself in the continuation and expansion of two groundbreaking initiatives taking place over the last two years, that is, an invigorated Global Plan to Stop TB 2011–2015 that gives a clear emphasis on Research and Development, and the International Roadmap for TB Research, that identifies key priorities for research on TB vaccines, spanning from the most fundamental research aspects to the more field-based epidemiological aspects.

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trials of various vaccines may be conducted in the near future, it is important to develop standardized immunological assays to allow better comparison of various vaccine candidates in different settings. In parallel, large and well controlled epidemiological cohort studies in infants and adolescents are needed to provide important baseline TB incidence data and help determine the suitability of sites for large-scale efficacy trials.\(^4\)

In addition, and in order to ensure an ample supply of quality candidate vaccines for clinical trials and minimize the lag time between licensure and worldwide distribution, it is imperative to invest in vaccine manufacturing capacity. Currently, some capacity exists in both the private and non-profit sectors, but additional investment will be needed in order to meet future demands for new TB vaccines, and emerging economies are called to play an important role in vaccine manufacture and delivery. Lastly, appropriate delivery, regulatory and access strategies for TB vaccines, including the development of effective regulatory pathways that shorten review timelines without compromising the ultimate quality of vaccines will have to be developed and implemented.

A series of groundbreaking initiatives have taken place over the last two years, with the view to help and address these various challenges. First, as a landscape-setting activity, the Global Plan to Stop TB 2006–2015 has been extensively revised in 2010 with a clearer emphasis on Research and Development. The new Global Plan to Stop TB 2011–2015 has a more detailed roadmap for meeting the 2015 research goals, including blueprints for fundamental and operational research in addition to the key areas of new diagnostics, drugs and vaccines development. With reference to TB vaccines, the updated Global Plan lists, in a coherent and coordinated way, the set of activities to be carried out in all aspects of vaccine development with the view to obtain a fully licensed vaccine by 2020. It also provides an estimation of the investments needed in research and development to reach the set goals by 2015\(^5\) (see Box 1).

Second, the International Roadmap for TB Research, developed in 2011 by the Research Movement of the Stop TB Partnership with the contribution of more than 150 TB research partners worldwide, includes a section which identifies key research priorities relevant to TB vaccines. These span the whole research spectrum, from the most fundamental research aspects (such as better understanding of the host–pathogen interaction and identification of the components of the host immune system that are critical for control and elimination of the bacilli) to the more field-based epidemiological aspects (including conduct of pre-vaccine epidemiological studies to facilitate TB vaccine development and identification of suitable criteria from basic research to vaccine approval and global introduction. The Blueprint also gives due consideration to “Good Participatory Practice” and in particular the involvement of affected communities.

**Box 1. Global Plan to Stop TB 2011–2015: Objectives for R&D in vaccine development**

By 2015, it is expected that:
- Four new TB vaccine candidates will have entered Phase III clinical trials for safety and efficacy;
- Assays to determine biomarkers and correlates of immune protection will be incorporated into clinical trials;
- Sufficient manufacturing capacity and licensing agreements will be in place to ensure ample supply of new TB vaccines at reasonable cost;
- Appropriate infrastructure and capacity will be in place at multiple sites – in endemic countries with high TB incidence, and in different regions of the world – to conduct large-scale clinical trials that adhere to international standards;
- Regulatory pathways and access/delivery strategies will be developed to minimize lag time between licensure and distribution of new vaccines;
- Increased public support for and increased investment in TB vaccine development will be ensured.

**Box 2. International roadmap for TB research: Key vaccine research priorities**

- The top priority research areas are:
  - (i) identification of correlates of protective immunity after vaccination;
  - (ii) identification of the immunodominant antigens associated with different metabolic states of M. tuberculosis (or components of these antigens) to be added to vaccines to increase protection;
  - (iii) determination of appropriate clinical end-points and immunological read-outs for vaccine trials (especially with children); and
  - (iv) search for novel model systems for preclinical and clinical (challenge model) testing of TB vaccines, including pre- and post-exposure models and models that mimic reactivation.
- Priorities in fundamental research for vaccine development should aim at determining the components of the host immune system that are critical for control and elimination of the bacilli. This will involve determining the respective roles of innate and adaptive immunity in preventing M. tuberculosis infection and reactivation of latent disease and better understanding of immune responses against different metabolic stages of the pathogen and in different populations (HIV-infected and uninfected; various ages, from infancy to adolescence and adulthood);
- A high priority is development of improved vaccines for prime–boost vaccination strategies (including improvement of BCG as prime) and their optimal conditions of use (duration of intervals, boosting dose and number of boosts);
- This will require better understanding of the immune responses to BCG and new vaccines (including a comparison of responses obtained in different preclinical animal models);
- Identification and standardization of assays to assess vaccine-induced immunogenicity are critical to allow better comparison of candidate vaccines in different settings;
- Epidemiological studies to facilitate TB vaccine development and implementation of vaccine trials are a high priority;
- In the longer term, suitable methods for standardizing and planning trials sites should be identified.

of the host immune system that are critical for the control and elimination of TB bacilli), to the more field-based epidemiological aspects (including conduct of pre-vaccine epidemiological studies to facilitate TB vaccine development and identification of suitable criteria from basic research to vaccine approval and global introduction. The Blueprint, while providing in-depth overviews of the necessary scientific steps, addresses the importance of a timely consideration of downstream regulatory strategies and well thought-through policy pathways. The Blueprint also gives due consideration to “Good Participatory Practice” and in particular the involvement of affected communities,
another novelty in this kind of TB research publication. WHO Prequalification and development of vaccination policy enter in effect only once a vaccine is licensed, yet preparation must start years before, in order to avoid long delays of implementation in populations where the need is greatest. It is noteworthy in this regard that the TB vaccine development strategy as laid out by the Blueprint is supported by the WHO Strategic Advisory Group of Experts on Immunization (WHO-SAGE), WHO's top-level advisory committee on vaccination policy.

The introduction of new, effective TB vaccines and vaccination strategies is crucial to meet the TB elimination target. In the face of the emergence of drug-resistant strains of *M. tuberculosis* and the dual pandemics of TB and HIV, there has never been a more urgent need for a new vaccine that would prevent all forms of TB. According to recent modeling studies, the introduction of new effective TB vaccines and vaccination strategies will make a crucial contribution to achieving the Stop TB Partnership’s goal to reduce the global incidence of TB disease to less than one case per million population by 2050, in close synergy with the introduction of novel diagnostic and treatment strategies.

Following the path traced by the Global Plan to Stop TB 2011–2015 and the International Roadmap for TB Research, the Blueprint for TB Vaccines provides a much-needed coordinated plan for rational vaccine development. Buy-in by relevant stakeholders will be crucial to translate it into intensified collaboration between vaccine developers, increased involvement of the private sector, enhanced coordination among funders and timely dialogue with future users. If all this can be achieved, the Blueprint will represent a key milestone to ensure the development and uptake of new TB vaccines and vaccination strategies as key components of a global strategy towards a world free of TB.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### References
