# Advances in Development of New Tuberculosis Vaccines

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**Title:**

**ADVANCES IN DEVELOPMENT OF NEW TUBERCULOSIS VACCINES**

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## Abstract

### Purpose of review

Tuberculosis (TB) remains a global public health emergency and caused 1.6 million deaths in 2021. The aim of this review is to provide recent updates on advances in TB vaccine development for prevention and adjunct therapy.

### Recent findings

Targets use indications guiding late stage TB vaccine development have been established, namely: (i) Prevention of disease (PoD), (ii) Prevention of recurrent disease (PoR), (iii) Prevention of established infection in previously uninfected patients (PoI), and (iv) Adjunctive immunotherapy. Novel approaches include vaccines designed to induce immune responses beyond established CD4+, Th1-biased T cell immunity, novel animal models for use in challenge/protection studies, and controlled human infection models (CHIM) to generate vaccine efficacy data.

### Summary

Recent efforts at developing effective TB vaccines for prevention and adjunct treatment utilising new targets and technologies have yielded 16 candidate vaccines demonstrating proof of concept for inducing potentially protective immune responses to TB which is currently under evaluation in different stages of clinical trials.

### Keywords

Tuberculosis; Vaccine; Prevention, adjunct therapy, Immunity.

## Introduction

Until the advent of the COVID-19) pandemic, TB was the leading cause of death from a single infectious agent. Globally, during the COVID-19 pandemic, the estimated number of deaths from TB increased between 2019 and 2021, reversing years of declining trends seen between 2005 and 2019. An estimated 10.6 million people fell ill with TB in 2021, an increase of 4.5% from 10.1 million in 2020, with 1.6 million deaths in 2021[1]. This was up from 1.5 million in 2020 and 1.4 million in 2019, and back to the level of 2017. These data emphasise the dire need for effective TB vaccines which provide long term protective immunity, and result in reductions in global TB incidence and mortality[2]. Whilst the only licensed TB vaccine available to date is the Bacille Calmette-Guerin (BCG) vaccine first used more than one hundred years ago, there is currently no licensed vaccine that is effective in preventing TB disease in adults and adolescents, either before or after exposure to TB infection. Still, substantial progress has been made over the past five years in TB vaccine development. Here, we provide recent updates and advances in TB vaccine development for prevention and adjunctive therapy.

## New TB vaccine development and pipeline

Multiple candidate vaccines demonstrating proof of concept of protection against TB in animal models are currently under evaluation in clinical trials, based on a variety of technological approaches that include live attenuated mycobacteria, killed whole cell mycobacteria, mycobacterial extracts, adjuvanted protein vaccines, and viral vectored vaccines . Candidates based on mRNA are also preparing for Ph1. Table 1 shows the current TB candidate vaccine pipeline. As per the TB Vaccine Initiative (TBVI), by October 2022[3], there were 16 in clinical trials: four in Phase I, eight in Phase II and four in Phase III. They included candidates for PoI, PoR, PoD, and as adjunctive treatment for TB disease. Results from a Phase II trial of the M72/AS01E candidate are particularly promising[4].

Novel emerging vaccine technologies for vaccine development, including mRNA[5], are currently under active investigation. There have also been advances in development of vaccines for use in infants and children, as safer and more efficacious replacements for BCG vaccination, and vaccines in development for co-administration or booster vaccines with BCG, intended to improve its protective efficacy[6].

## Prevention of Infection (POI)

As of now, the only available licensed TB vaccine, BCG, is a pre-exposure vaccine based on a PoI approach. BCG, given at birth, is not sufficiently effective at reducing disease burden in all target populations. New, improved vaccine approaches are urgently needed[7]. A previously conducted PoI study of a novel adjuvanted protein candidate TB vaccine, H4:IC31 versus BCG re-vaccination conducted in adolescents in South Africa concluded that neither approach prevented initial QuantiFERON (QFT) conversion, a surrogate measure of new TB infection, although BCG vaccination did reduce the rate of sustained QFT conversion to a greater extent than H4:IC31[8]. More recently, a study of a TB subunit vaccine composed of antigens not shared with BCG, was conducted to explore the benefit of a BCG plus non-BCG subunit vaccine coadministration vaccination strategy. Eight protective antigens were selected to create a Mycobacterium tuberculosis (*Mtb)*-specific subunit vaccine, named H107. This candidate vaccine had been previously demonstrated to be immunogenic in mice and humans[9], and to lack any cross-reactivity to BCG. Results of the study indicated that H107 has inherent potential as a standalone TB vaccine candidate, as well as utility in co-administration with BCG vaccination in infants or with BCG

(re)vaccination in adolescents and adults. The results also suggested that co-administration of BCG with H107 (formulated with the CAF®01 adjuvant) may increase vaccine efficacy. Further clinical testing is planned for this promising candidate vaccine.

The value of PoI as a target indication for novel TB vaccines has been called into question, owing to the fact that only an estimated 10% of individuals who are infected with *Mtb* have a lifetime risk of progression to develop active TB[10] thereby indicating that the majority would otherwise not require vaccination to prevent progression to disease. Furthermore, endpoints for assessment of PoI, based primarily on either the purified protein derivative (PPD)-based tuberculin skin test (TST) or interferon gamma (IFN-ɣ) release assays (IGRA) such as the QFT, are less than 100% sensitive or specific, although IGRA conversion from a negative to a positive test is currently considered the most robust biomarker of acquisition of *Mtb* that could be used as a suitable endpoint in clinical trials[11]. Despite higher levels of IFN-ɣ detected by IGRA being associated with higher risk of TB progression, neither the TST nor IGRA accurately identify healthy individuals who will progress to develop disease following exposure and infection[12]. The use of PoI in clinical trials of TB vaccines as a surrogate endpoint for prediction of PoD is therefore contentious, for these reasons, albeit potentially attractive due to a possibility for significant reduction in the costs of conducting such trials[11]. Despite these considerations, it is recognized that a PoI vaccine will likely be of significant public health value in preventing the subset of *Mtb* infections that would otherwise progress to TB disease[13].

**Prevention of Disease (PoD)**

The indication with the highest priority for an effective TB vaccine is PoD, and mathematical modelling predicts that the quickest way to achieve control of the global TB epidemic would be through preventing TB disease in adolescents and adults[14, 15]. However, the cost of conducting late-stage efficacy trials in healthy populations, which require large sample sizes, which may not be feasible, and prolonged periods of post-vaccination follow up, is prohibitive. As a result, more recent clinical trials have been designed to target clinically meaningful biological effects in carefully selected high-risk populations, thereby allowing for the conduct of less expensive efficacy trials of shorter duration.

To achieve the goal of licensure of a PoD vaccine the selection of efficacy endpoints in PoD trials will need to be optimised, and consensus established on the definition of “TB disease”. This will help to determine optimal baseline screening procedures to rule out pre-existing TB disease in recipients of candidate vaccines in clinical trials, and to determine the tests to be used for ascertainment of incident disease outcomes, thereby facilitating more accurate estimation of vaccine efficacy[16, 17, 18]. Additional considerations for diagnostic testing apply to paediatric TB and extrapulmonary TB (EPTB)[19, 20].

**Prevention of Recurrence (PoR)**

Clinical trials using PoR endpoints may be “classical PoR trials”, in which administration of the candidate vaccine occurs towards the end or at the end of TB treatment (and can therefore only affect post-treatment outcomes). Alternatively, they may be “therapeutic trials” during which the candidate vaccine is administered during TB treatment (and therefore may affect both on- and post-treatment outcomes)[21]. There is growing interest in PoR trials due to their significantly lower costs than PoD trials,

more rapid accrual of trial endpoints for PoR than for PoD, and the potential to fast-track vaccine development[22]. The primary efficacy endpoint for both classical and therapeutic PoR trials is microbiologically confirmed pulmonary TB, occurring in the post-treatment period and/or at the end of treatment respectively[23].

**New technological approaches to TB vaccination - Messenger RNA**

Messenger RNA (mRNA)-based vaccines for SARS-CoV-2 infection have demonstrated high degrees of efficacy and effectiveness during the recent pandemic. This technology has been explored for TB vaccine development for many years, with the first report of an RNA vaccine for TB published in 2004, when an mRNA vaccine demonstrated modest but significant protection against *Mtb* in mice[24]. They promise the potential to deliver a balanced cellular and humoral antigen-specific immune response, stimulating both innate and adaptive responses and inducing both CD4+ and CD8+ T-cell responses. They obviate the issue of anti-vector immunity, unlike some viral vectored platforms, and offer speed of production using a non-cell culture-based manufacturing platform. There are potential concerns with adverse events associated with the mRNA platform, which call for a careful benefit-risk assessment[25]. The specific advantages of a TB vaccine based on an mRNA platform include the ability to induce potent polyfunctional T-cell responses targeted to the lungs, the ability to co-express multiple antigens, and the potential for multiple possible routes of administration, including intradermal (ID), intramuscular (IM), subcutaneous (SC), intranasal (IN), aerosol (AE), and intravenous (IV).

**Vaccines for replacement of BCG in children**

The ability for BCG to protect against pulmonary TB is largely unproven, with conflicting results in observational versus randomised controlled clinical trials in children. Effectiveness studies have also shown inconsistent results, with multiple potential confounding factors being expounded as the reason for this[26]. The BCG vaccine is currently administered via the ID route, however, there has been recent interest in eliciting potentially greater efficacy using alternative routes that permit broader diffusion in lung tissue, including via inhalation or AE[27], or to improve systemic bioavailability via IV delivery[28]. Two very promising candidate vaccines for replacement of BCG are VPM 1002 and MTBVAC.

VPM1002 is a recombinant BCG vaccine (rBCG) in which a listeriolysin gene has been added to the BCG genome, with deletion of a urease gene. This permits the rBCG to escape the macrophage phagolysosome, which does not occur with BCG. The resulting innate immune response is stimulated to a greater extent than with BCG. VPM1002 is being studied both as a replacement for BCG in infants and children, and as a TB vaccine in adolescents and adults[29, 30]. A Phase III, double-blind, multicenter, randomised, single administration, active-controlled, parallel-group design clinical trial with two groups of newborn infants receiving either VPM1002 or BCG SII is currently underway to assess the efficacy, safety, and immunogenicity of VPM1002 against *Mtb* infection (Clinicaltrials.gov: NCT04351685).

MTBVAC is a live attenuated *M. tuberculosis* (Mtb) vaccine generated by deleting the virulence transcription factor *PhoP*, and the fatty acid AMP ligase, *fadD26*, that is responsible for the production of PDIM, the major lipid implicated in virulence[31]. Each of both deletions is independently attenuating the original wt *M.tuberculosis* strain. MTBVAC is primarily being developed as an alternative for BCG as a

priming vaccine, aimed specifically at vaccinating newborns that are not sensitised to BCG, Mtb, or environmental mycobacteria, thereby avoiding "masking" or "blocking" effects on protection induced by MTBVAC against TB disease in infants. A Phase III clinical trial in which the safety, immunogenicity, and efficacy of MTBVAC is being evaluated in HIV-uninfected infants born to HIV-infected and HIV-uninfected mothers, as compared to the standard BCG vaccination regimen, is also underway (Clinicaltrials.gov: NCT04975178).

**Vaccines for replacement, co-administration with, or booster vaccination, for BCG**

DAR-901 is a whole-cell, heat-killed vaccine derived from *Mycobacterium obuense*, a non-pathogenic bacterium found in soil that has been evaluated in cancer immunotherapy. It is manufactured using a scalable broth culture technique. It has previously been shown to be safe and to demonstrate protective efficacy in a preclinical mouse model of TB, inducing both cellular and humoral immunity and demonstrating the ability to boost protection against aerosol challenge of *Mtb* compared to a homologous BCG boost[32]. A Phase I clinical trial conducted in IGRA-negative healthy volunteers found it to be safe and well tolerated, inducing both cellular and humoral immune responses to the constituent mycobacterial antigens[33]. A Phase II "Randomised, Placebo-Controlled, Double-Blind, Study of the Prevention of Infection With Mycobacterium Tuberculosis Among Adolescents Who Have Previously Received BCG" has been completed (Clinicaltrials.gov: NCT02712424). A three-dose series of 1 mg DAR-901 was safe and well-tolerated but did not prevent initial or persistent IGRA conversion. Further studies of this candidate vaccine are warranted to determine whether it could have a role in prevention of TB disease, given that protection against disease may require different immunologic responses than protection against infection[34].

**Adjunctive immunotherapy**

Emerging interest has been documented for therapeutic vaccines that have the capacity to shorten treatment and improve outcomes. A potential mechanism to achieve these outcomes may involve priming or boosting novel anti-TB immune responses[35]. The heat killed, non-tuberculosis variant *M.vaccae* is the most advanced immunotherapeutic available and has been approved for concomitant administration with standard TB chemotherapy in China (NCT01979900)[36].

**Conclusion**

In recent years there have been a number of significant advancements in the development of TB vaccines with improved efficacy over BCG. These have been facilitated by the refinement of targets for TB vaccine development defined in terms of prevention of infection, disease, recurrence or based on their potential for adjunctive therapeutic vaccination in the context of treatment. Novel technological approaches offer safer and more efficacious alternatives to replace or complement BCG, most notably mRNA. The results of ongoing late-stage clinical trials of the most promising candidate vaccines are eagerly awaited. There is much hope that further investment to provide support for these vaccines will

pave the way for a solution to the recently reversing trend in many years of declining incidence and mortality from TB.

**Key points**

- The estimated number of deaths from TB increased in recent years, reversing years of declining trends previously seen.
- Whilst the only licensed TB vaccine available to date is the BCG vaccine developed over 100 years ago, there is currently no licensed vaccine effective in preventing TB disease in adults.
- Endpoints for clinical trials of TB vaccines should be selected based on one or more of defined targets of PoI, POR, PoD, and efficacy as adjunctive therapy.
- Substantial progress has been made over the past 5 years in TB vaccine development, with the introduction of novel technologies that enhance or boost the BCG vaccine-induced immune response, further development of which should be supported through adequate investment.

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Table

Table 1: Current pipeline of tuberculosis vaccine candidates in pre-clinic and in clinic*

| Candidate Vaccine | Technology | Phase(s) of development | Trial Endpoint** | Target population | Therapeutic use | Adjuvant use |
|---|---|---|---|---|---|---|
| MTBVAC | Live | 3 | POD | Infants and neonates | No | None |
| MTBVAC | Live | 2a | POD | Adolescents and adults | No | None |
| VPM1002 | Live | 3 | POI, POD | Infants and neonates | Yes | None |
| VPM1002 | Live | 3 | POR, POD | Adolescents and adults | Yes | None |
| BCG Revaccination | Live | 2b | POI, POD | Adolescents and adults (POI) Children and adolescents (POD) | No | None |
| BCG ZMP1 | Live | Pre-clinical | N/A# | Infants and neonates | No | None |
| BCG ZMP1 | Live | Pre-clinical | N/A | Adolescents and adults | No | None |
| RUTI | Whole cell | 2a, 2b | Therapeutic | Adolescents and adults | Yes | None |
| DAR-901 | Whole cell | 2b | POI | Adolescents and adults | No | None |
| Whole-cell *M.. indicus pranii* (MIP) | Whole cell | 3 | POD | Adolescents and adults | No | None |
| H107 | Protein subunit | Pre-clinical | N/A | Adolescents and adults | Yes | CAF®01 |
| CysVac2/Ad | Protein subunit | Pre-clinical | N/A | Adolescents and adults | No | Advax$^{CPQS}$ |
| AEC/BC02 | Protein subunit | 1 | N/A | Adolescents and adults | No | CPG/ Aluminum hydroxide |
| ID93/GLA-SE | Protein subunit | 2a/2b, 2b/3 | POR, POD | Adolescents and adults | Yes | GLA-SE |
| H56:IC31 | Protein subunit | 1, 2b | POR | Adolescents and adults | Yes | IC31 |
| H56/ASO1E | Protein subunit | 2b | POR | Adolescents and adults | No | ASO1E |
| M72+ASO1E | Protein subunit | 2b | POD | Adolescents and adults | No | ASO1E |
| GamTBvac | Protein subunit | 3 | POD | Adolescents and adults | No | Dextran/Dextran DEAE/ CPG |
| ChAdOx/MVA PPE15-85A (BCG Prime) | Viral vectored | Pre-clinical | N/A | Adolescents and adults | No | None |
| CMV-6Ag | Viral vectored | Pre-clinical | N/A | Adolescents and adults | No | None |
| MVA-based Multiphasic vaccine MVATG18377*** | Viral vectored | Pre-clinical | Therapeutic | | Yes | None |
| Ad5 Ag85A | Viral vectored | 1 | N/A | Adolescents and adults | No | None |
| ChAdOx1.85A MVA85A (Aerosol) | Viral vectored | 1 | N/A | Adolescents and adults | No | None |
| TB/Flu04L | Viral vectored | 1 | N/A | Adolescents and adults | Yes | None |
| BNT164a1 BNT164b1 | mRNA | 1 | N/A | | | None |

**Original*

** Trial endpoints for efficacy trials only

***A recombinant Modified Vaccinia Ankara (MVA) vector expressing 14 antigens representative of the three phases of TB infection (active, latent and resuscitation)

N/A# Not applicable