WHO Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes
# Contents

Methodology, acknowledgments ........................................................................................................ 4

1. **Introduction** .......................................................................................................................... 6
   - Tuberculosis burden ............................................................................................................... 6
   - Drug treatment recommendations and outcomes ................................................................. 6
   - Therapeutic vaccination ........................................................................................................ 7
   - Biologic feasibility ................................................................................................................. 7

2. **Public health goals, target population** .............................................................................. 8
   - Public health goals ............................................................................................................... 8
   - Target population ................................................................................................................. 8

3. **Clinical development strategy** ........................................................................................... 9
   - Timing of immunization ....................................................................................................... 9
   - Standards of care, efficacy and effectiveness ....................................................................... 10
   - Safety considerations ......................................................................................................... 11

4. **The PPC for a Therapeutic Vaccine for TB** ....................................................................... 12

5. **Conclusions and strategic goals** ......................................................................................... 14
Methodology, acknowledgments

This work is the result of a consensus-generating wide-expert, stakeholder and public consultation process. Throughout, the WHO Tuberculosis Vaccine Working Group (Padma Chandrasekaran (National Institute of Research in Tuberculosis, India), Bernard Fritzell (Tuberculosis Vaccine Initiative, The Netherlands), Mark Hatherill (University of Cape Town, Republic of South Africa), Paul-Henri Lambert (University of Geneva, Switzerland), Helen McShane (Oxford University, United Kingdom), Nadia Tornieporth (Hannover University of Applied Sciences & Arts, Germany)) provided critical input. We thank Payam Nahid (University of California, USA), Kelly Dooley (John Hopkins School of Medicine) and Norbert Ndjeka (Department of Health, South Africa) for input. Kathryn Rutkowski (IAVI) provided sample size estimates. We are grateful to all who attended a WHO consultation meeting on Tuberculosis vaccine development in Geneva on the 3rd and 4th October 2017, to all who provided input on draft versions, and to the members of the WHO Product Development for Vaccines Advisory Committee.

WHO Secretariat
Nebiat Gebraselassie, Lewis Schrager (consultant), Johan Vekemans, Matteo Zignol.

Overall coordination and document writing
Johan Vekemans (WHO).

Image credits
Cover: U.S. Centers for Disease Control and Prevention-Medical Illustrator, Public Health Image Library
Page 5 WHO
Page 8 WHO/Olivier Asselin
Page 10 Riccardo Venturi
Summary

Treating tuberculosis (TB) requires a multidrug course of treatment lasting 6 months, or longer for drug-resistant TB, which is difficult to complete and often not well tolerated. Treatment failure and recurrence after end-of-treatment can have devastating consequences, including progressive debilitation, death, the transmission of *Mycobacterium tuberculosis* — the infectious agent responsible for causing TB — to others, and may be associated with the development of drug-resistant TB. The burden on health systems is important, with stiff economic consequences. Vaccines have potential to serve as immunotherapeutic adjuncts to antibiotic treatment regimens for TB. A therapeutic vaccine for TB patients, administered towards completion of a prescribed course of drug therapy or at certain time(s) during treatment, could improve outcomes through immune-mediated control and even clearance of bacteria, potentially prevent re-infection, and provide an opportunity to shorten and simplify drug treatment regimens. The preferred product characteristics (PPC) for therapeutic TB vaccines described in this document are intended to provide guidance to scientists, funding agencies, public and private sector organizations developing such vaccine candidates. This document presents potential clinical end-points for evidence generation and discusses key considerations about potential clinical development strategies.
1. Introduction

Tuberculosis burden

Developing interventions against tuberculosis (TB), including new TB vaccines, represents a critical global health priority (1). TB is the leading cause of death globally from a single infectious agent, Mycobacterium tuberculosis (Mtb), killing approximately 1.6 million persons in 2017, including approximately 300,000 HIV-infected people (2). An estimated 10 million people developed TB in 2017. Approximately 1.7 billion people — 23% of the world’s population — harbour latent TB infection (LTBI) (2). Approximately 5% develop active TB in the first 18 months after initial infection while an additional 5% would be expected to develop TB over the remaining years of their lives (3). The transmission of TB caused by Mtb strains resistant to TB drugs represents a growing threat to public health. An estimated 558,000 people developed drug-resistant TB in 2017, 82% being multidrug-resistant. 230,000 deaths were due to drug-resistant TB. Globally, 3.5% of new TB cases and 18% of previously treated cases had drug-resistant TB (2).

Drug treatment recommendations and outcomes

Active TB is most commonly a disease of the lungs, but can be extra-pulmonary and disseminated (3). If untreated, TB often results in months to years of progressively diminishing productivity, while the cough serves to spread Mtb through the air, putting persons sharing the same home, school, social or work environment at risk of Mtb infection. Without treatment, the TB case-fatality rate in HIV-uninfected individuals is approximately 70% within 10 years of disease onset (4).

The first use of streptomycin against TB in 1944, and subsequent development of multiple other compounds, provided hope for patients (5). Despite the availability of antimycobacterial drugs, treating TB remains a long and difficult endeavor. Even in cured patients, there can be pulmonary sequelae and respiratory disability (6). Due to the slow rate of replication of Mtb and the difficulty that some of the drugs have in reaching and maintaining therapeutic concentrations within tissue involved with active TB infection, multiple drugs, over several months, are recommended for treatment of TB, based on a careful analysis of the balance between efficacy and the burden associated to treatment length, complexity and toxicity. The recommended first line regimen for treating pulmonary TB comprises an intensive phase of 2 months of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) followed by a continuation phase of 4 months of INH and RIF. The emergence and transmission of drug-resistant Mtb strains, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), has further complicated attempts to treat TB disease, requiring a combination of five or more drugs be administered for nine months or longer (7), sometimes requiring injections. The toxicity of the drugs included in the regimens can be devastating, with potential hearing loss, nephrotoxicity, skin rashes and neurological disorders (7). Additionally, the costs of treating patients with MDR-TB and XDR-TB are very high (2, 8).

Globally, an estimated 85% of cases of drug-sensitive TB, and only 55% of cases of drug-resistant TB and 30% in XDR-TB, are successfully cured, at the end of the initiated treatment (2). Adverse outcomes considered here include treatment failure and recurrences. Outcome definitions are presented in the Panel. Recurrence can occur either due reactivation of the incompletely eliminated initial infecting organism, or from reinfection (9, 10). Reports of recurrence rates vary, often between 2 and 15%, with higher rates seen in countries demonstrating high TB incidence and poor TB control (10—13). Individual patient risks for recurrence include irregular compliance with the initial drug regimen, initial infection with a drug-resistant strain, smoking, HIV infection, cavitation (1, 8). Most recurrence occur between 6 months and two years of completing treatment (11—14).

New strategies in treating drug-resistant TB, utilizing drug combinations that include more recent TB drugs such as bedaquiline, delamanid, and linezolid offer the hope for better treatment of drug-resistant TB cases, but strains resistant to each of these new drugs have already been identified, sounding a note of caution against reliance on drug therapy to cure drug-resistant TB well into the future (15—18).
Given the challenges inherent in drug treatment of TB, including the development of multidrug-resistant Mtb strains, developing vaccine strategies with the potential to improve outcomes of drug treatment regimens for persons with TB caused by either drug-sensitive or drug-resistant strains represents an important global public health imperative.

**Therapeutic vaccination**

Therapeutic vaccines are administered to persons who have already manifested signs and symptoms of infection by the targeted organism. This contrasts with prophylactic vaccines aimed to prevent primary infections. The scope of this report relates to therapeutic vaccination against TB intended to stimulate an individual’s immune response in combination with drug treatment, in an effort to improve treatment outcome (19). A related TB vaccine indication relates to the prevention of progression to TB disease in individuals with LTBI, sometimes referred to as a post-exposure vaccine strategy. This is an important vaccine target indication when considering the need to protect exposed contacts, some of whom can be identified as recent converters by diagnostic tests for LTBI, but this is not in scope of the present report. WHO Preferred Product Characteristics for vaccines aimed at preventing primary pulmonary TB in subjects with and without LTBI have been described elsewhere (20).

The potential for therapeutic vaccine strategies to improve TB treatment outcomes has been recognized since the time of Robert Koch and his attempt to use tuberculin to treat disease, prior to the advent of antibiotic treatment (21, 22). Several vaccine candidates are presently considered for use as therapeutic TB vaccines, including attenuated and inactivated-whole organisms, fragmented mycobacteria and adjuvant-ed protein subunit molecules (23).

**Biologic feasibility**

Although the immunological mechanisms of in vivo killing of Mtb are poorly understood, several observations argue in favor of the feasibility of development of a therapeutic vaccination for TB:

- **Effective immunity resulting from natural exposure:** Following natural Mtb exposure, an estimated 90% of individuals do not progress to active disease, showing evidence of host capacity to limit TB progression (24–26). Boosting protective host responses through immunization during treatment for active disease could enhance killing of mycobacteria during ongoing drug treatment, thereby reducing the proportion of subjects at risk of relapse due to residual, viable mycobacteria following treatment cessation.

- **Animal models support the therapeutic vaccination strategy:** Studies of therapeutic vaccination in animal TB models indicate potential for improved drug treatment outcomes (27, 28). Observed changes that may have contributed include a reduced number of myeloid-derived suppressor cells in the lung, an increased number of natural killer T-cells, CD4 T cell activation and TNF-α release. Favorable results have also been found in animal models of post-exposure vaccination (29). Whether these observations are predictive of protection in humans is however unknown.

- **Vaccination of Mtb infected individuals:** Primary results from a phase 2B clinical trial assessing the effect of 2 doses of the M72/AS01E candidate TB vaccine on rates of progression to TB disease in individuals with LTBI demonstrated 54% efficacy at 2.3 years following vaccination for the primary endpoint of bacteriologically confirmed active pulmonary TB (95% CI, 2.9 to 78.2; P=0.04) (30). These results show that this vaccine generates an immune response capable of preventing LTBI or new infections from developing into overt, active pulmonary TB disease. Whether such an immune response can be stimulated in persons already receiving drug treatment for active TB, and, if so, whether it contributes to the effectiveness of the drug regimen, remains to be explored. Additionally, a meta-analysis of data from more than 40 studies assessing the ability of Vaccae™, derived from Mycobacterium vaccae and licensed in China as an immunotherapeutic adjunct to drug treatment of TB in adults, suggested the potential therapeutic utility of this vaccine (31, 32) although the strength of evidence, based on data currently available in the public domain, is limited.
2. Public health goals, target population

Public health goals

Public health goals for therapeutic vaccines include reducing the rate of recurrence following completion of a full course of drug therapy; increasing the proportion of patients cured; shortening the necessary treatment duration and number of drugs to achieve a cure, all both for TB caused by drug-sensitive and drug-resistant Mtb strains.

1. Reducing the rate of recurrence following completion of a full course of drug therapy
   This goal, often referred to as prevention of recurrent disease (PoR), which may result from relapse or re-infection, represents an important public health outcome. In addition to providing benefit for the patient, reducing rates of recurrent disease would also reduce the chance of Mtb transmission to family members, friends and co-workers, medical personnel and the community at large that otherwise could occur if these individuals once again developed active pulmonary TB.

2. Increasing the proportion of patients surviving to cure
   This would represent a major advance for public health, particularly in cases of drug-resistant TB given the poor rates of cure when treating MDR-TB and, particularly, XDR-TB (33). Increasing cure rates would reduce the number of persons required to receive extended periods of treatment, particularly with second-line and third-line injectable drugs, thereby potentially reducing the risk of serious, potential debilitating adverse effects associated with these drugs. Prevention of long-term pulmonary disability is also an important patient-centered goal.

3. Shortening the duration of drug treatment and/or reducing the number of drugs necessary to affect cure
   The many months required for treating drug-sensitive TB and furthermore MDR-TB and XDR-TB frequently result in poor patient compliance with necessary drug regimens (34). Lengthy and complex drug regimens needed to treat drug-resistant Mtb frequently result in drug-related toxicities that also diminish compliance and increase the possibility of both treatment failure and the development of resistant Mtb strains. Shortening and/or simplifying treatment regimens is considered an essential public health goal, but, in absence of reliable animal or early clinical models for therapeutic vaccines and in order to manage risk in study participants, proof-of-principle for therapeutic vaccine efficacy should first be established in study participants receiving standard of care drug regimens, before attempts are made to shorten or simplify new drug regimens in combination with vaccination.

Target population

Ultimately, the target population for therapeutic TB vaccines is all persons, regardless of age, during or towards the end of treatment for active TB disease, due to drug-sensitive or drug-resistant strains. The medical need for a therapeutic vaccine against TB is global. TB patients otherwise healthy as well as patients with co-morbidities or other risk factors should be allowed to benefit from an intervention proven effective.
3. Clinical development strategy

In order to reduce background heterogeneity, maximize safety and efficacy data interpretability and manage risk exposure in a vulnerable, sick population, proof-of-concept testing may be best done in adults with TB and without comorbidities known to either reduce the likelihood of curing their TB disease or diminish the potential effectiveness of a vaccine. When proof-of-concept is established, when appropriate, effectiveness in special population groups should also be evaluated (e.g., HIV infection, diabetes, pregnant women, the elderly, young children), as no-one should be excluded from potentially benefitting from this intervention, if proven safe and effective.

Although subjects with drug-resistant TB represent a very important potential target for therapeutic vaccines, the large variation between individuals in disease course and types of resistance is likely to influence treatment outcome, increasing background variability and potentially affecting estimation of the vaccine effect. Additionally, enrolling a cohort of persons with drug-resistant TB into large-scale clinical efficacy trials is likely to prove difficult, requiring multiple sites and high costs. Such an investment may be more responsible after proof-of-concept is established in individuals with drug-sensitive TB.

Timing of immunization

A therapeutic vaccine could be administered to TB patients around the time of completion of drug treatment. Assessing the efficacy of a vaccine administered at this time necessarily would focus on reducing the rate of TB recurrence. This may correspond to a time at which the load of viable bacteria potentially able to cause relapse may be minimal, and immune functions restored following a time of suppression associated with overt disease and bacterial replication, altogether allowing for a most effective immune effector response. Administering a therapeutic vaccine at the end of standard treatment would not provide an opportunity to study the vaccine effect on cure rates or options to simplify and/or shorten drug treatment regimens but could constitute a first step for establishing proof-of-concept of beneficial vaccine activity before investigating the effects of vaccine administration at an earlier time-point in the treatment course. If multiple vaccine doses are required, the question of compliance with immunization schedule will require careful consideration, and it may be desirable to plan for all doses to be delivered before end of treatment.

Figure 1. Overview of key design features for a double-blind, randomized, controlled proof-of-concept trial of a therapeutic TB vaccine candidate

**THERAPEUTIC VACCINES FOR USE WITH STANDARD RECOMMENDED TB DRUG TREATMENT**

- Diagnosis and treatment initiation
  - Sputum screen, Mtb characterization if positive

**INTENSIVE PHASE**
- Possible vaccination timepoint for cure and PoR* endpoints

**CONTINUATION PHASE**
- Sputum screen, Mtb characterization if positive

**FOLLOW UP**
- Possible vaccination timepoint for PoR* endpoint
  - Proportion of subjects free of recurrence after 12 months or more
  - Proportion of cure

**Measurable endpoints**

* PoR – Prevention of recurrence
Another potential time for therapeutic vaccine administration is around the conclusion of the initial, intensive phase of drug treatment. This relatively early point of immunization may provide an opportunity for the immune response engendered by the vaccine to act in concert with drug treatment to kill remaining live Mtb organisms and offer the potential to increase cure rates in addition to reduce rates of recurrence. Eventually, in a secondary step, vaccination at this time point also would provide the opportunity to investigate the potential for a therapeutic vaccine to reduce the duration and number of drugs required for treatment.

A third possible time for administering a therapeutic vaccine would be at or around the time of TB diagnosis or initiation of treatment. However, vaccine responses administered at this time of maximal mycobacterial load have the potential to be affected by the profound impact of active TB disease on innate immunity (35). Also, symptoms associated to TB may obscure the ability to characterize vaccine safety.

Early vaccine administration during treatment may have the potential to influence immune-pathology leading to long term pulmonary disability, which should be evaluated.

Whatever the timing of therapeutic vaccination, it will be important to prospectively obtain and bank mycobacterial specimens prior to the onset of initial drug treatment to support strain characterization in the context of outcome monitoring. More specifically differentiating relapse from re-infection during the post-treatment phase, and de novo emergence of drug-resistant strains, will provide valuable information.

### Standards of care, efficacy and effectiveness

Before confirmation of any therapeutic vaccine efficacy in a proof-of-concept trial, standard TB drug treatment recommendations for drug-sensitive TB (36) or drug-resistant TB (7) should be followed. It would be ethically inappropriate to provide participants with a shortened or simplified treatment regimen before any demonstration of vaccine-induced increased cure rates and/or reduction of relapses, in absence of reliable pre-clinical or early clinical models establishing strong confidence in protective immunotherapeutic effects of a specific vaccine candidate. Participants should have access to local delivery of care in a routine setting according to national and WHO recommendations, with local ethics committee oversight.

Access to care should include basic radiological and microbiological services to ensure that Mtb microbiological samples can be stored and locally or remotely typed. For vaccines administered during drug treatment, monitoring of sputum clearance and relapse should be planned at various moments including end-of-treatment. For vaccines administered towards the end-of-treatment, active or passive monitoring of recurrence should be planned, over at least one year post treatment.

The degree of treatment adherence and quality of treatment administration provided in the context of a trial will assuredly impact cure and recurrence rates and the sample size needed to demonstrate efficacy of a therapeutic vaccine (sample size assumptions and estimates are presented in Table 1). Based on the assumption of an interaction between drug treatment and an immunotherapeutic vaccine effect (illustrated by the fact that a therapeutic vaccine would not be expected to provide protection alone, replacing the need for treatment), capacity strengthening efforts leading to increased access and delivery of care may affect the generalizability of the effect of therapeutic vaccines as measured in a trial to real life settings. The administration of vaccines at the end of treatment in individuals enrolled only after end of treatment delivered in a routine setting, for initial proof-of-concept generation, may be an appropriate way of mitigating the generalizability question associated to a possible statistical interaction between the drug and vaccine effect.
### Table 1.

Total sample sizes required for demonstration of vaccine efficacy against recurrence after treatment, according to assumptions about the baseline cumulative incidence (cum. Inc.), the true vaccine efficacy (VE), the desired lower bound of the 95% confidence interval (LB), rates of lost to follow-up (LTFU) and ineligibility of cases for compliance with primary case definition (excl.), for a trial with 80% power, a two-sided alpha = 0.05 (LB>25%, one-sided alpha = 0.025). The same sample sizes would be required to estimate vaccine efficacy treatment failure instead of recurrence, using the same assumptions.

<table>
<thead>
<tr>
<th>LTFU / Excl</th>
<th>Cum. Inc. (Control)</th>
<th>True VE = 50%</th>
<th>True VE = 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LB &gt; 0%</td>
<td>LB &gt; 25%</td>
</tr>
<tr>
<td>0%/0%</td>
<td>4%</td>
<td>2278</td>
<td>6744</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>1492</td>
<td>4428</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>1100</td>
<td>3270</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>864</td>
<td>2576</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>708</td>
<td>2114</td>
</tr>
<tr>
<td>10%/10%</td>
<td>4%</td>
<td>2734</td>
<td>8093</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>1790</td>
<td>5314</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>1320</td>
<td>3924</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>1037</td>
<td>3091</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>850</td>
<td>2537</td>
</tr>
</tbody>
</table>

### Safety considerations

The potential for the injection of antigenic components of Mtb precipitating a delayed-type (Type IV) hypersensitivity reaction, resulting in necrosis at the site of injection, in persons with Mtb infection or active TB (37) represents a possibility that must be considered when testing therapeutic TB vaccines on persons with active TB disease. The possibility of pulmonary and systemic inflammatory reactions (38), and the breakdown of granuloma structure potentially resulting in Mtb dissemination should be considered and monitored. Respiratory function tests may be useful to monitor lung safety. Mostly minor adverse events have been observed in most therapeutic vaccine studies conducted to date (19, 30, 39, 40), but enrollment in a phase 2 trial of the M72/AS01E vaccine candidate was interrupted prematurely after the observation of local reactions (pain, redness, swelling) larger than expected in tuberculosis patients (41). A careful safety risk management plan should be instituted to identify and mitigate potential risks. Safety data will need to be interpreted in context of co-administered drug treatment to sick individuals. The potential severity of TB, as compared to vaccines aimed for healthy people at minimal risk of health outcomes, may justify considering acceptable safety thresholds differently.
**Panel**

**CASE DEFINITIONS, AS PER AVAILABLE WHO RECOMMENDATIONS (42)**

| **Bacteriologically confirmed case of TB** | Preferred endpoint for TB vaccine efficacy assessment. A bacteriologically confirmed case is one from whom a biological specimen is confirmed positive by culture or WHO-approved rapid diagnostic method. |
| **MDR-TB** | Defined as Mtb isolates resistant to the two, first-line treatments for TB: rifampicin (RIF) and isoniazid (INH). |
| **XDR-TB** | Defined as Mtb isolates resistant to INH and RIF, as well as any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin or capreomycin). For drug-sensitive cases — a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who is smear-negative or culture-negative at the last month of treatment and on at least one previous occasion. For drug-resistant cases - treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase. |
| **Cure** | |
| **Treatment failure** | Refers to a case where cure is not achieved. |
| **Recurrence** | In a bacteriologically confirmed case of TB, recurrence refers to reversion to sputum positivity after successful end of treatment cure. Recurrence may include cases of reactivation of the incompletely eradicated Mtb strain responsible for the initial episode of TB (here referred to as relapse), and cases of re-infection with a new Mtb strain. These can be differentiated through molecular Mtb strain characterization. |

**4. The PPC for a Therapeutic Vaccine for TB**

The primary audience for this WHO PPC document includes all entities involved in the development of therapeutic vaccines for improvement of TB treatment outcomes. This PPC is presented as a complement to the existing WHO PPC on the development of TB vaccines intended to prevent TB disease (20), providing guidance to scientists, funding agencies, and public and private sector organizations developing therapeutic TB vaccine candidates. It is anticipated that PPCs provide a framework for developers to design their development plan and define in more details specific target product profiles.

WHO PPCs are developed following a consensus-generating wide consultation process involving experts and stakeholders in the field. Key policy considerations are highlighted, but preferred attributes expressed here do not pre-empt future policy decisions. The PPC criteria proposed are aspirational in nature. Some aspects of a potentially effective therapeutic vaccine may diverge from those proposed in this PPC, which would not necessarily preclude successful licensure and policy decision for clinical application.
WHO Preferred Product Characteristics for Therapeutic TB Vaccines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Protection against TB recurrence, following initial cure. Increase the proportion of cure at end of drug treatment.</td>
<td>Reducing the cumulative incidence of recurrence after initial, drug-mediated cure, and increasing the proportion of cure at the end of drug treatment represents the highest priorities to demonstrate in clinical studies. The possibility of reducing the number of drugs and treatment duration are essential long-term goals. Ethical standards would require that initial proof-of-concept be established while TB patients receive a standard recommended treatment regimen. Changes to the treatment regimen could be investigated after an initial demonstration of efficacy.</td>
</tr>
<tr>
<td>Target population</td>
<td>All persons being treated for active TB, both drug-sensitive and drug-resistant Mtb strains.</td>
<td>Initial proof-of-concept might best be established in subjects with no specific, increased risk of adverse outcome with drug-sensitive tuberculosis. After initial demonstration of efficacy and safety, investigations in cases of MDR-TB and XDR-TB, as well as studies in special populations (children, pregnant women, subjects with HIV/AIDS and other high-risk individuals), should be started promptly.</td>
</tr>
<tr>
<td>Outcome measure and efficacy</td>
<td>50% or greater efficacy in reducing the rate of recurrent TB after a standard course of drug treatment, and/or 50% or greater reduction in treatment failure at the end of drug treatment.</td>
<td>These preference levels are selected by analogy with other severe diseases and expert opinion. Further research is required on the correspondence between vaccine efficacy and Mtb transmission and the TB epidemic as a whole including the spread of drug-resistant TB. Further research is also required to define strategy and targets for reduction in the number of drugs needed for treatment, and the duration of drug therapy, as long-term objectives. See panel for case definitions. Impact on long term pulmonary function should be evaluated.</td>
</tr>
<tr>
<td>Duration of Protection against recurrence</td>
<td>Initial proof-of-concept for prevention of recurrence could be demonstrated on the basis of one year of follow-up.</td>
<td>Recurrence can result from both reactivation and reinfection. Most reactivations occur in the first year post treatment.</td>
</tr>
<tr>
<td>Safety</td>
<td>A safety and reactogenicity profile similar to other current WHO-recommended routine vaccines for use in adolescents and adults would be preferred.</td>
<td>The benefit/risk balance will need to be considered. Given the severity and public health concern associated to the target disease, mitigations may be considered for mild reactions or rare events.</td>
</tr>
<tr>
<td>Schedule</td>
<td>A minimal number of doses required.</td>
<td>A requirement for more than three doses to achieve immunization would not be desirable due to logistical and cost concerns.</td>
</tr>
<tr>
<td>Co-administration</td>
<td>N/A</td>
<td>Issues generally relevant to co-administration of a preventive vaccine with other vaccines are not applicable here given the intended administration of this therapeutic vaccine to individuals with active TB disease. The potential for adverse interactions with drugs administered for treatment of TB or comorbidities should be considered.</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Identification of a correlate/surrogate of protection, using a validated assay.</td>
<td>Little is presently known about immune determinants of protection, and no confirmed correlate/surrogate of clinical efficacy of a TB vaccine currently exists. The identification of marker of risk if recurrence and immune correlates/surrogates of protection should be included as immunogenicity objectives in TB vaccine efficacy studies. In the absence of established correlates of protection, markers of immune ‘take’ should be characterized. The conservation of biological specimen for future use upon advances in technology and knowledge is encouraged.</td>
</tr>
</tbody>
</table>
WHO PREFERRED PRODUCT CHARACTERISTICS FOR NEW TUBERCULOSIS VACCINES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred Characteristic</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programmatic suitability and prequalification</td>
<td>General guidance from WHO expectations about clinical evaluation of vaccines should be followed (43). The WHO defined criteria for programmatic suitability of vaccines should be met, following guidance on vaccine presentation, packaging, thermostability, formulation and disposal (44). The vaccine should be pre-qualified to support purchasing by United Nations agencies (45).</td>
<td>Beyond the minimum requirements for WHO prequalification, innovation related to programmatic suitability, such as ease of administration and thermostability, would lead to major public health benefits and is strongly encouraged.</td>
</tr>
<tr>
<td>Value proposition</td>
<td>Dosage, regimen, and cost of goods should be amenable to affordable supply. Favourable cost-effectiveness should be established and price should not be a barrier to access, including in low- and middle-income countries.</td>
<td>Modelling public health value and impact of TB vaccines with various characteristics on the TB epidemic in general, and on drug-resistant TB specifically, as well as on TB-associated anti-mycobacterial drug use would be valuable. The vaccine impact on health systems (such as reduction of TB-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in both modelling and real vaccine use studies.</td>
</tr>
</tbody>
</table>

5. Conclusions and strategic goals

Achieving proof-of-concept for a therapeutic vaccine based on the ability of the vaccine to reduce recurrence rates over one year or more following a drug-mediated cure represents the preferred short-term strategic goal of therapeutic TB vaccine development. Assessing the efficacy of a vaccine delivered at some point during treatment, possibly at the end of the initial intensive treatment phase, against end-treatment failure and recurrence, may also be considered as a short-term goal. Initial studies should be conducted in the context of standard recommended drug treatment. Mtb samples obtained prior to the initiation of treatment should be available to assess whether a recurrence that may occur is due to reactivation of the same, initially infecting Mtb strain, or whether it results from a de novo, Mtb infection that occurred post-end-of-treatment. While initial proof-of-concept may best be generated in patients with drug-sensitive tuberculosis, reducing the emergence of drug-resistant TB represents an important strategic goal. Investigations in special population groups should be initiated rapidly after initial demonstration of efficacy. The potential for shortening and simplifying drug regimens represent essential long-term goals. Proof-of-concept should imperatively trigger vaccine evaluation for other indications including prevention of TB in the general population or in recently exposed individuals. Initial demonstration of vaccine efficacy in other target populations should trigger evaluation of a potential therapeutic adjunct, as these various indications are of importance to public health.
References


