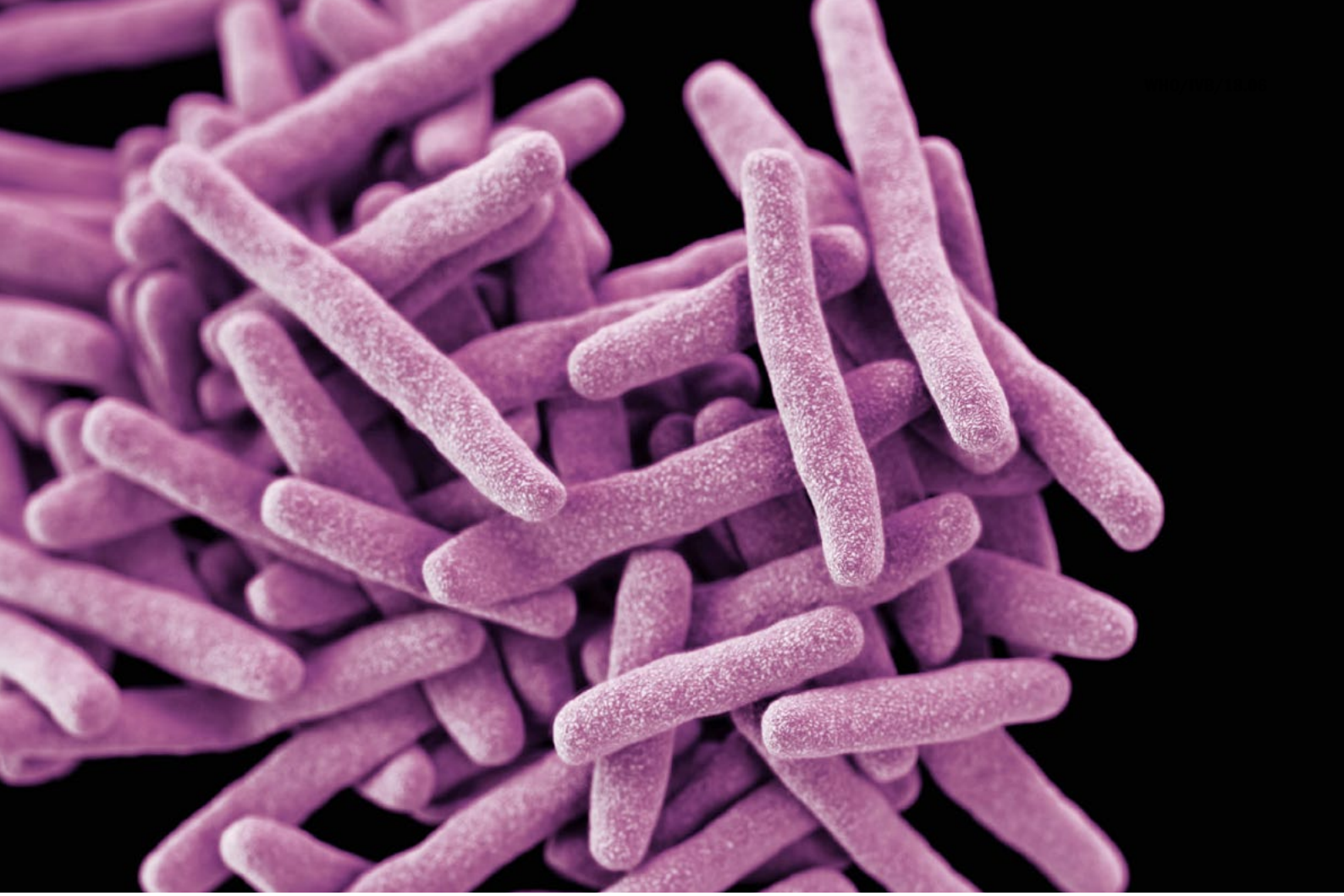

WHO Preferred Product Characteristics for Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes

DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS

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Contents

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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 adjuvanted 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