1. Purpose of a 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 over 9 million new cases and 1.7 million deaths each year. An estimated one third of the world population is latently infected 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 Bacille Calmette-Guérin (BCG) protects against severe progressive TB in children but is inconsistent in protecting against the predominant adolescent or adult forms of TB. Furthermore, BCG has been recently shown to be unsafe in HIV-infected infants and its use in this population is not recommended. New vaccines are needed that are safe, also in immuno-compromised individuals, and effective against all forms of TB in all age groups and in all global populations.
In the last decade much progress has been made: a rich pipeline of new vaccines candidates has emerged, fourteen of which 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 now exists. The effectiveness of these vaccines in controlling TB will be revealed over the next few years and plans for regulatory approval, delivery and access need to be developed.

However, since there still is a profound lack of understanding of what constitutes protective immunity in different age groups and populations, and as there is no correlate or surrogate of immunity the success of new TB vaccines cannot be predicted or assured. It is unlikely that the current TB vaccine pipeline will covers all target profiles required for an effective, global TB vaccination strategy and continued research on TB vaccines and TB Biomarkers needs to be supported. New (preclinical) models and objective criteria for down selecting vaccines for the various target profiles including those directed against latency in an as early a stage as possible; and to achieve that effective advocacy, communication and fundraising strategies will be required.

**VISION:** Through partnerships, innovative strategies and creative mechanisms, to introduce the safest and most effective tuberculosis vaccines that reduce tuberculosis worldwide.

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 and 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 in earnest at the Second Global Forum on TB Vaccines (Sept 22-24, 2010, Tallinn, Estonia) and has continued with input from various vaccine developers, stakeholders and the scientific TB vaccine related community. The process has been coordinated through the StopTB Working Group on Vaccines with support from the WHO, Bill & Melinda Gates Foundation, Aeras Global TB Vaccine Foundation, TuBerculosis Vaccine Initiative and other organizations interested in 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 the problems of 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 Task Force on New Approaches to TB Vaccine Development of STOP TB working Group on New TB vaccines), the Keystone Symposium on Tuberculosis January 2011, the TBVI Symposium February 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 2011). The critical priorities and major activities appearing in this Blueprint have been assembled from the thoughtful contributions of many during this year long process.

We want to recognize that this current effort stands on the shoulders of the first “Blueprint for Tuberculosis Vaccine Development” developed at a Workshop held in 1998 chaired by Barry Bloom which 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 1940’s 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 international effort to develop TB vaccines that will have a significant global impact on tuberculosis and have identified five key priority areas 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  
Rationale Selection of TB vaccine Candidates  
The Critical Need for Advocacy, Community Acceptance and Funding

Each of these “Keys to Progress” are discussed in detail below. Critical activities for each of the priority area are described and are provided as action items and as areas where interested parties should focus their efforts. We also hope this document encourages additional creative ideas to help us reach our goal of having safe and effective TB vaccines within a reasonable time to prevent and control this devastating disease.
III A. 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 selection, screening using available TB animal models, selection of a delivery approach as a live recombinant, adjuvanted protein or viral-vectored vaccine and partnering with a manufacturer who can produce GMP lots of vaccine for human testing. Fourteen of these TB vaccine candidates are in clinical trials and data from these studies will be available in the next few years. Since it is unclear if these vaccines will be successful and address the major or even all forms of TB disease, and since there is a lack of knowledge in key areas of tuberculosis immunology, microbiology, pathology, molecular biology and vaccinology, including which immune mechanisms afford protective immunity to the human host, innovative research approaches are needed to address these critical areas in TB vaccine research. The TB vaccine field would benefit greatly if scientists and clinicians with various expertise were supported by donors 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. Improve the antigenic vaccine repertoire to prevent infection and provide sterilizing immunity

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

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 *M. tuberculosis* pathogen control the disease and are “latently” infected but show none of the hallmarks of active disease. The immune mechanisms responsible for this “resistance” to disease remain elusive. Induction of Th1 immune responses by the host seems to be necessary for long-term protective immunity but may also be detrimental if not held in check by suppressive mechanisms such as regulatory T cells. CD4 and CD8 T responses may provide protection but, to date, no specific population of T cells as been found to correlate with protection in animal models or human studies. There is an urgent need for innovative approaches designed to reveal the true nature of the immune mechanisms responsible for natural resistance to disease and to how it can be applied to vaccine development.

Current evidence from animal models suggests an important role of early phase innate immune responses, including migration of infected cells from the lung to the draining lymph node and an inhibitory role of regulatory cells. An open question is what implications this has for vaccination, as most vaccines solely aim at inducing and/or improving adaptive immune responses.

There is considerable debate as to whether antibody-based mechanisms contribute to protection and if they may be particularly important for the development of infection or transmission blocking vaccines. The pursuit of vaccines containing mycobacterial glycolipids or polysaccharides are of particular interest since they are thought to interact with (TLR and Non-TLR) pathogen recognition receptors of the innate immune system, and blocking such interactions by specific antibodies may interfere with pathways that help the mycobacterium to survive or establish itself inside the host cell. The role of such antibodies in inducing specific immune protection and in diminishing pathology could be further explored.

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

While the efficacy of TB vaccines in humans is unknown at this stage, in mouse, guinea pig, and nonhuman primate models a number of new vaccines have demonstrated improved efficacy as compared to BCG by showing improved survival, by histopathological analysis and by reduced colonization of tissues by *M. tuberculosis*. However, no vaccine has provided clear evidence that it can block lung infection, provide sterilizing immunity or reduce transmission within populations. It may be that, similar to meningococcus, the dominant antigenic repertoire, which is the basis of most current TB vaccines, might act as a decoy that misdirects the immune system and that use of the most immunogenic antigens in vaccines will induce suboptimal immunity. This is
supported by recent studies which demonstrate that dominant Mtb epitopes are highly conserved in many different Mtb strains in different geographical regions suggesting that their conservation is beneficial for Mtb maintenance and survival in the human population. In addition, the current 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. The antigenic repertoire currently used for TB vaccine development is suboptimal and the use of stage specific, less dominant, and more variable antigens should be explored for developing more effective vaccines.

One avenue for enhanced investigation is the identification and exploration of antigens that are specific for the different infectious phases. One focus of discovery has been to identify antigens from the so-called latent stage of infection. This stage is thought to be dominated by the presence of metabolically different and so-called dormant bacteria and such bacteria may predominantly express other antigens. Mimicking this situation in nutrient starved Mtb bacilli, several new antigens have been identified.

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. Several lipid antigens have been identified that are recognized by T-cells in the context of CD1 molecules, and the protective efficacy to some (eg di-acylated sulfoglycolipid) are currently being evaluated in preclinical studies. In addition to their antigenic properties, lipids often have intrinsic adjuvant properties which may make these molecules very 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, variable antigens of Mtb such as those belonging to the PPE and PE family of proteins for vaccine development might be a way forward. 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.

Current adjuvants being investigated in TB vaccine development stimulate both TLR4 (eg AS01/02/GLA), TLR9 (eg IC31) and Non-TLR Mincl receptors (eg CAF01). If the induction of a Th1 response is an essential element of TB vaccines, exploration of adjuvants that activate TLR7, 8 and 9 receptors seems to hold specific promise. Such avenues might be combined with adjuvants that stimulate non-TLRs and which may act synergistically in enhancing the immunogenicity of TB vaccines. There is an urgent need for collaborative efforts to advance the use of novel adjuvants for TB vaccines.
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 mouse latency and models that mimic immunosuppression have an important role in TB vaccine development and there is considerable room for improvement in both how these models measure immunoprotection and how well they mimic human TB disease. The specific antigenic immune responses required for successful TB vaccines are dependent on the different human target profiles that need to be addressed including those already infected with Mtb and those whose immune system may be compromised by heterologous infections including HIV. New or better animal models that enable assessment of immuno-protective responses for specific target populations including natural infection and for defining correlates of immune protection are urgently needed. Studies in a cattle model have shown that vaccines have the potential to protect against natural transmission of virulent *M. bovis*, therefore, cattle may be an excellent model to explore development of human transmission blocking vaccines. An area of increasing interest in human vaccinology is the study of therapeutic TB vaccines in post-infected or persons with active disease. Models that mimic the action of vaccines in infected or diseased animals are needed. There is also an urgent need for standardization of existing models and for development of new promising models such as the pig model.

New technologies for measuring vaccine responses in animal models should also be explored. Use of imaging technology for longitudinal quantification of disease progression and for studying the microenvironment in disease states in animal models is a good example of new technologies being applied to TB modeling. Imaging technologies that allow longitudinal study of the micro-environment of individual granuloma may particularly to studying the evolution of different types of T, B and plasma cells in the microenvironment of individual granuloma.

Considerable expertise in animal models exists within the European NEWTBVAC consortium and within the U.S. National Institutes of Health where comparative studies can be performed following a selection procedure to assess safety, protective efficacy, and immunogenicity of TB vaccine candidates. Coordination of these efforts 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 (comparison of viral vectored vaccines for example using those in clinical trials as lead candidates) are very important for selecting new candidates to enter into the vaccine pipeline. There is growing evidence that Mtb strains can differ both genotypically and phenotypically, therefore, there is a need to use human clinical isolates as challenge strains in preclinical models to demonstrate that vaccines are effective against varied human isolates as well as lab strains commonly used in animal experiments.

In general, there is a need to have a meaningful data profile for each vaccine product arising from basic research so that informed decisions can be made for the selection of best candidates to move forward into human clinical studies (see Section III D). Since
preclinical data is critical for entry into early clinical trials it is also 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 and that these data should be published or made available through information sharing mechanisms. Also, TB vaccine development can profit from the successes and failures of others especially those researching malaria and HIV vaccines.

Key Questions

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?

IIIB. Correlates of Immunity and Biomarkers for TB Vaccines

Next to identification of a safe and effective TB vaccine no issue is more critical to the success of testing and introducing new TB vaccines than the discovery of biomarkers that correlate with vaccine efficacy or can serve as useful markers of vaccine success or natural protection / 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. Substantial efforts to identify an immuno-biological marker for TB vaccines have led to a small number of signatures that are now being evaluated and validated. However, most of these efforts have to date not been successful and new innovative approaches are required. This is an area where new technologies and the willingness to create innovative partnerships across scientific fields will likely yield the most benefit.
IIIC. Clinical Trials: Harmonization & Cooperation

Hassan Mahomed (South African TB Vaccine Initiative, University of Cape Town), Bernard Fourie (Dept Medical Microbiology, University of Pretoria)

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 and developing countries and present investigators with scientific and logistical challenges. All aspects of clinical studies beyond phase I including disease endpoints, secondary immunological objectives, safety profiles, immunization regimens and laboratory capabilities are being implemented in endemic countries which can tax the regulatory and ethical as well as the clinical infrastructure. Improved clinical capabilities for testing novel TB vaccines in target populations which include all age groups, individuals infected with Mtb and/or HIV and those BCG vaccinated in a timely and cost effective manner in difficult environments is a major challenge for the TB vaccine community. Innovative partnerships, sharing of sites, harmonization of endpoints and other clinical trial parameters and mechanisms for acquiring efficient regulatory review are critical needs in this key area.
Three Critical Activities in Clinical Trials

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

5. Determine TB prevalence and incidence, select trial sites and choose target populations for TB vaccines that result in the greatest reduction in disease

6. Define and implement appropriate trial designs to assess new delivery platforms and routes of administration

Critical Activities

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

[ Major issues: Develop clinical paths and endpoints for multiple target populations (i.e. for mass vaccination); Integrate new diagnostics into vaccine trials; Establish multicenter cohort studies to measure progression from latency to active disease; Understand vaccine responses in HIV/TB co-infection; Standardize clinical immunoassays; Validate and incorporate correlates of protection in trials; Explore new delivery platforms and routes of administration; Develop a human challenge model for TB]

Epidemiological diversity in risk of infection and disease is quite marked in tuberculosis. Equally so, the protective efficacy of BCG observed over many decades has been shown to be highly variable in populations around the world. Furthermore, recent studies with new candidates also underline the fact that, given the distinctly different features of the stages of pathogenesis of the disease, a lack of understanding of the immune mechanisms to prevent, contain and/or repress infection, still pose major challenges for vaccine development. A further complication resides in factors such as specific population-associated features which might result in marked differences in immune responses to the same vaccine in similar age cohorts from different parts of the world. It emphasizes the need for clinical assessment to take into account geographic and genetic diversity. It also suggests that clinical outcomes in human vaccine trials need to be interpreted in the context of epidemiological variables that might impact efficacy assessment. It is inevitable that even smaller Phase II trials would need a multi-center approach or be repeated across continents, allowing for the vaccine to be assessed in similar age-cohorts but taking into account factors that are known to affect the risk of TB infection or disease in different populations. These include concomitant diseases with high prevalences (particularly HIV and parasitic infections), exposure to environmental mycobacteria, predisposing environmental conditions, socio-economic factors and population demographics. There is a need, therefore, to investigate such factors comprehensively in
relation to target endpoints, and to standardize the collection and interpretation of data on those with greatest significance for all trials progressing into Phase II/III.

It is known that, in the absence of an underlying HIV co-infection, the greatest proportion of TB incidence is generally driven by disease arising from TB infections acquired in the two years prior to its clinical progression. There are exceptions: In young children up to the age of 5 years, and in adolescents, the progression is sometimes continuous following infection and in pre-adolescent years, latency is mostly maintained. There is also the almost universally observed higher rate of disease in males than in females in high prevalence settings. HIV co-infection, however, has changed this picture. Latent TB infections are exacerbated in young adults, and the two-year rule is no longer valid. Moving forward on re-defining a clinical pathway for assessment of vaccine efficacy, the dynamic of latency and progression to disease needs to be understood for every population where vaccine trials are being run. Multi-country cohort studies in different target age-groups, and taking into account the various other potential confounding factors mentioned above, 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.

The development of clinical paths and endpoints to assess vaccine efficacy in mass vaccination campaigns post product licensure/registration (vaccine effectiveness) would essentially target outcomes that could reasonably be observed and documented by control programme staff and primary health care service providers. The integration of modern molecular diagnostic procedures for detection of pathogen, and of any relevant assays to detect enhanced immunogenicity, into a pre-defined set of investigations to be conducted as part of ongoing vaccine safety and efficacy surveillance, is necessary. There are special challenges for setting hard immunogenicity or vaccine efficacy targets for paediatric cohorts, with more concerted research into what constitutes a protected or a diseased child still being required.

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. Trials using a microbiologically endpoint would be prohibitively expensive. Thus, evidence of exposure to tuberculosis in combination with symptoms and radiological features have been proposed as an endpoint for this target group. However, these features lack specificity even in combination and there is a risk of undermining efficacy measures where specificity is in doubt. This will be a key area for further attention as we move into efficacy trials over the next period since infants are a priority target for TB replacement and prime-boost vaccines.

Fourteen new TB vaccine candidates had entered clinical trials by the end of 2010. While not all are currently under active development, this is a promising sign of the progress made in TB vaccine development over the last decade. However, the breadth of candidates has also brought challenges to the TB vaccine development arena. A range of efficacies from 60% and 90% have been proposed as acceptable levels for licensure to be considered. The lack of consensus highlights the importance of this issue, particularly in
populations where the benefits of a new TB vaccine are potentially great. Lessons can be learned from the malaria field, where the acceptance of a 35-55% efficacy measurements in phase II trials for a malaria vaccine was regarded as sufficient for moving forward into a phase III trial. A number of factors influence discussions about an acceptable level of efficacy for TB vaccines. One factor is the discrepancy in BCG vaccine efficacy since although it has a wide use in infants and relative consistent efficacy against disseminated TB in this population, it has variable efficacy against pulmonary TB. Another key question is to determine what level of efficacy has both a significant public health impact and a compelling cost/benefit ratio. Mathematical modeling may help to answer these difficult questions. TB is a massive public health problem and there is a need to have in-depth discussions (that include clinicians in endemic countries) that address issues such as the initial acceptance of fairly modest gains in efficacy over BCG given the breadth of the current pipeline and the potential for more effective next generation vaccine candidates.

While trials may use a number of categories to describe safety, these may be reduced in trial reports or publications. Different terms may be used to describe the same adverse event when different sponsors are involved. Standardization of safety assessments across different TB vaccine candidates is of high priority and work with groups such as the Brighton collaboration may assist with this.

An interesting issue is the standardization of the development pathway. For example, 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 jump straight from adults to infants. This partly reflects an evolution in regulatory approaches. However, not all vaccines in proof of concept IIb trials have undergone interference assessments with other vaccines. This is an important step in planning towards implementation where in all likelihood, and should a vaccine be efficacious and licensed, it would best be given with other vaccines. Safety in the HIV positive community is crucial and all vaccines should be required to be tested in this group for safety assessments since this will be a key target group in adults and infants given the high prevalence HIV in many high TB burden countries.

The development of suitable human challenge models should also be explored. This will help with prioritizing the myriad of TB vaccines at an early stage for selection of the most promising candidates before proceeding to the costly process of clinical trials.

2. **Determine TB prevalence and incidence, select trial sites and choose target populations for TB vaccines that result in the greatest reduction in disease**

- **Major Issues:** Increase site capacity and reduce trial costs through novel partnerships; Overcome roadblocks to performing comparative studies with different vaccine products; Conduct comparative human studies using multiple TB vaccine candidates; Pursue creative regulatory approaches that will enable vaccine licensing outside traditional phase III requirement; Define role of WHO in facilitating vaccine access and rational use

Given the fact that BCG has in some populations and age cohorts managed to reach a protective efficacy of 80%-90%, there is little scope for any vaccine to do much better in
similar target groups, unless 100% efficacy can be achieved. But this 10% room for improvement is a real and unchallenged target. Currently, the emphasis is to do better than BCG on average, i.e. better than 50% protection irrespective of where, when and to whom the vaccine is administered. Even in such a situation, large numbers of subjects would need to be enrolled in order to demonstrate enhanced efficacy. However, where BCG is of limited benefit, efficacy trials may be easier. It is obvious that populations with the highest prevalence of disease would be natural choices for establishing vaccine trial sites, and such efforts are currently widely pursued in especially sub-Saharan Africa where TB rates are fuelled by the high prevalence of HIV co-infection. But even the highest prevalence areas might still not deliver sufficient numbers of cases over shorter periods of time, in order to demonstrate conclusively that new candidate vaccines or vaccination strategies are superior to current measures. It is inevitable that trial capacities be integrated (but not necessarily merged), in order to access large populations at risk of disease so that small margins of vaccine efficacy enhancement could be detected.

But, even if vaccine developers work together on sharing trial sites (already happening to some extent, and greatly facilitated by bodies such as the EDCTP, 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 efficacy trial, perhaps not many more than 2 of the strongest candidates entering Phase III trials could be accommodated.

A 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 required: (A) Live mycobacterial vaccines designed for replacing BCG; (B) Subunit vaccines designed to boost BCG; and (C) Therapeutic vaccines designed as 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 how to measure, and would likely have access to specialised clinical laboratory infrastructure. Focus would largely be on definitive Phase II trials.

For B, access to adolescent and adult populations is important. This is likely to be the largest requirement for the immediate future. Significant networking across diverse geographical areas are beginning to be utilized for certain advanced candidates, but not 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 outcome indicator of vaccine efficacy, and a rapid diagnostic infrastructure to detect 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 populations 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 drug research groups might be useful.

To date, all clinical trials of the candidate TB vaccines have been preceded by the generally accepted phases of clinical development for a new vaccine and current candidates have all been shown to be safe in Phase I trials in adults, adolescents and children. Clinical development programmes have included Phase-II dose-escalation and age de-escalation stages with appropriate Independent Safety Monitoring at each step.

Although the clinical development, to date has shown that the candidate vaccines are safe (in the groups tested) and provoke a range of immune responses, there is, as yet, no indication of vaccine efficacy. Phase IIb trials are in progress in infants and HIV positive adults with efficacy objectives. These trials will help guide future vaccine development. However, given the challenges of demonstrating efficacy in these two target groups, it may need an efficacy trial in HIV negative adolescents/ adults to confidently assess vaccine efficacy. Candidates thus achieving measured efficacy may then be rolled out 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.

One of the main criteria for selecting a site for efficacy trials is the TB incidence rate in the community where the trials are to be conducted. A site which has a high incidence rate either in the general population or in the target group of interest would be more suitable for efficacy trials since this would limit the sample size required to evaluate TB vaccine candidates. The question is what source of data should be used to establish such rates. Some sites have conducted cohort studies which provide strong evidence of incidence rates in relevant populations such as infants and adolescents. Most sites do have access to routine TB program data but this evidence is weaker, subject to errors and may be incomplete. Some argue that true incidence for clinical trials will only be evident in the clinical trial population itself. This argument has merit in that some selection of participants occurs during the enrolment for clinical trials and this introduces a bias. However, one usually needs to have this kind of data before embarking on a trial. Good quality data through epidemiological studies would be ideal as a guide for planning efficacy trials but the challenge would be how this would be funded. Since trials are costly, it could be argued that such an investment in epidemiological studies would be worthwhile.

An adaptive trial design that can drop ineffective or reactogenic candidates, or modify group sizes based on predefined criteria could shorten the clinical development of a vaccine. However, the robustness of the statistical analysis will be changed by dropping groups that were originally planned for analysis or revising group numbers. Such changes should be considered when including flexibility into a trial protocol. 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 protocol design difficult.

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.

Head to head comparisons have not occurred to date in human trials. This is an intriguing idea for a number of reasons. Firstly, it may be a way to cut the 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 used for this. Secondly, this may be an important way in 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. Contractual arrangements may be complex where there are a number of partners participating in the same trial. Thirdly, if these trials are done at early phases, we 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.

As we move towards efficacy trials which require bigger numbers and are therefore more expensive, at the same time there is recognition of the fact that funding for such trials will be limited. We would need to have a rational approach for selecting candidates for efficacy trials as clearly there will not be enough funding for many candidates to undergo such trials.

On the other hand, there should be exploration of reducing the costs of such trials. One suggestion that has come through is to utilize existing trial site networks such as HIV Vaccines Trial Network (HVTN) and IMPAACT for such trials 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.
3. Define and implement appropriate trial designs for assessing new delivery platforms and routes of administration

[Major Issues: Assess alternative delivery platforms for vaccines that might hold potential advantages to TB vaccine development; Consider innovative approaches including pulmonary, oral or transdermal (microneedle patch) routes of delivery; Explore innovative vaccine formulation technologies]

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 or even BCG, showing promising results.

Several recent investigations involving room-temperature stable oral microparticle preparations of BCG already show promising results in bovine models, and this route of delivery might hold promise for application in humans as well. Although not yet having been explored in the context of TB vaccines, skin patches containing microneedles coated with dried solutions of various other vaccines, also might hold promise. 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.

Key Questions

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?
IIID. Rationale Selection of TB Vaccine Candidates

Although perhaps not as thought-provoking or as intuitively important as scientific challenges, establishing comprehensive, measurable and globally acceptable criteria for selecting (or down-selecting) vaccine candidates that are in the pipeline is one of the most crucial issues in the TB vaccine community. Currently eleven vaccines are being tested in clinical studies in individual clinical trials often using different endpoints and immunological measures for analyzing outcomes. Unless these vaccine candidates fail or are studied in comparative clinical studies it will be very difficult to determine which are the most safe and effective until they are introduced and followed in large postmarketing studies. Likewise, identifying acceptable criteria that can select the most promising candidates from among a large portfolio of vaccine candidates arising from the research arena to move forward into human clinical studies is a significant challenge in the TB vaccine field. It is critical that specific and measurable selective criteria be established based on vaccine type, target population, delivery approach, mechanism of action, clinical testing, regulatory and manufacturing feasibility as well as business and marketing issues. Identifying these criteria at different stages of development is one challenge but just as challenging is obtaining general consensus for the use of these criteria within the TB vaccine community.

Key Questions

Will all vaccine developers 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 there 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?

[ This section under construction ]
IIIE. The Critical Need for Advocacy, Partnerships and Funding

The TB vaccine field is both blessed and cursed by the fact that BCG vaccines have been used to immunize humans for 80 years. BCG vaccines have a solid safety record but have not been successful in stemming the worldwide epidemic of TB. Since new TB vaccines need to be introduced into communities that believe BCG has value, new vaccines have to prove they are superior to BCG in safety and effectiveness. This effort is complicated by the fact that the specific efficacy of current BCG vaccines is unknown and therefore serves as a questionable standard upon which to compare new TB vaccines. This is a conundrum for the TB vaccine field both in designing useful clinical trials that will provide the appropriate answers to safety and efficacy questions but also in building enthusiasm for a new “unknown” vaccine for TB in the communities that the vaccine will serve. In the current economic environment this is also a critical issue for perspective donors where enthusiasm is dependent upon not only a clear path forward for new TB vaccine development but also recognition that there is a keen desire within the target countries for a new vaccine. There is a critical need to mobilize more resources for TB vaccines through better public awareness campaigns. As has been observed for other successful global vaccine programs such as the introduction of pneumococcal and meningococcal vaccines, without the efforts of all parties including scientists, global organizations, public health agencies, pharmaceutical companies and community advocates working together with support from donors, the introduction of a new TB vaccine will be at best significantly delayed.

Key Questions

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?

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