Key issues in the clinical development and implementation of TB vaccines in South Africa


1. Introduction

Developing new effective vaccines that will prevent infection by Mycobacterium tuberculosis (M. tb) and/or reduce the risk of developing tuberculosis (TB) disease is the world’s best hope for controlling and eventually eliminating TB as a global health threat.1-3 The only existing licensed vaccine against TB is a modified, attenuated strain of Mycobacterium bovis, Bacille Calmette

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doi:10.1016/j.tube.2012.05.001
Guérin, or (BCG). This vaccine, developed around the turn of the last century and first administered in 1921, is given to a large proportion of newborn infants throughout the world to protect them against TB. While BCG has consistently been shown to reduce the risk of disseminated disease and averting death in infants, the protection it confers against pulmonary TB is incomplete, variable and not durable. The last 5 years has witnessed significant progress in the field with at least 15 new vaccine candidates entering clinical trials, of which 12 are still actively being evaluated, and at least 3 new generation TB vaccine candidates are in the advanced stages of clinical testing. As the number of new candidate vaccines entering the clinical pipeline grows, a number of critical barriers to the development of new TB vaccines have become evident and include:

- The lack of a validated preclinical or animal model to predict the efficacy of a vaccine candidate in humans
- An incomplete understanding of the components of a protective immune response
- A lack of standardized assays to evaluate vaccine induced immune responses, which limits the ability to compare immunogenicity across vaccines

Progression of new TB vaccine candidates to licensure, and ultimately implementation in vaccination programmes, therefore requires large, expensive efficacy trials with long follow-up periods in target populations. This presents many challenges to vaccine developers, such as:

- Establishing and expanding clinical trial sites, often in areas with limited health care resources.
- Characterizing TB incidence in target populations to assist in trial planning and resourcing.
- Standardizing case definitions for TB disease.
- Designing trials with composite endpoints, such as TB incidence and all-cause or TB-specific mortality, given the varied presentation and challenges in TB diagnosis, especially in young children.
- Including health economic evaluations, in order to provide cost-effectiveness and affordability information to policy makers and health care providers responsible for introducing and implementing vaccine uptake.

A meeting of mainly South African key experts and stakeholders was convened by the Oxford-Emergent Tuberculosis Consortium (OETC) in order to share information and to explore harmonization of trial design and study procedures of future vaccine efficacy trials. The meeting was held in South Africa, which has one of the world’s worst TB epidemics and where the need for a new TB vaccine is therefore greatest. Furthermore, South Africa has substantial expertise in conducting clinical trials, particularly in the HIV prevention field and has growing expertise in conducting TB vaccines trials.

The goal of this paper is to summarise discussions and consensus arising from the key stakeholders’ meeting. It is anticipated that this paper will contribute to an ongoing dialogue about planning TB vaccine development efforts and optimizing clinical development pathways. The meeting focused on (i) understanding TB epidemiology, particularly disease incidence and implications for TB vaccine candidate efficacy trials; (ii) scaling up vaccine trial site capacity; (iii) evaluating correlates of protection; (iv) standardizing efficacy endpoints; (v) developing innovative trial designs to accelerate progress towards licensure; (vi) identifying vaccination strategies and licensure pathways; and (vii) forecasting cost, demand, and commercialization and access needs.

2. Understanding TB epidemiology – and implications for TB vaccine candidate efficacy trials

Understanding the epidemiology of TB, in particular the incidence of TB among infants, adolescents and young adults, and HIV-infected persons that are at high risk of TB is essential for sample size estimation, recruitment planning, determining the number of sites and staff required to run large multi-centre trials, as well as cost estimations for budgeting and funding applications. Although some clinical trial sites have clinical and epidemiological data available from previous observational studies and clinical trials in infants and adolescents, there is limited data on microbiologically determined age-specific TB incidence to support the design and conduct of TB vaccine candidate efficacy trials in high TB incidence target groups.

Because of their immature immune systems, infants are at high risk of TB disease, particularly of the disseminated form and remain a primary population targeted for efficacy trials. The second peak in incidence commences in adolescence and peaks in adulthood. While TB disease rates are lower in this adolescent age group, they are an ideal group to target for a TB vaccination boost before the sharp rise in disease incidence seen in young adult populations. Further, adolescents are an attractive target group as they may be more easily reached through the school system in vaccination programmes and thus ultimately drive good vaccine coverage should an effective boost vaccine for the prevention of TB become available. Currently, TB disease incidence is several fold higher in the HIV-infected population in all age groups than in the uninfected population. Ultimately, the primary aim of TB vaccination is the interruption of transmission and the impact will be greatest with vaccination of the adolescent/young adult target groups as HIV-uninfected adults contribute most to TB transmission, even in high-HIV settings. HIV-uninfected adolescents and adults should therefore be included as key targets populations for TB vaccination.

Available information from general health care services is often inaccurate because routine data collection is dependent on passive case finding or mandatory notification statistics, which have less specific case definitions that are often based on clinical suspicion and a presumptive diagnosis. The data is rarely derived from prospective cohorts. Routine data therefore may over or underestimate the true incidence of TB, making study design and accurately statistical powering difficult for efficacy studies. As trial size is dependent on disease incidence, solid epidemiological data are essential for site selection. As many more clinical trial sites than are currently available will be required to conduct efficacy trials, having well characterized epidemiological data will be essential for site selection. Whilst the most accurate population-specific incidence rates can only be derived from large, costly, prospective cohort studies with trial definitions of participant selection and endpoint assessments, the urgency for such data and the resource constraints involved in emulating a full-scale trial may preclude this line of investigation. Rapid, retrospective analyses of existing routine or research based data are required as an alternative, preferably at trial sites already established to study other indications.

3. Scaling up vaccine trial site capacity

While some well-established clinical trial sites, capable of undertaking high quality efficacy studies, exist in areas with high TB incidence rates, many more additional trial sites will be required as more vaccine candidates enter advanced clinical trials. A challenge facing TB vaccine developers, however, is the relative lack of funding to develop new trial sites. TB vaccine candidate efficacy trials are very costly, because of their large size and the duration of
follow-up required to accrue incident TB cases, given the lack of an immunological correlate of protection. Such trials therefore require well-established sites before their commencement can be justified. The result is that without further site development, a restricted number of vaccine candidates will be able to progress to Phase IIb and III efficacy trials.

Over the last 15 years, the importance of developing infrastructure for TB vaccine trials in high incidence countries has been more clearly recognized. South Africa has led the way in building this infrastructure with funding support from Aeras,\(^1\) European Developing Countries Clinical Trial Partnership (EDCTP),\(^2\) European Commission (EuropeAid),\(^3\) and National Institute of Health (NIH),\(^4\) but unless further investment is made, and more sites are developed, the progress of many promising vaccine candidates may be stalled. Criteria need to be developed for site selection and to facilitate site development.

A set of minimum but essential trial site characteristics is listed in Table 1; additional site requirements are also presented. They are divided into “Must have” characteristics — if these do not exist, it will not be possible or will be very difficult to run TB vaccine candidate trials at the site — and “Nice to have” characteristics — if these do not exist, it will be difficult but still possible to run TB vaccine trials at the site.

Despite efforts to build capacity for TB vaccine candidate trials, the limited number of clinical sites that meet these criteria, and are capable of conducting TB vaccine candidate efficacy studies, remains a critical bottleneck in developing a growing pipeline of new candidate vaccines.\(^5,6\) Even for a single vaccine candidate, approval for use in infants, adolescents and HIV-infected adults may be reliant on separate Phase IIb and Phase III studies for each indication, each requiring access to different expertise and study populations at different trial sites. Furthermore, there is

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<td>Essential (“must have”) and desirable (“nice to have”) characteristics of potential TB vaccine efficacy trial sites.</td>
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<th>Essential/“must have” characteristics</th>
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<tr>
<td>Political support for TB vaccine development in the country, province and district, including in the affected community/ies.</td>
<td>Community support crucial and should go beyond simple information sharing and acquiring assent from a few decision makers</td>
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<td>Competent and efficient regulatory authority</td>
<td>Competency an absolute requirement, efficiency a relative requirement which can be improved</td>
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<tr>
<td>Competent and efficient local IRB/research ethics committee</td>
<td>Competency an absolute requirement, efficiency a relative requirement which can be improved</td>
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<td>Competent investigators and clinical research staff</td>
<td>Professional qualifications and Good Clinical Practice are minimum requirements</td>
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<td>Affordable cost of doing research (i.e. the cost of obtaining/identifying one case of TB in the control arm of any trial)</td>
<td>This is absolute in the sense that there is only so much funding for TB vaccine development — it is relative in the sense that additional funding can be raised, but this usually takes time. There may be good reasons for selecting more expensive sites. Cost is closely linked to incidence rate — see below.</td>
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<td>Adequate infrastructure to support laboratory endpoints — immunological, microbiological and safety</td>
<td>Some specimens can and possibly should be shipped to central laboratories (e.g. for immunological assays). However, shipping specimens for TB culture is probably not logistically possible. Results which impact participant well-being need to be available to investigators in real time.</td>
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<td>Adequate infrastructure to support clinical endpoints — investigation of suspected cases including clinical and radiological assessment.</td>
<td>The diagnosis of TB in certain target groups is difficult and requires the efforts of highly skilled nurses and physicians as well as special facilities — a good example is infants and young children. If the disease cannot be reliably diagnosed, there is no point in doing the trial at that site.</td>
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<td>TB incidence rate in target population ≤0.5% per annum</td>
<td>Important but not entirely absolute — offset to some degree by per subject cost. May be possible to conduct trials in lower incidence areas if per subject cost is driven down (e.g. by governmental/health department involvement and assistance).</td>
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<td>Practical feasibility of conducting research in the area (e.g. telecommunications, transport, personal safety issues, weather and natural disaster issues, co-morbidity issues)</td>
<td>Some areas of the world are simply more clinical research friendly than others. Something as basic as severe daily traffic congestion may make conducting a trial at a particular site unfeasible.</td>
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<td>Functional TB control and primary health care programs</td>
<td>TB vaccine candidate efficacy trials by nature detect individuals who have evidence of TB disease and/or TB infection, or who have other health related conditions such as HIV infection. It is essential that they are able to be referred to appropriate structures for ongoing care and management. If these do not exist then the sponsor/investigator has to provide them, which may not be feasible or affordable.</td>
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<td>Experienced clinical researchers, units, teams.</td>
<td>Previously, funders appeared to be happy to work with less experienced sites and support the development of their research teams. This is still the case with some funders, but is becoming increasingly uncommon. Funders are now looking for sites with previous trial experience. At the very least they seek sites where staff (clinical and laboratory) are well trained in most if not all core aspects of the work to be undertaken, so that only “fine tuning” will be needed.</td>
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competition by drugs, microbicides and HIV and malaria vaccines efficacy trials for existing clinical trial sites in many high TB and HIV disease burdened countries.\textsuperscript{10,17}

In order to develop the required TB vaccine candidate clinical trials site capacity for future Phase Iib and Phase III efficacy studies, additional investment is required, particularly to support:

- Conduct of epidemiological studies to determine baseline TB incidence in target populations
- Physical site infrastructure development, including vaccine storage facilities, data management facilities and laboratories
- Introduction of new molecular diagnostics technology, in particular GeneXpert MTB/RIF
- Training of research staff
- Core support provided to existing and new trial sites funding so that they can retain skilled staff between trials
- Development of site quality assurance systems compliant with Good Clinical Practice
- Advocacy and education amongst local populations to encourage understanding of and participation in trials

Additionally, in communities where vaccine trials are recruiting participants, there is likely to be limited access to basic health services in general, and optimal pregnancy prevention and HIV and TB treatment and care in particular. These considerations present both ethical and economic challenges to trial execution. Moreover, neither a readily available inventory of present and prospective vaccine clinical trial sites, nor any coordinating mechanisms for the optimal development and use of these sites, is in place. Development of trial site infrastructure not only has benefits for new TB vaccine candidates, but also provides a lasting resource for the conduct of other clinical trials and for the local communities in the form of access to ancillary medical expertise and diagnostic facilities.

4. Evaluating correlates of protection

TB vaccine development is burdened by the total lack of validated animal models for predicting efficacy and preclinical or Phase I clinical correlates of efficacy.\textsuperscript{20,21} With such markers and models absent, the testing of candidate vaccines that will satisfy licensure requirements must make a large presumptive leap, from relatively small safety trials testing of candidate vaccines that will satisfy licensure requirements on identifying immune correlates of protection in preparation for optimal development and use of these sites, is in place. Development of trial site infrastructure not only has benefits for new TB vaccine candidates, but also provides a lasting resource for the conduct of other clinical trials and for the local communities in the form of access to ancillary medical expertise and diagnostic facilities.

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6. Developing innovative trial designs to accelerate licensure

The current clinical trial development pathway for licensure of an effective vaccine is lengthy and requires large-scale safety and efficacy trials. Innovations in trial designs are therefore required to reduce the number, size and duration of trials to select the best vaccine candidates to advance to efficacy trials. There is also a need for innovative designs of registration trials that bridge to other age groups.

In order to deal with these same challenges, HIV vaccine researchers have recently proposed an innovative approach using an adaptive trial design.\textsuperscript{24} A similar approach may be used for the development of TB vaccines. In brief this approach involves evaluating: multiple vaccine regimens against placebo; long term durability only if there is evidence of efficacy over the first 18 months following vaccination; and pre-determined immune correlates of protection only if there is evidence of vaccine efficacy, without requiring unblinding of data. The design uses sequential monitoring for operational futility, harm, non-efficacy and efficacy to substantially reduce the time to identify poorly or highly efficacious vaccines.

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have been undertaken. Similar approaches need to be adopted for the marketing approval of novel TB vaccines whereby technical assistance is provided by regulatory authorities from developed countries in specific areas such as product characterization. The U.S.A. Food and Drug Administration’s (FDA’s) guidance on “General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases” implemented in December 2011 enables the FDA to license vaccines to protect against infectious diseases or conditions that are not endemic or have not been reported to occur in the U.S.A. (e.g. TB). The European Medicines Agency (EMA) through article 58 of regulation 726/2004 may provide scientific advice and assist regulatory review. Furthermore some regulatory authorities in developing countries have bilateral agreements that make provision for regulatory cooperation. Thus sponsors have two options available to them. The first is to conduct Phase 2 and 3 clinical trials in developing countries and submit for licensure to the FDA with subsequent submissions to developing countries medicines regulatory authorities. Alternatively they can request joint or collaborative reviews. The risk in the sequential model is that there may not be automatic acceptance by the local regulatory authorities and hence sequential filings may result in delayed market access in the countries that need the TB vaccines the most. Collaborative or joint reviews are however complex and require regulatory authorities to agree to such processes. Sponsors should present their development plans when filing for regulatory approval to conduct phase 2 or 3 clinical trials as the regulatory pathway requires careful planning by the local regulatory authority. Local regulatory authorities need to have these mechanisms of review available to sponsors.

8. Forecasting cost, demand, and commercialization and access needs

TB has an enormous socio-economic impact in developing countries by causing death and morbidity in young adults during their most productive years of child-bearing and working. TB is estimated to cause lost productivity of 4–7% of the gross domestic product in high-disease burden countries. Approval of an effective TB vaccine will reduce the number of TB cases significantly, thus reducing the financial burden of treating TB and allowing the allocation of health care resources to other important unmet needs in high endemic areas.

The importance of economic analyses in guiding policy and implementation strategies for new vaccines has received increasing recognition. When considering introduction of a new vaccine into a national immunization schedule, the level of disease burden (mortality, morbidity and disability) in the absence of vaccination, as well as treatment costs avoided from introduction of the vaccine, should be weighed against the costs of producing and delivering the vaccine. Such evaluations should also consider local factors, such as the national health budget, to facilitate assessing affordability and longterm sustainability. Cost-effectiveness of a new vaccine also depends upon context and varies with many socio-economic and acceptability issues.

Ultimately decision making is dependent on what policy makers value most, for instance the most efficacious TB vaccine may be sacrificed for the most affordable or the most implementable vaccine. It is important to think about cost-effectiveness of a new TB vaccine in the early stages of vaccine development. A number of aspects should be considered including the price that would make it affordable, and the type of subsidy/donor support that would allow for scaling up of manufacturing capacity and supply. An ongoing challenge in all forms of forecasting is capturing enough epidemiological data to produce plausible population level scenarios on which to base formal costing, and impact evaluation. A vaccine may affect TB acquisition, disease (re)activation, clearance, re-infection, and mortality. Given the previously noted difficulty of measuring a single primary outcome, which will in practice be primarily an aggregate of acquisition and (re)activation, it is apparent that no trial can measure all of these efficacy parameters. This suggests that in framing long term options for TB control, dynamic models (and especially semi-static models) will have limited scope in terms of specific quantitative cost and benefit/effect projections, though they may be very useful in framing strategic challenges, system interdependencies, and monitoring requirements.

9. Mapping the way forward – prioritizing actions

As the lead candidate vaccines navigate the uncharted territory of bringing a new TB vaccine to licensure, one clear message has emerged. There is a need for to collaborate and to establish establishment of strong partnerships to prioritize and systematically address the challenges ahead, listed below:

- Developing and standardizing efficacy/challenge animal models
- Establishing a site inventory that includes an assessment of “readiness/preparedness” that is accessible to product developers and sponsors
- Increasing the capacity of existing TB vaccine sites and tailoring sites used for other trials towards TB vaccine needs
- Understanding the costs of ongoing trials and the funding needed to support sites between trial activities
- Determining the incidence of TB in target populations
- Fostering collaborative research on development of biomarkers and correlates of protection
- Standardizing immunological assays and endpoints for efficacy trials
- Creating an international database of safety and other data from trials such as immunological markers to facilitate comparative analyses
- Establishing an open and ongoing dialogue with regulators to identify the most efficient strategies for evaluating TB vaccine candidates including “orphan drug status”; endpoint consensus; use of correlates of protection and alternate study designs to facilitate licensure of an effective vaccine
- Beginning a dialogue on commercialization and access; gathering information on cost and pricing; creating awareness of barriers to implementation and building stakeholder support

This discussion document outline the challenges and gaps and also identifies potential solutions for developing an effective TB vaccine with the aim of promoting ongoing dialogue to encourage wider collaboration and synergies in TB vaccine development. The anticipated outcome is therefore to build awareness of the issues and to start increasing efficiencies in planning and implementing strategies for late stage clinical development of TB vaccines.

Ethical approval: Not required.

Funding: None.

Conflict of interest: Drs. R Rustomjee; R Mcleod; J Shea; X Tong and S Lockhart are employees of Emergent BioSolutions, which has commercial rights to the vaccine MVA85A and majority ownership of OETC.

References