Tuberculosis 6

New vaccines for tuberculosis

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New vaccines are urgently needed if we want to reach the goal of substantially reducing the incidence of tuberculosis by 2050. Despite a steady increase in funding over the past decade, there is still a striking financial shortfall for vaccine research and development for tuberculosis. Yet, around ten vaccine candidates have left the laboratory stage and entered clinical trials. These vaccines are either aimed at replacing the present vaccine, BCG, or at enhancing immunity induced by BCG. However, these pre-exposure candidates are designed for prevention of disease and will therefore neither eradicate the pathogen, nor prevent stable infection. Long-term vaccination strategies need to target these more ambitious goals. Even though vaccine development will have a price, the return on investment will greatly exceed original costs.

Introduction

Better understanding of immunological mechanisms can form the basis for rational design of new vaccination strategies against tuberculosis.6,7 Latent infection with Mycobacterium tuberculosis is actively controlled by the immune response and once immunity wanes, reactivation occurs, which leads to active tuberculosis disease. The quality and magnitude of the immune response, therefore, decides whether the infected individual remains healthy for life, despite harbouring the pathogen, or whether infection transforms into disease. Successful control of M tuberculosis occurs in 90% of the 2 billion infected individuals worldwide, whereas 10% will develop active disease.14 The importance of the immune response in controlling M tuberculosis is further emphasised by the substantially increased risk of tuberculosis disease in individuals co-infected with M tuberculosis and HIV. In co-infected individuals, 10% lifetime risk of disease outbreak is increased to a 10% risk of disease outbreak within the first year of co-infection.1 The pathology of tuberculosis—ie, destruction of affected lung areas—has a pronounced immunological component. Thus, solid granulomas, which contain M tuberculosis and impair functions of affected tissue sites, and necrotic and caseous lesions, which destroy substantial areas of the lung, are the result of concurrent damage of the immune response in tuberculosis.6,7

Many successful vaccines have been developed through trial and error, not least the BCG vaccine, which was developed between 1906 and 1919 by attenuation of the virulent Mycobacterium bovis, but without any immunological insights.6,7 BCG protects against severe forms of tuberculosis in newborn babies, as originally proposed by its discoverers Albert Calmette and Camille Guérin.1 However, the present regimen of BCG vaccination soon after birth has little or no effect

Key messages

• The present BCG vaccination regimen protects newborn babies (not adults) against severe tuberculosis, has a proven safety record after more than 4 billion administrations, but faces safety issues in infants with HIV infection.
• Protection induced by BCG vaccination against adolescent and adult tuberculosis, the most prevalent form of the disease, is insufficient.
• New vaccines can contribute to the ambitious goal of reducing the yearly incidence of tuberculosis to less than one new case per million population by 2050.
• 11 vaccine candidates have entered clinical trials: most are pre-exposure vaccines and will most likely prevent tuberculosis disease. They are intended to either replace BCG (recombinant live vaccines) or to be given after BCG prime as boosters (either protein adjuvant formulations or recombinant viral carriers).
• Post-exposure vaccines are also needed and, ultimately, vaccines are needed that either prevent infection or achieve sterile eradication.
• Vaccine trial sites with appropriate infrastructure are urgently needed.
• After decades of inactivity, research and development for tuberculosis vaccines is slowly increasing, although there is still a substantial shortfall in funding. New partnerships and incentives need to be created.

Search strategy and selection criteria

We searched PubMed for publications containing the terms “vaccination”, “immune response”, “therapy”, “prevention”, “HIV/AIDS”, “dormancy”, “latency”, “tuberculosis”, “mycobacterium”, “BCG”, “vaccine safety”, “clinical trials”, or “biomarkers”. Only English language papers were reviewed where appropriate. We mainly selected publications from the past 10 years, but did not exclude relevant older publications. Additionally, we searched reference lists of these publications for relevant articles. We also included personal knowledge on the topic. Finally, we used information published by Treatment Action Group, Stop TB Partnership, WHO, and George Institute for International Health.
on the rate of pulmonary disease in adults. The worldwide appearance of HIV in the 1980s was followed by a re-emergence of tuberculosis. Hence, there is an urgent need to exploit our knowledge of basic immunology for the rational development of new vaccines against tuberculosis. An overview of the immune response as it relates to tuberculosis vaccine development is shown in figure 1.

**BCG**

BCG vaccination has been part of the Expanded Programme on Immunization since 1974, with coverage in infants exceeding 80%. The vaccine’s safety record after more than 4 billion administrations is as impressive as its low cost of US$0·10–0·20 per dose of product. Serious adverse events after BCG vaccination in individuals without HIV infection are rare. However, the risk of disseminated BCG disease in HIV-infected infants is substantially higher than the risk in infants without HIV infection. This finding led the WHO Global Advisory Committee on Vaccine Safety to recommend that the BCG vaccine should not be used in children diagnosed as HIV positive, even though such an approach will be difficult to implement. Recent studies have also shown that HIV infection severely impairs the BCG-specific T-cell response in infants. BCG might therefore provide little, if any, vaccine-related benefit in HIV-infected infants.

Despite its widespread use in newborn babies, BCG does not prevent adult pulmonary disease satisfactorily and therefore has not reduced the global burden of tuberculosis. This finding probably reflects a lack of effectiveness in adults, especially in the context of early exposure to environmental mycobacteria. All currently developed vaccination strategies for tuberculosis involve vaccination with a viable vaccine, either as prime for a subunit boost or as replacement for BCG, and particular care needs to be given to safety issues in individuals with HIV infection. At this stage, BCG still represents an excellent basis for newly developed prime-boost strategies. However, in the near future, its replacement by a safer product for priming will be urgent need to exploit our knowledge of basic immunology for the rational development of new vaccines against tuberculosis.

Non-tuberculous mycobacteria are common pathogens and commensal organisms in developing countries. Exposure to non-tuberculous mycobacteria can affect the immune response induced by BCG and possibly also by novel tuberculosis vaccines. Effects include induction of antimycobacterial immunity that is not improved after subsequent immunisation (sometimes called masking) and induction of antimycobacterial immunity that fails to provide protection and impairs induction of an adequate immune response after subsequent vaccination (blocking). Both mechanisms are not mutually exclusive.

Helminth infection might increase the occurrence of tuberculosis disease or compromise the effectiveness of BCG vaccination. The suggested mechanism for this association is attenuation of the protective T-helper (Th) 1 immune responses induced by vaccination, which might be caused by polarisation of host immunity towards a Th2 profile, T-cell exhaustion, or increased regulatory T-cell (Treg) activity (figure 1).

**Novel vaccination strategies**

To reduce the global burden of disease, new vaccination strategies (figure 2) against tuberculosis need to induce a more efficient immunity than that achieved with BCG vaccine, not only in infants but also in adolescents and adults. In infants, an optimum vaccine would fully prevent initial infection. Present vaccination candidates are intended to only reduce the initial bacterial burden with containment of remaining *M tuberculosis* organisms (figure 2). Immunologically contained *M tuberculosis* is thought to transform from a metabolically active replicating form into a dormant form with minimum metabolism and absent or low replication that can lead to disease reactivation at a later stage. Therefore, appropriate post-exposure vaccines are needed to target dormant *M tuberculosis* and prevent reactivation. Post-exposure vaccines should also prevent reinfection of individuals with latent infection, notably in regions with high tuberculosis prevalence.

**Present candidates**

The crucial underlying mechanism of action of present vaccine candidates is stimulation of Th1 cells, which activate antimycobacterial capacities in macrophages (figure 1). Of central importance are memory T cells that produce several cytokines concomitantly—notably, interferon γ, tumour necrosis factor, and interleukin 2. Additionally, CD8 T cells directly attack *M tuberculosis* by means of perforin and granulysin, and Th17 cells support Th1 responses.

**Live mycobacterial vaccines**

Live mycobacterial vaccines are based either on improvement of BCG vaccine through addition of relevant genes or on attenuation of *M tuberculosis* through deletion of virulence genes (figure 2, table). Because of
the widespread use of BCG vaccine, it can only be replaced by a vaccine that is safer or more effective, or both. Assessment of the safety and efficacy of new vaccines will require careful analyses with assays and trials that are harmonised as much as possible. Two improved recombinant BCG (rBCG) vaccines have already started initial clinical assessment. Results of preclinical studies suggested that both replacement vaccines were more potent and safer than the currently used BCG vaccine.40,41 rBCG30 was the first vaccine candidate shown to induce substantially greater protection than did parental BCG in different animal models. The second vaccine, rBCGtureC:Hly (VPM1002), is a recombinant strain that secretes listeriolsin produced by Listeria monocytogenes and sustains an acidic phagosomal pH for optimum listeriolsin activity. Perforation of the phagosomal membrane probably promotes antigen translocation into the cytoplasm and facilitates cross-priming and stimulation of Th17 cells through increased apoptosis.41–43 Other live mycobacterial vaccines are expected to enter clinical trials in the next few years.36 Attention has focused on constructs resulting from the genetic attenuation of Mycobacterium tuberculosis. The most advanced of these is the MTBVAC01 vaccine that was constructed by disruption of the transcriptional regulator gene phop, which is associated with M tuberculosis virulence, and the fadD26 genes.44,45

Figure 1: Overview of the immune response in tuberculosis
Control of Mycobacterium tuberculosis is mainly the result of productive teamwork between T-cell populations and macrophages (Mφ). M tuberculosis survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment.11 Gene products of MHC class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol46 or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides.47 These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarise into different subsets.48 DCs and macrophages express pattern recognition receptors (PRR),49,50 which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL) 2 for T-cell activation, interferon γ (IFNγ), or tumour necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination.47–49 Th2 cells and regulatory T cells (Treg) counter-regulate Th1-mediated protection via IL4, transforming growth factor (TGF β), or IL10.48 CD8 T cells produce IFNγ and TNF, which activate macrophages.51 They also act as cytolytic T lymphocytes (CTLs) by secreting perforin and granulysin, which lyse host cells and directly attack M tuberculosis.52 These effector T cells (T eff ) are succeeded by memory T cells (TM).53,54 TM cells produce multiple cytokines, notably IL2, IFNγ, and TNF.55–57 During active containment in solid granuloma, M tuberculosis recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system.58 Treg cells secrete IL10 and TGF β, which suppress Th1.59 This process allows resuscitation of M tuberculosis, which leads to granuloma caseation and active disease. B=B cell.
Figure 2: Different vaccination strategies

Present strategy: (A) pre-exposure vaccination with BCG protects against early childhood tuberculosis but does not eradicate Mycobacterium tuberculosis. Future vaccination strategies: (B) pre-exposure boost with subunit vaccine in children primed with BCG to prevent tuberculosis in early childhood and to delay tuberculosis disease outbreak in adults; (C) post-exposure boost with subunit vaccine in adults who had been primed with BCG during early childhood to delay tuberculosis disease outbreak in adults; (D) pre-exposure vaccination with superior BCG replacement to prevent tuberculosis in early childhood and to delay tuberculosis disease outbreak in adults; (E) therapeutic vaccination in adjunct to chemotherapy in patients with active tuberculosis; (F) heterologous prime-boost vaccination with superior BCG replacement and subunit vaccine, to achieve sterile eradication; (G) heterologous prime-boost vaccination in individuals with latent infection by prime with superior BCG replacement and subunit vaccine boost to prevent tuberculosis disease outbreak; and (H) pre-exposure vaccination to prevent stable infection with M tuberculosis.
Another attenuated *M tuberculosis* vaccine candidate is *M tuberculosis* ΔRD1ΔpanCD.46

**Subunit and live vector-based vaccines that boost BCG prime**

Several vaccines use a prime-boost strategy to complement the immune response induced by BCG (figure 2, table). Subunit vaccine candidates are based on antigens that are recognised by T cells from patients with latent infection or whose tuberculosis has been cured. Two types of products have been developed: recombinant fusion proteins consisting of two or three dominant *M tuberculosis* or BCG antigens and live viral vectors that express one or several mycobacterial proteins. Recombinant protein vaccines can be given repeatedly but need an adjuvant that promotes Th1 immune responses. Live viral vector vaccines do not require adjuvant but can be inhibited by previous exposure to the vector. They trigger a Th1-dominated immune response to the expressed heterologous antigen and induce CD8 T-cell responses. All developed prime-boost candidate vaccines protect mice and guinea pigs to a similar level to that obtained with BCG vaccine; several have also been shown to be protective in non-human primates.45

*Ag85B*-ESAT-6 (H1) candidate vaccine was designed with a strong Th1 adjuvant, IC31 (Intercell, Vienna, Austria), which is a mixture of oligodeoxynucleotides and polycationic aminoacids.50,51 This vaccine has been assessed in two phase 1 clinical trials. It seems to be well tolerated, without any serious adverse reactions, and highly immunogenic in human beings.46 It induces a strong persisting Th1 response to the Ag85B protein of *M tuberculosis*. The transitory response to early secretory antigenic target 6 (ESAT-6) does not seem to interfere with ESAT-6-based diagnostic assays done a few months after immunisation.50 *Ag85B*-TB10.4 (H4, AERAS-404) was developed as an alternative to Ag85B-ESAT-6.52 In this fusion protein, ESAT-6 was replaced by TB-10.4 to reduce the putative risk of interference with ESAT-6-based diagnostic assays.

M72 is a hybrid protein that is formulated in a vaccine adjuvant system containing monophosphoryl lipid A and QS21. This vaccine had acceptable tolerability and induced profound T-cell responses in healthy adults.52,53 Additional trials continuing

### Table: New tuberculosis vaccines in clinical trials*

<table>
<thead>
<tr>
<th>Description</th>
<th>Developmental stage</th>
<th>Sponsor or funder</th>
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<tbody>
<tr>
<td>MVA85A</td>
<td>Phase 1 completed and phase 2 continuing; phase 2b in infants started</td>
<td>Wellcome Trust, Aeras, Emergent BioSolutions</td>
</tr>
<tr>
<td>rBCG30</td>
<td>Phase 1 completed</td>
<td>University of California, Los Angeles, Aeras</td>
</tr>
<tr>
<td>AERAS-402</td>
<td>Phases 1 and 2 continuing</td>
<td>Aeras</td>
</tr>
<tr>
<td>AdAg85A</td>
<td>Phase 1</td>
<td>McMaster University</td>
</tr>
<tr>
<td>M72</td>
<td>Phases 1 and 2 completed, additional trials continuing</td>
<td>GlaxoSmithKline, Aeras, Tuberculosis Vaccine Initiative</td>
</tr>
<tr>
<td>H1-IC31</td>
<td>Phase 1 completed</td>
<td>Statens Serum Institut, Tuberculosis Vaccine Initiative</td>
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<tr>
<td>H1-CAF01</td>
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<tr>
<td>H4-IC31 (AERAS-404)</td>
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<td>Statens Serum Institut, Aeras</td>
</tr>
<tr>
<td>rBCGΔUreC:Hly (VPM1002)</td>
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<td>Vakzine Projekt Management, Tuberculosis Vaccine Initiative, Max Planck Institut</td>
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<tr>
<td>M vaccar</td>
<td>Phase 3 completed</td>
<td>National Institutes of Health</td>
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MVA=modified vaccinia Ankara. Ag=antigen. Ad=adenovirus. AS=adjuvant system. ESAT-6=early secretory antigenic target 6. CAF=cationic adjuvant formulation. Hly=haemolysin. *11 new tuberculosis vaccines that have gone into clinical trials. Two of them, MVA85A and AERAS-402 Mycobacterium vaccar, have gone into phase 2 trials and one, M vaccar, has completed a phase 3 trial. 

### Table: New tuberculosis vaccines in clinical trials*
Heparin-binding haemagglutinin (HBHA) is an interesting but challenging vaccine candidate because the protein is highly methylated. This structure renders it difficult to produce the protein as a recombinant product in an unrelated expression system. HBHA is a mycobacterial surface protein that interacts specifically with non-phagocytic cells.\(^{29,30}\) HBHA vaccination boosted BCG-induced protection in mice.\(^{31,32}\) The protective value of the vaccine, and its antigenicity in patients with latent infection, strongly depend on the methylation pattern of HBHA.

**Killed whole bacterial vaccines as adjunct**

Vaccines that accelerate or complement the effects of tuberculosis chemotherapy would be most welcome. Many attempts to make such a vaccine have been made, but these have been especially cautious because of the potential risk of disease enhancement known as Koch’s phenomenon.\(^{41}\) Two different approaches are now being assessed in clinical trials: one based on killed *Mycobacterium vaccae* and another one based on mycobacterial fragments (figure 2, table).

Whole heat-killed *M vaccae*, an environmental saprophyte, has been tested as an immunotherapeutic agent in tuberculosis. The vaccine is usually given intradermally in a multidose series. Clinical studies show that vaccination might improve radiological and clinical outcomes, decrease time to negative sputum culture, and improve cure rate in some patients with positive-sputum culture (including patients with multidrug-resistant tuberculosis).\(^{42}\) Three major trials have been undertaken in Africa with discrepant outcomes.\(^{43}\) The DarDar phase 3 trial, a randomised, placebo-controlled, double-blind study in BCG-vaccinated patients with HIV infection, reportedly shows that this vaccine reduces the number of tuberculosis cases.\(^{44}\) However, at this stage, the publically available data do not allow any definitive conclusions about the potential usefulness of this approach.

RUTI is another proposed therapeutic vaccine candidate.\(^{45,46}\) *M tuberculosis* is grown under stress conditions and bacilli are then fragmented, detoxified, and delivered in liposomes.

**Near-future candidate vaccines**

Vaccine candidates that are less well advanced aim to reduce tuberculosis burden by use of two strategies (figure 2). In the first proposed strategy, post-exposure vaccines target dormant *M tuberculosis* and help to eliminate the pathogen during its dormant or slowly replicating phase of infection, thereby preventing later tuberculosis reactivation. There are many latency antigens; their expression in dormant mycobacteria reflects the metabolic status of the organism.\(^{47}\) The identification of *M tuberculosis* stage-specific genes has been greatly aided by the development of genome-wide expression arrays.\(^{48,49}\) Remarkably, BCG vaccination apparently does not induce immunity to dormant antigens, or does so only weakly.

In the second strategy, use of new combinations of prime with BCG (or BCG substitutes) and new boost vaccines is aimed at achieving sterile eradication of *M tuberculosis* rather than containing persistence. Some of these boost vaccines might eventually be considered as replacements for BCG.

Three types of vaccines have to be considered in a comprehensive tuberculosis vaccination strategy. First, BCG or, if available, a BCG replacement to prime the immune system and prepare it for subsequent subunit boost that would improve the initial level of immunity. Prime vaccination should induce memory T cells that are restimulated by boost vaccination to reach higher levels of effectiveness. In case of early tuberculosis exposure, such a vaccine would at least reduce the initial bacterial burden, slow down bacterial growth, and protect against early tuberculosis disease.

Second, a subunit vaccine should be given in the next step, a few weeks to several years after BCG or its replacement, to boost and possibly reorient the BCG-induced memory response. The goal would be to increase duration of immunity and improve protection conferred by the prime event. Such boosting vaccines might have to be repeatedly administered during an individual’s lifespan with changing antigen composition.

Third, boost vaccines for post-exposure administration are expected to target latent infection and to clear persisting mycobacteria, or at least prevent reactivation of dormant *M tuberculosis*. Such vaccines could be given to adolescents and adults who have latent infection.

Hybrid 56 adds the dormancy antigen Rv2660 to the antigen 85B and ESAT-6 in IC31 of the Ag85B-ESAT-6 vaccine to achieve a booster effect in individuals with latent *M tuberculosis* infection.\(^{46}\) This vaccine is due to enter clinical trials in 2010.

**Distant-future candidate vaccines**

The vaccine candidates that we have discussed have already entered, or will soon enter, clinical trials. Thus, the development pipeline for tuberculosis vaccines has become more active than ever before. However, the end is still not in sight, and further improvements are needed. As information flows back from phase 1 and 2 clinical trials, both efficacy and safety of the vaccine candidates tested can be refined. In parallel, rational vaccine development based on deeper insights into immunology, microbiology, and molecular genetics will be pursued. Live vaccines can be made more effective by introduction of additional antigens, such as dormancy antigens (eg, to facilitate post-exposure boost vaccination of individuals with latent infection).\(^{50,51}\) Finally, viable vaccine candidates can be endowed with immunopotentiating activity (eg, by introduction of stimulatory cytokines that favour relevant T-cell subsets or by deletion of antiapoptotic genes to strengthen cross-priming). Improvement of subunit vaccine effectiveness involves introduction of novel adjuvants in protein vaccine formulations and selection of...
better viral carriers. Different combination strategies need to be exploited to identify the most appropriate heterologous prime-boost vaccination schedule for pre-exposure and post-exposure vaccination. Ideally, such combinations would not only delay tuberculosis reactivation, but also cause sterile eradication of *M tuberculosis*.

In addition to continuing efforts, new strategies need to be envisioned. One such strategy would be a vaccine that prevents infection with *M tuberculosis*. In an era of HIV/*M tuberculosis* co-infection, such a vaccine would be highly desirable because weakening of vaccine-induced immunity by HIV greatly increases risk of active tuberculosis disease. One option would be the stimulation of highly effective antibodies in the lung. These antibodies would target *M tuberculosis* molecules essential for its survival and then block uptake by phagocytes, and at the same time induce humoral effector molecules that kill the pathogen. Alternatively, these antibodies would promote uptake and subsequent killing of *M tuberculosis* by strongly activated phagocytes and prevent uptake by non-professional phagocytes that could be misused by the organism as a safe niche. Since only few *M tuberculosis* organisms enter the alveolar system of the lung, this strategy warrants experimental verification.

In cavitary tuberculosis disease, the burden of extracellular *M tuberculosis* often exceeds $10^{12}$ microorganisms, which serve as a source of transmission and dissemination. Hence, future design of a therapeutic vaccine against tuberculosis could benefit from stimulation of antibodies that attack *M tuberculosis* in the caseous detritus.

### Clinical trial site development

Promising tuberculosis vaccine candidates will soon be entering phase 3 clinical trials, requiring the enrolment of large cohorts of 10 000 or more individuals. To generate data that can be extrapolated to countries with genetically, culturally, and environmentally diverse populations, such trials should be done in several countries in different regions of the world. Developing a field site for the assessment of new tuberculosis vaccine candidates is difficult. In the absence of a well defined surrogate marker of protection, clinical studies are essential to establish efficacy and need long-term follow-up, high cohort retention, and good surveillance systems for monitoring trial endpoints such as morbidity and mortality. A major problem in tuberculosis trials in children is that there is no easily identifiable and measurable clinical endpoint.

At present only one site (the South African Tuberculosis Vaccine Initiative; SATVI) has the capacity to undertake phase 3 trials of tuberculosis vaccines on the African continent. Availability of multiple sites that can provide similar high standards is urgently needed. Aeras—with the technical support and advice of SATVI, and additional funding from the European Developing Countries Clinical Trials Partnership and the Research Council of Norway—has embarked on a capacity-building programme and is supporting several cohort studies in target populations of infants and adolescents in Kenya, Uganda, Mozambique, and India as a prelude to undertaking clinical trials of new tuberculosis vaccine candidates. The African sites have established a network to share experiences; support exchange visits and training in clinical research; provide guidelines for good clinical practice, good laboratory practice, and quality management; and to strengthen expertise in clinical diagnosis, microbiology, and immunology. Additional sites that meet basic requirements will certainly be needed for phase 3 trials (panel). Large-scale phase 3 clinical trials that take several years to complete will be a costly undertaking. Unfortunately, the countries that are most in need of new vaccines, and where the trial sites will be located, are those with the least ability to support these costs. The Stop TB Partnership estimates that the cost for a new tuberculosis vaccine to be licensed by 2015 is approximately $3·5 billion, for which there is currently a funding shortfall of over $1 billion.

### Monitoring of vaccine trials

As for any new vaccine, the first objective of initial clinical trials for new tuberculosis vaccines is to assess safety. Special attention has to be given to live vaccines in populations at risk of HIV infection. Biomarkers of immunity are of primary importance to assess vaccine responses as described in the fourth report of this Series. Assays measuring T-cell responses are routinely used with a particular focus on responses to peptide epitopes contained in the vaccine. Unfortunately, these assays are so far not directly correlated with protective effects of vaccination. There is hope that further characterisation of the responding T-cell populations will better reflect the degree of protection. Efforts are now in progress to exploit biomarkers for tuberculosis biomarker design and to introduce functional bactericidal assays into clinical trials, as done for several bacterial vaccines (eg, meningococcal vaccines).

### Ethical and regulatory issues

The target populations to be studied for phase 2 and 3 trials of tuberculosis vaccines live in areas where the disease is endemic and can generally be described as being research-naive, poorly educated, socially insecure, oppressed, and unaccustomed to insisting on their basic human rights. Poverty is endemic, unemployment rates are high, and most people subsist on less than $1 per day. To avoid violations of participants’ human rights, clinical trials need to be undertaken in accordance with the international ethical principles and practices that have their origin in the Declaration of Helsinki. Additionally, trials need to adhere to Good Clinical Practices and the applicable regulatory requirements.

Many developing countries do not have regulatory authorities; where they do exist, they need to be strengthened in the areas of preclinical product review and protocol review for initial phase 1 testing of new
tuberculosis vaccines. WHO has convened a series of meetings since 2005 to specifically discuss the regulatory challenges for testing and introducing new tuberculosis vaccines in countries where the disease is endemic.73

Furthermore, WHO is exploiting ways to develop capacities at national and regional levels. Until this development occurs, the most efficient regulatory pathway is to have the first tuberculosis vaccine phase 1 trials in countries non-endemic for tuberculosis with established regulatory authorities. Regulatory authorities in developing countries will then be more likely to accept clinical testing of tuberculosis vaccines in their regions.

The informed consent process and enrolment of participants poses enormous logistical and ethical challenges. Although most participants might have a basic understanding of English, they have poor literacy skills. To resolve this problem, partnerships should be formed with local communities to assist with literacy and related issues.73

**Funding**

An estimated $400–500 million per year was available for tuberculosis research and development worldwide in 2007–08. 15–20% of these funds was allocated specifically for vaccines and 20–25% for basic science, part of which was dedicated to vaccine discovery.75–77 However, this amount is substantially lower than the $2 billion needed every year, over the next 10 years, to fund tuberculosis vaccine research and development.

Public-private-philanthropic partnerships are becoming more common in tuberculosis vaccine research. The US National Institutes of Health and the European Commission are the major representatives of the public sector, and the Bill & Melinda Gates Foundation and the Wellcome Trust represent the philanthropic sector. Pharmaceutical companies involved in these partnerships include major firms such as GlaxoSmithKline and Sanofi-Aventis and small start-up companies such as Crucell, Intercell, and Emergent BioSolutions.77 Moreover, north–south collaborations and capacity building have been notably strengthened by the European Developing Countries Clinical Trials Partnership and Aeras.79

Additional efforts are needed, such as targeted funding for research and development for antituberculosis drugs.80 To secure an affordable price for newly developed products, a global access strategy is requested by some funders—eg, the Bill & Melinda Gates Foundation requires available and affordable access in poor countries to all products developed with Gates Foundation funding. To stimulate interest in the development of new vaccines, the World Bank, GAVI Alliance, and other stakeholders have created Advanced Market Commitments (AMC) for vaccines, which in principle guarantee purchase of a predetermined number of doses of a newly developed vaccine at an affordable fixed price.81 The first product benefiting from the AMC approach is a new pneumococcal vaccine. In the past, tuberculosis vaccines have been under consideration for an AMC proposal on the basis of the calculation that a vaccine to replace BCG could avert 7.7 million deaths and a new boost vaccine could lead to a further 40% reduction in deaths.

**Outlook**

The targets of the Stop TB Partnership are to halve tuberculosis prevalence and mortality by 2015 compared with 1990 levels, and to reduce the annual incidence of new tuberculosis cases to less than one per million population by 2050.82 These ambitious goals will only be achieved by the combined introduction of new diagnostics, drugs, and vaccines. Several predictions based on mathematical models have been used to forecast the effects of different scenarios. The most recent prediction calculates a reduction in tuberculosis incidence of 39–52% by 2050 as a result of new pre-exposure vaccines; a reduction in incidence of 10–27% from new drugs that shorten duration of treatment and are effective against drug-resistant strains; and an additional reduction of 13–42% from new measures allowing reliable and fast diagnosis of tuberculosis. Combined, these three new measures could reduce tuberculosis incidence by up to...

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**Panel: Basic requirements for study sites for phase 3 trials of tuberculosis vaccines**

**Epidemiological**
- High rates of tuberculosis in the target population (>0.5% per year)
- Ability to detect, investigate, and document a high proportion of important health events that might occur for assessment of safety and efficacy
- Good surveillance system with the ability to detect each and every case of tuberculosis that occurs

**Clinical**
- Ability to diagnose tuberculosis infection and disease as accurately as possible, including capacity for microbiological tuberculosis culture
- Competent clinical research team willing and able to prioritise tuberculosis vaccine studies
- Adequate referral structures for detected cases of infection and disease

**Immunology laboratory**
- Ability to at least process and dispatch specimens for analysis of immunogenicity

**Ethics and regulatory**
- Competent and efficient local and national ethics and regulatory authorities

**General**
- Good physical infrastructure: roads, telecommunications, power, security
- Political stability and commitment
- Established relationship with the local community
71%. Incidence could be further reduced by up to 94% by mass vaccination campaigns, new post-exposure vaccines, and drugs for latent infection. Although the elimination of tuberculosis as a global public health problem by 2050 is a particularly ambitious goal, development of new intervention measures and novel vaccines could make a substantial contribution to achieving it.

Contributors
All authors wrote and revised the report. All authors saw and approved the final version.

Steering committee
This article is part of The Lancet Series on tuberculosis, which was developed and coordinated by Alimuddin Zumla (University College London Medical School, London, UK); Mario C Ravignione (Stop TB Department, WHO, Geneva, Switzerland); and Ben Marais (University of Stellenbosch, Stellenbosch, South Africa).

Conflicts of interest
SHEK is co-inventor of the rBCGΔUreC:Hly vaccine candidate and a member of the Scientific Advisory Board of Intercell and Vaccine Project Management. GH is the founding director of the South African Tuberculosis Vaccine Initiative (SATVI). P-HL is the Chairman of the Tuberculosis Vaccine Initiative and a member of the Aeras Vaccine Selection Advisory Committee. He is also a member of the Scientific Advisory Board of Novartis Vaccines and Diagnostics and has received consultancy fees from GlassSmithKline.

Acknowledgments
We thank M L Grossman and S Sihaei for help in preparing the report. SHEK’s laboratory receives financial support for tuberculosis vaccine research and development from EU FP6-TBVAC, FP6-MUVAPRED and FP6-PRIIBM, FP7-TBVIR, FP7-NEWTBVAC, and Bill & Melinda Gates Foundation Grand Challenges in Global Health GC6-74 (number 37772) and GC12-82 (number 37885). GH’s research group (SATVI) is funded by Aeras, the European and Developing Countries Clinical Trials Partnership, Oxford University, National Institutes of Health, and Bill & Melinda Gates Foundation Grand Challenges in Global Health GC6-74 (number 37772) and GC12-82 (number 37885).

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