Pipeline Report » 2024

Tuberculosis Vaccines

TAG
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Tuberculosis Vaccines

Vibe Shifts / Seismic Upsets

by Mike Frick

Forgive the Gen Z colloquialism headlining this year's *Tuberculosis Vaccines Pipeline Report*, but the descriptor is apt: the vibe has shifted. Something about tuberculosis (TB) vaccine research and development (R&D) is different. The field is not the same as it was ten, five, or even two years ago, and a big part of that difference is in the outlook. The prevailing mood not only feels more optimistic, but also more elastic: able to stretch toward ambitious goals and absorb disappointments without snapping back to a place of regret or futility. Scientists, funders, and advocates are spending more time looking forward, anticipating success, than they are looking backward, ruing failure.

For evidence of the vibe shift, look no further than how the field reacted to negative trial results over the past year. Let's take the disappointing news first:

- First came word at the 2024 Conference on Retroviruses and Opportunistic Infections (CROI) in Denver, Colorado, that the subunit vaccine H56:IC31 failed to prevent recurrent TB disease in a phase IIb **POR** trial among 831 adults who had recently finished treatment for drug-susceptible TB.[1] Researchers observed more recurrent TB (driven mainly by relapse, rather than reinfection) among participants who received H56:IC31 compared with those who received placebo — raising the possibility that the experimental vaccine had the opposite of its intended effect and may have increased the risk of recurrence. Statens Serum Institute (SSI) announced that it would halt further development of the vaccine based on these results.[2]

- Weeks later, and back in Colorado at a Keystone Symposia meeting, the Gates Medical Research Institute (Gates MRI) presented results of a phase IIb **POI** trial of BCG revaccination among 1,800 South African adolescents. The trial failed to reproduce a signal seen in an earlier phase IIa study that found BCG revaccination had modest efficacy against a secondary endpoint of sustained **IGRA** conversion.[3] In the larger follow-on trial, which treated sustained IGRA conversion as the primary endpoint, revaccination with BCG did not prevent sustained *Mycobacterium tuberculosis* (MTB) infection. These results, and those from the POR trial of H56:IC31, are discussed in more detail in the following section, "Reporting results, falling out the pipeline."

POR = prevention of recurrence. POR trials test whether vaccines prevent disease recurrence (defined as either reinfection or relapse).

POI = prevention of infection. POI trials test whether vaccines prevent MTB infection, usually measured by IGRA test conversion (negative to positive).

IGRA = interferon-gamma release assay, a blood-based test that detects cell mediated immune responses to MTB indicative of infection, but not a direct measure of infection itself.

In other times, either of the above setbacks could have triggered more existential rethinking about the direction of the field. This writer vividly remembers publishing his first *TB Vaccines Pipeline Report* in 2013 in the wake of negative results from a phase II trial in infants of a former vaccine candidate called

MVA85A.[4,5] The years following the MVA85A infant trial were characterized by what some actors called a "shift to the left [of the pipeline]" to privilege basic science over clinical trials.[6] As summarized by TAG at the time:

MVA85A phase II infant trial NCT00953927.

> "After years of focusing on phase II clinical trials, some of the field's largest players are now redirecting attention and resources to the beginning of the pipeline — basic discovery and preclinical development. This change is motivated by a growing consensus that the guiding assumptions of the last 10 years of TB vaccine research require updating in the face of emerging evidence from the clinic and the lab."[7]

Negative results released over the past year have not dislodged the prevailing positive outlook or sparked a field-wide about-face. The narrative has changed, and that is a powerful thing. In his keynote address at the 7th Global Forum on TB Vaccines in Rio de Janeiro, Brazil, World Health Organization (WHO) chief scientist Jeremy Farrar reflected on an insight gleaned from his prior tenure as executive director of Wellcome, a major philanthropic funder of global health research:

> "Optimism brings support. Funders like to support things that will work. Funding attracts young people. Optimism is crucial if we're to make progress. Let's grasp the optimism and hope that I think many of us feel for the first time in 100 years."[8]

The 100-year timestamp invoked by Farrar is a reference to the only existing vaccine against TB, BCG, which was first introduced in 1921. It affords lifesaving protection against TB to young children, who receive it soon after birth in most countries. It also exerts so-called nonspecific effects that protect children against infectious diseases other than TB during infancy and, in some studies, has been linked to significant reductions in all-cause mortality.[9] Because BCG does not protect adults and adolescents against pulmonary TB, there is a need to develop new vaccines, particularly ones that can prevent TB in the middle age groups that account for most of the world's incident TB disease and deaths each year (and thus also most onward transmission).

With 1921 far in the rearview, the story told about TB vaccine R&D until recently was one of slow progress, near penury, and regular disappointments, with this melancholic plot saved by occasional forward advances. Unlike in 2013, the field can handle hearing the bad news first, because the potential for receiving good news later remains strong. The month of March 2024 brought negative results for H56:IC31 and BCG revaccination, but it also contained a landmark event: the opening of the M72/AS01E phase III trial. On March 19, 2024, the Gates MRI announced it had vaccinated the first participants in South Africa.[10] From those first vaccinations, enrollment proceeded at a stunning pace. By November 2024, at the Union World Conference on Lung Health, Ann Ginsberg, deputy director of TB vaccines at the Gates Foundation, shared that 15,000 of 20,000 total participants had joined the trial.[11] The fact that in the space of a year, the field can nearly fully enroll the largest TB vaccine trial mounted in decades is a tangible manifestation of the more favorable vibe many feel.

Ginsberg pointed out that M72/AS01E is not without company: over the next five years, scientists and developers can expect "an unprecedented bolus of efficacy trial results," more than ever available before. As Ginsberg explained, this means that even negative results will grant scientists the opportunity to learn from human data that they can back-translate to fuel advances in basic discovery and preclinical development.[12]

And yet — changing the story told about TB vaccine research should not be mistaken for changing the underlying foundations on which scientific progress is built and sustained. Even as scientists and advocates have embraced the more optimistic vibe, many have acknowledged real vulnerabilities to continued progress. Some of these vulnerabilities are structural: clinical development activity is heavily weighted toward late-stage trials of legacy candidates that have been moving through the pipeline for over a decade, while phases I and II remain devoid of new vaccines. The few notable exceptions — the first mRNA TB vaccine constructs from BioNTech, a new subunit vaccine from SSI called H107e/CAF10b, a viral-vectored candidate from CanSino called **Ad5-105K**, and a lyophilized mRNA vaccine named **RH119** from Wuhan Ruiji Biotechnology — only emphasize the alarming emptiness of the early pipeline. Several preclinical development initiatives are poised to shepherd new candidates into phase I in the coming years, but the fact that the early pipeline has stayed this sparsely populated for so long should be read as a concerning vital sign.

Ad5-105K is new to the pipeline. A viral vectored vaccine, it uses human adenovirus type 5 (Ad5) to deliver the MTB antigens 75K and Ag85A.

Ad5-105K has started a phase I trial in Indonesia NCT06732583.

RH119 is a new mRNA TB vaccine candidate from China that began a phase I trial in late 2024 ChiCTR240009409.

What if none of the candidates now in late-stage trials work? Even if one or more shows efficacy, there will be a need to develop next-generation vaccines that improve on the protection offered by the first successful vaccine(s). In a talk on vaccine design at the 7th Global Forum, Elly Van Riet of the TuBerculosis Vaccine Initiative (TBVI) pointed out that developers can optimize first-generation vaccines along multiple dimensions including efficacy, reactogenicity, cold chain requirements, suitability for priority populations, and cost.[13] In other words, the pipeline should not dry up when the first new TB vaccine achieves licensure. The field must harness the excitement generated by efficacy trials to spur vaccine discovery through innovation in antigen selection, adjuvant development, routes of administration, and other vaccine platform improvements.

There is another inescapable reality shading today's optimistic spirit: sponsors cannot run clinical trials on vibes. They need adequate and predictable funding, access to experienced clinical trial sites, the engagement of informed communities, and political environments supportive of vaccine research and immunization. Regarding funding, the $550 million pledged to the M72/AS01E phase III program by Gates Foundation and Wellcome is a windfall that has already proven difficult to reproduce. To give just one example: despite a $40 million commitment from **Open Philanthropy**, IAVI and Biofabri have not raised the additional tens of millions of dollars required to conduct a full phase III trial of MTBVAC. They have settled instead for a smaller phase IIb trial smartly designed to produce evidence

Open Philanthropy awarded $40 million for MTBVAC development through a regranting challenge to the Gates Foundation, which is also supporting the trial alongside the German government.

that the sponsors hope might motivate accelerated regulatory approval should MTBVAC prove safe and effective.[14] The difficulty of securing funding for more than one large-scale phase III trial indicates that the **chronic funding constraints** that have held back TB vaccine development for decades remain in place.

Chronic funding constraints for TB vaccine research are explored in TAG's report *TB Research Funding Trends, 2005–2023*. In 2023, the world spent $227 million on TB vaccine R&D.

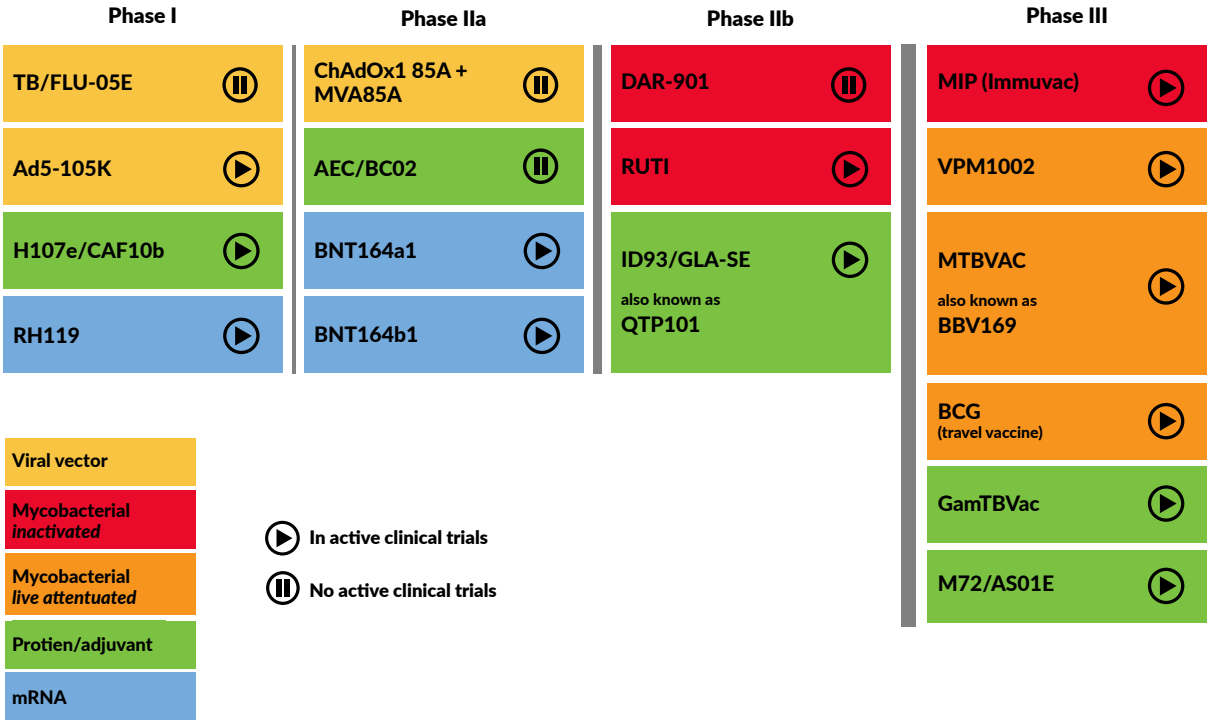
"Vibe shift" is perhaps too irreverent a frame for an endeavor as serious as developing new vaccines against the world's deadliest infectious disease. Its utility is in the reminder that changed narratives are as ephemeral as they can be powerful — all too easily undone by scientific surprises, economic crises, cultural drifts, and political upheavals. The return of Donald Trump to the U.S. presidency, and the elevation of vaccine cynics and deniers to the highest levels of the U.S. government, are a seismic upset that threatens vaccine science generally and portends particular trouble for TB vaccine development. In 2023, 33% of the money spent on TB vaccine R&D came from the U.S. National Institutes of Health,[15] now under the direction of Health and Human Services Secretary Robert F. Kennedy Jr. This is someone who has talked about taking "a break" from infectious disease research.[16] Someone who has cast doubt on the safety and efficacy of routine childhood vaccinations used for decades.[17] Someone who petitioned the U.S. Food and Drug Administration to "immediately remove COVID vaccines from the market" just six months after their approval and at a time when the pandemic was killing thousands of Americans every week.[18,19]

The anti-vaccine turn in the United States is more than a vibe shift. It is a seismic disturbance for global health science born of a muscular anti-science movement dovetailing with a far-right political resurgence hostile to the multilateralism and international cooperation required to advance common good projects like new TB vaccines. If public funding and public trust are at stake, public leadership may already be lost: the Trump administration's day one executive order withdrawing the United States from the WHO, and subsequent actions to freeze foreign aid and unlawfully dismantle USAID, will deal a major blow to TB elimination efforts, including the nascent work of the WHO TB Vaccine Accelerator Council.

Treatment Action Group's *Tuberculosis Vaccines Pipeline Report* surveys major developments in the clinical development of new TB vaccines at this moment of scientific promise and political peril. The pipeline contains 17 candidates (Figure 1). **Table 1** reviews vaccines that have reached phase III trials, and Table 2 lists candidates in phase I and II. For each listed candidate, the tables summarize ongoing, recently completed, or planned clinical trials known to TAG. To streamline the visual presentation, studies completed more than two years ago have been removed from the tables. The narrative entries below discuss notable updates for some of the candidates that generated the most news over the past year, because they either reported clinical trial results, kept everyone waiting for more information, or began major new studies.

References to most studies in **Table 1** and elsewhere link to ClincalTrials.gov. TAG acknowledges that this website may not remain intact following Trump executive orders. All study records are on file with TAG.

Figure 1: The TB Vaccine Pipeline



Reporting results, falling out of the pipeline

H56:IC31

Readers will notice that Table 2 no longer lists a familiar name: **H56:IC31**. TAG has removed this vaccine from the pipeline based on negative **phase IIb POR trial** results and the subsequent announcement by SSI that it would not pursue further development of this vaccine.[20] The phase IIb trial was conducted by the Prevention of Tuberculosis Recurrence Consortium (POR-TB) at six sites in South Africa and Tanzania with funding from the European and Developing Countries Clinical Trials Partnership (EDCTP). The trial assessed whether vaccination with H56:IC31 at the end of TB treatment lowered the risk of experiencing recurrent TB compared with placebo. (Whole-genome sequencing on paired sputum samples was used to distinguish between recurrence caused by relapse of the initial illness versus reinfection with a new TB strain.) Participants received standard-of-care treatment for drug-susceptible TB in the public health sector and, in order to enroll, had to be smear negative at month five of the six-month treatment course (indicating successful treatment by programmatic definition). Participants then received either two doses of H56:IC31 or placebo — one during treatment, one after — and were followed for recurrent disease for an additional 12 months.[21]

H56:IC31 was a subunit vaccine with three MTB antigens paired with the IC31 adjuvant from Valneva.

H56:IC31 phase IIb POR trial NCT03512249.

Results of the study were published in the *Lancet Infectious Diseases* on March 5, 2026.

The study enrolled 831 HIV-negative adults 18–60 years of age. The primary endpoint was recurrent TB defined as culture-confirmed pulmonary TB identified

after day 70 (to exclude late treatment failures; vaccine and placebo were administered on days 0 and 56). POR-TB investigators observed 37 cases of recurrent TB: 23 among 400 people who received H56:IC31 and 14 among 406 participants who received placebo. The overall vaccine efficacy of H56:IC31 was -73.8% (-246.9, 9.8). The arms looked similar in terms of reinfection, but 12 participants who received H56:IC31 relapsed compared with six who received placebo.[22] This difference suggests that the vaccine may have increased the risk of recurrent TB driven by relapse.

Work now turns to understanding this disappointing finding. Broadly speaking, ideas fall into two realms of possibility. Despite the careful randomization, was there an imbalance in baseline risk factors for recurrent disease between the two groups (e.g., differences in disease severity or treatment adherence)? Or did the H56:IC31 vaccine have an effect that increased the risk of recurrence (and if so, was this effect specific to H56:IC31 or would it apply to any vaccine tested in a POR trial among people treated for TB?) Regrettably, trialists have limited information about participants at the start of and during their TB treatment: no X-rays, no knowledge of treatment adherence, and no culture results at the end of treatment (just confirmation of negative sputum).

Using samples and data collected during the trial, the POR-TB team is embarking on a program to identify immune correlates of risk of recurrence. What they find will shape the future of the **POR endpoint**. This was the first POR trial to report results, and its findings therefore speak not only to the efficacy of H56:IC31 but also to the utility of conducting POR studies to set up phase III **POD** trials. Disease recurrence among people who have already had TB is a more frequent event than TB disease itself, and most people who develop recurrent disease do so within the first year of completing treatment. POR studies are therefore smaller, faster, and less expensive than larger, longer, more costly POD efficacy trials. The press release announcing the start of the H56:IC31 trial justified it in these terms: "The trial will use prevention of TB recurrence after TB treatment as an indicator for the ability of a vaccine to prevent TB disease in the broader population, and is the first of its kind to be investigated."[23] The outcome, however, casts doubt on the strategy of running POR studies in phase II to generate proof of concept for moving a vaccine into a phase III POD trial.

One more thing about the H56:IC31 phase IIb trial merits mention: SSI and the POR-TB investigators deserve praise for their proactive, transparent communication. Before formally presenting at CROI in March 2024, the POR-TB team shared results with important stakeholders, starting with the participants themselves and site-level community advisory boards. On a series of calls organized in December 2023, investigators gave topline results, key messages, and preliminary analyses of safety and efficacy outcomes to researchers running similar POR studies, funders, global policymakers, and representatives of affected communities. At the time, TAG and **Global TB CAB** released a statement thanking the POR-TB consortium for "set[ting] an example of early, honest, and transparent results sharing that other developers in the field should follow."[24]

POD = prevention of disease. POD trials test whether vaccines prevent TB disease (usually pulmonary TB that is microbiologically confirmed).

Other ongoing trials with a **POR endpoint** include a phase III trial of VPM1002 NCT03152903.

An NIH-funded trial of ID93/GLA-SE (NCT06205589) resembles the H56:IC31 study in some respects but is testing ID93/GLA-SE as a therapeutic vaccine given at earlier time points during TB treatment.

The **Global TB CAB** statement on the H56:IC31 POR trial put forward five questions from community advocates for scientists to answer.

BCG revaccination

The pipeline is missing another familiar contender: BCG. More specifically, trials investigating a strategy of BCG revaccination. The idea that a second dose of BCG given in adolescence or adulthood might protect against either TB disease or MTB infection offered the tantalizing possibility of an "easy win," one that now appears remote.

At the 7th Global Forum, Alex Schmidt of the Gates MRI presented results from a **phase IIb** study of BCG revaccination among 1,800 South African adolescents (10–18 years old). The study was designed to interrogate a "glimmer of efficacy" observed on a secondary endpoint in an **earlier phase IIa** study that published results in 2018.[25] In that earlier study, BCG revaccination did not demonstrate efficacy against the primary endpoint of prevention of MTB infection (defined as IGRA conversion from negative to positive) but showed modest efficacy of 45.4% (95% CI: 6.4–68.1) against a secondary endpoint of sustained infection (defined as IGRA conversion from negative to positive and staying positive at repeat testing six months later).[26] The box below compares the phase IIa study with the follow-on phase IIb trial conducted by the Gates MRI.

BCG revaccination **phase IIb** study NCT04152161.

Earlier phase IIa study of BCG revaccination NCT02075203.

Box: Comparing Recent BCG Revaccination Trials

	Phase IIa trial NCT02075203	Phase IIb trial NCT04152161
Sponsor	Aeras	Gates MRI
Study start	2014	2019
Size	989 adolescents enrolled	1,836 adolescents enrolled
Participant profile	12–17 years BCG vaccinated HIV negative IGRA negative at screening	10–18 years BCG vaccinated HIV negative IGRA negative at screening
Country	South Africa	South Africa
Sites	Single site: SATVI in Worcester, South Africa	Five sites across South Africa
BCG vaccine	BCG SSI*	BCG SSI
IGRA test for MTB infection	QFT Gold**	QFT Gold Plus
Primary endpoint	IGRA conversion = initial conversion from negative to positive (Secondary endpoint of sustained IGRA conversion = initial conversion and still IGRA positive 6 months post-conversion)	Sustained IGRA conversion = initial conversion and still IGRA positive three and six months post-conversion

* BCG SSI is the BCG vaccine formerly manufactured by Statens Serum Institut, which sold its vaccine manufacturing business to AJ Vaccines in 2017.

** QuantiFERON®-TB Gold and QuantiFERON®-TB Gold Plus are types of IGRA tests manufactured by Qiagen and often abbreviated as QFT.

Investigators in the larger phase IIb trial observed no significant difference between arms: 62 sustained IGRA conversions among 871 participants revaccinated with BCG (7.1%) compared with 59 conversions among 849 individuals who received placebo (6.9%). To quote Schmidt: "We didn't see any efficacy at all."27 Nor did investigators see anything unexpected in terms of BCG safety or reactogenicity. A slide summarizing lessons learned from **BCG revaccination trials** drew some clear conclusions:

- "BCG revaccination of QFT-negative adolescents and adults does not prevent MTB infection, as assessed by QFT conversion.
- Currently, there is no compelling evidence to support BCG revaccination as a public health intervention for the prevention of TB.
- BCG vaccination of infants does prevent TB and should continue."[28]

BCG revaccination trials in Malawi (1996) and Brazil (2005) observed no efficacy in prevention of disease.

A trial of BCG given to Brazilian healthcare workers during the COVID-19 pandemic showed no effect on initial IGRA conversion NCT04327206.

That last point bears repeating in today's world: BCG is lifesaving for children, and nothing about the BCG revaccination studies changes the longstanding WHO recommendation to give BCG "as soon as possible after birth."[29] In this sense, BCG is one of the earliest gifts a newborn receives after entering this world. It shields infants against TB and its most threatening manifestations (TB meningitis, disseminated TB), trains young immune systems to encounter other pathogens, and gives children the chance to enjoy a healthy childhood and thrive.

While these results do not change existing BCG vaccination policy, they have affected other planned studies of BCG revaccination. Several studies of BCG revaccination listed in previous *Pipeline Reports* are now marked as **"withdrawn"** or **"suspended"** on ClinicalTrials.gov. The remaining entry for BCG in Figure 1 refers to an ongoing phase III trial of BCG given as a pre-travel vaccine to United States healthcare workers traveling to high-TB-burden countries for short-term work assignments or to long-term travelers (any occupation) with plans to reside in such places for at least six months. This is very different from the revaccination strategy tested in previous trials.

Withdrawn BCG revaccination trials include:

NCT05541952, a phase IV study of BCG revaccination in Brazilian prisons.

NCT05539989, a phase I/II study of BCG revaccination and VPM1002 in pre-adolescents.

Suspended studies of BCG revaccination include NCT05330884, a phase III trial among child and adolescent household contacts in India.

Is there a future research agenda for BCG as more than a potential travel vaccine? A commentary published in the *Lancet Respiratory Medicine* shortly before the Gates MRI phase IIb trial results became known posed the question: "What is next for BCG revaccination to prevent tuberculosis?"[30] A successful phase IIb POI trial might have led to a recommendation to revaccinate adolescents with BCG to prevent MTB infection. But more likely, as the piece explains, it would have bolstered the argument for carrying out a phase III trial built around a POD endpoint. This is because a vaccine that prevents MTB infection cannot be assumed to also prevent disease, which is the main reason for developing new TB vaccines since disease is associated with morbidity, mortality, and transmission. POD trials are also seen as more likely to result in regulatory and policy endorsement than POI trials because infection endpoints, which rely on IGRA tests, are less stable and precise than disease endpoints, which can be microbiologically confirmed.[31]

Like the rationale for conducting phase II POR studies, many POI studies were seen as efficient steppingstones to POD licensure trials. The TB vaccine field has now had two disappointing phase II POI trials: the Gates MRI BCG revaccination study and a trial in Tanzania of **DAR-901**. POI and POR trials may continue, but their role in generating necessary evidence for POD efficacy trials may diminish.

DAR-901 is a whole-cell vaccine candidate consisting of inactivated *M. obuense*.

DAR-901 phase II POI trial NCT02712424.

A phase III POD trial of BCG revaccination is very unlikely. However, the authors of the *Lancet Respiratory Medicine* commentary raised another possibility: "Given the BCG vaccine is already licensed, an evaluation of the programmatic rollout of BCG revaccination (i.e., a phase IV study) could also be carried out." The Indian government has embarked on just such an endeavor.

In 2024, the Indian Ministry of Health and Family Welfare, in collaboration with the Indian Council of Medical Research (ICMR), launched a "programme implementation research study" of BCG revaccination in adult close contacts of people with TB disease. The study is not a clinical trial but a cluster-randomized study that will compare districts that implement the intervention (BCG revaccination) with control districts (those that continue with routine TB program activities per national guidelines). A manual of standard operating procedures obtained by TAG provides detail on the study design:[32]

- **Where:** Twenty-three Indian states elected to participate in the study; each state contains districts randomized to implement BCG revaccination and districts allocated to control. A total of 274 districts were randomized to the BCG revaccination arm and 273 to the control.
- **What:** The primary objective is to evaluate the effectiveness of BCG revaccination "on the occurrence of notified TB cases up to a period of 36 months post intervention." More specifically, the "difference in proportion of TB cases per 100,000 population notified through **Ni-kshay** between intervention and control districts." Secondary objectives will evaluate safety as well as effectiveness against active TB disease based on an annual review repeated every year for five years (using Ni-kshay data).
- **Who:** The study manual describes participants as adults (≥18 years) "vulnerable to TB," defined as history of TB disease (within the past five years); close contact with current TB patients (or any person with TB notified to India's national TB program as of January 2021); individuals with low body mass index (<18); elderly people (≥60 years); people with a history of tobacco smoking; and individuals with diabetes. The study does not include people living with HIV.

Ni-kshay is India's national online TB notification and patient management system.

The programmatic implementation study appears to have replaced a clinical trial of BCG revaccination among **child and adolescent household contacts** that ICMR registered with ClinicalTrials.gov in 2022. The last update to the study registry in December 2023 changed its status to "suspended," citing "changes in protocol," which ICMR first confirmed with TAG in September 2023.[33] As designed, that

Planned ICMR trial of BCG revaccination among **child and adolescent household contacts** NCT05330884 (now listed as "suspended").

study would have compared BCG revaccination to TB preventive treatment (TPT). The implementation study now underway has switched focus from children and adolescents to adult close contacts and has a different approach to TPT. There is no direct comparison to TPT; rather, both intervention and control districts may implement TPT as part of routine program activities since it is recommended in national guidelines. People currently taking TPT cannot receive BCG but can be vaccinated four weeks after completing TPT, and, similarly, individuals who receive BCG are eligible to receive TPT four weeks post-vaccination.[34]

Waiting for more information

VPM1002

One way to understand the BCG implementation study in India is to see it as laying the groundwork for other vaccines in the pipeline being studied among close contacts. In particular, the two whole-cell candidates — VPM1002 and MIP — are being evaluated in an ICMR-funded **phase III POD trial**.

Phase III POD trial of VPM1002 and MIP CTRI/2019/01/017026.

The trial is evaluating the efficacy, safety, and tolerability of VPM1002 and MIP (each compared to placebo) among nearly 13,000 HIV-negative household contacts six years of age and older. VPM1002 is a **recombinant BCG vaccine**, initially developed in Germany and now licensed to the Serum Institute of India (SII). MIP is an inactivated whole-cell vaccine consisting of *Mycobacterium indicus pranii*, an organism closely related to MTB. It is approved in India as a vaccine against leprosy and manufactured by Cadila Pharmaceuticals.

Recombinant BCG vaccine (rBCG) = genetically modified version of BCG designed to provide better safety and efficacy.

Rumors that ICMR might release results from this trial circulated all year, but multiple opportunities came and went without presentation or publication. What is known: the trial is complete. What remains unknown at the time of writing (and this may change by the time readers open this *Pipeline Report* edition) is whether either vaccine offered any protection against TB in this high-risk population of people exposed to TB through close contact. A hint came from a comment eminent TB scientist Soumya Swaminathan, who previously held the posts of ICMR director and WHO chief scientist, gave to Indian newspaper *The Tribune* in October 2024:

> "The results were very recently un-blinded. And essentially, what it shows is that overall, there's not much of a difference between the arms. But in younger individuals under the age of 18, the recombinant BCG vaccine has some moderate efficacy in the range of 30 percent."[35]

The "recombinant BCG vaccine" Swaminathan refers to is VPM1002; her comment suggests that younger participants who received VPM1002 may have had a slightly lower risk of TB disease compared with those who received placebo (but that the same was not true for those who received MIP). Per the trial's protocol, which ICMR published in 2024, this analysis by age is a secondary endpoint; the trial planned secondary analyses of vaccine efficacy within four age groups: <18

Table 1. TB Vaccines in Phase III Clinical Development

Agent	Type	Sponsor(s), Major Partners and Funders	Status[α]
Notable recently completed, ongoing, and planned clinical trials. The abbreviations appearing in red boxes give the primary indication for which a vaccine is being studied. **POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence**			
MIP (Immuvac)	Inactivated whole-cell *M. indicus pranii*	ICMR, Cadila Pharmaceuticals	Phase III
POD	Results anticipated from a phase III trial evaluating the efficacy, safety, and immunogenicity of MIP and VPM1002 (each vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) in 12,721 household contacts (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026; PreVentTB). Completion: 2024.[β]		
VPM1002	Live rBCG	SII, Serum Life Science Europe, ICMR, EDCTP	Phase III
POD	Results anticipated from a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 and MIP (each vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) in 12,721 household contacts (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026; PreVentTB). Completion: 2024.		
POI	Results anticipated from a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection in 6,940 newborns (HIV-unexposed and HIV-exposed/uninfected) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685; priMe). Completion: October 2024.		
POR	Results anticipated from a phase II/III trial evaluating efficacy, safety, and immunogenicity of VPM1002 (vs. placebo) in preventing TB disease recurrence (pulmonary or extrapulmonary) in 2,000 HIV-negative adults ages 18–65 successfully treated for pulmonary TB in India and Bangladesh (NCT03152903). Primary completion: 2024.		
MTBVAC (BBV169)	Live, genetically attenuated MTB	Biofabri, Bharat Biotech, IAVI, TBVI, University of Zaragoza, EDCTP, NIH (ACTG/HVTN)	Phase III
POD	Undergoing a phase III trial evaluating the efficacy, safety, reactogenicity, and immunogenicity of MTBVAC (vs. BCG) in preventing TB disease in 7,120 newborns (HIV-unexposed and HIV-exposed/uninfected) in South Africa, Senegal, and Madagascar (NCT04975178; MTBVACN3). Primary completion: January 2029.		
	Undergoing a phase IIb trial evaluating the efficacy, safety, and immunogenicity of MTBVAC (vs. placebo) in preventing TB disease in 4,300 HIV-negative, MTB-infected adolescents and adults ages 14–45 in Kenya, South Africa, and Tanzania (NCT06272812; IMAGINE). Primary completion March 2028.		
Other	Undergoing a phase IIa safety/immunogenicity study of MTBVAC (vs. BCG) in 276 adolescents and adults ages 12–55 living with and without HIV in South Africa (NCT05947890; HVTN 605/ACTG 5421). Primary completion: February 2026.		
	Preparing to open a phase IIa safety and immunogenicity study of MTBVAC (vs. BCG) in 164 BCG-vaccinated, HIV-negative, MTB-infected and uninfected adolescents and adults ages 12–65 in India (CTRI/2024/07/070928). Primary completion: 2026.		
	Completed a phase I safety, reactogenicity, and immunogenicity study of MTBVAC in 30 BCG-vaccinated, MTB-uninfected adults ages 18–65 in India (NCT06438978). Completion: January 2024.		

Agent	Type	Sponsor(s), Major Partners and Funders	Status[α]
BCG	Whole-cell *M. bovis*	Henry M. Jackson Foundation	Phase III
POI	Presented results from a phase IIb trial evaluating the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in preventing sustained MTB infection in 1,836 BCG-vaccinated, MTB-uninfected, HIV-negative adolescents ages 10–18 in South Africa (NCT04152161). Completion: 2024.		
	Undergoing a phase III trial evaluating the efficacy and safety of pretravel BCG vaccination (vs. placebo) in preventing MTB infection among 2,000 BCG-naive, MTB-uninfected adults ages 18–65, either health care workers or long-term travelers to high-TB-burden countries from the United States (NCT04453293). Primary completion: September 2027.		
GamTBvac	Protein/adjuvant subunit vaccine	Gamaleya Federal Research Center for Epidemiology & Microbiology, Ministry of Health of the Russian Federation	Phase III
POD	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of GamTBvac (vs. placebo) in preventing TB disease among 7,180 HIV-negative, BCG-vaccinated, MTB-uninfected adults ages 18–45 in the Russian Federation (NCT04975737). Primary completion: November 2025.		
M72/AS01E	Protein/adjuvant subunit vaccine	Gates MRI, Wellcome, GSK Biologicals (AS01E adjuvant)	Phase III
POD	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of M72/AS01E (vs. placebo) in preventing TB disease among 20,000 adolescents and adults ages 15–44 in Indonesia, Kenya, Malawi, Mozambique, South Africa, Vietnam, and Zambia (NCT06062238; CommuniTB). The trial contains three cohorts: 20,000 HIV-negative, MTB-infected participants; 1,000 HIV-negative, MTB-uninfected participants; and 1,000 people with HIV (any MTB infection status). Primary completion: April 2028.		
Other	Presented results from a phase II safety/immunogenicity study of M72/AS01E (vs. placebo) in 402 adults living with HIV ages 16–35 who are on ART, are virally suppressed, and have previously taken TPT in South Africa (NCT04556981; MESA-TB). Completion: August 2022.		
	Completed an epidemiologic study assessing IGRA positivity at 45 potential trial sites for the phase III trial listed above. The study enrolled 7,203 adolescents and adults ages 15–34 in Bangladesh, Brazil, Democratic Republic of Congo, Gambia, India, Indonesia, Kenya, Mozambique, Peru, Philippines, South Africa, Uganda, Vietnam, and Zambia (NCT05190146). Completion: August 2024.		

α Status indicates the most advanced phase of either ongoing or recently completed trials.

β For ongoing/planned studies, "primary completion" is the "estimated primary completion date" in ClinicalTrials.gov or the date of final data collection for the primary outcome measure. For completed studies, "completion" is the "actual study completion date" in ClinicalTrials.gov (or date provided by study sponsor).

Sources: Information compiled from ClinicalTrials.gov and other clinical trial registries as of 2025 February 28. Information checked against pipeline information collected by the Stop TB Partnership Working Group on New TB Vaccines and supplemented with information provided to TAG by sponsors.

ACTG: Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

ART: antiretroviral treatment

BCG: bacillus Calmette-Guérin

EDCTP: European and Developing Countries Clinical Trials Partnership

Gates MRI: Gates Medical Research Institute

HVTN: HIV Vaccine Trials Network

IAVI: International AIDS Vaccine Initiative

ICMR: Indian Council of Medical Research

M. bovis: Mycobacterium bovis

MIP: *Mycobacterium indicus pranii*

MTB: *Mycobacterium tuberculosis*

NIH: National Institutes of Health (USA)

SII: Serum Institute of India

TB: tuberculosis

TBVI: TuBerculosis Vaccine Initiative

TPT: TB preventive treatment

years, 19–35 years, 36–60 years, and >60 years.[36] Current ICMR chief Rajiv Bahl seemed to confirm Swaminathan's statement in a similar comment to *The Tribune* on January 28, 2025, which paraphrased him saying: "[a] study that tested the recombinant BCG vaccine in contacts of TB patients did not yield good results."[37] No conclusions can be drawn without full presentation and publication of results and access to the underlying data.

The delay in releasing results even though they appear to be known to many involved parties is frustrating. But ICMR does deserve credit for publishing the trial protocol, which contains information not available on the trial's **ICTRP** registration. Salient design details include:[38]

ICTRP = International Clinical Trials Registry Platform, hosted by the WHO and similar to ClinicalTrials.gov.

- **Vaccine efficacy:** Sample size calculations assumed that each vaccine would lead to a 50% reduction in TB incidence among household contacts compared with placebo. (In its *Preferred Product Characteristics for New Tuberculosis Vaccines*, the WHO specified that new vaccines should have an efficacy of "50% or greater" against confirmed pulmonary TB to meet the End TB Strategy goal of ending the TB epidemic by 2035.[39])
- **Immunology:** The study is collecting blood at screening for immunological testing from the first 500 participants enrolled at three sites in Chennai, Delhi, and Pune. At each of these sites, 150 participants will undergo further blood draws after receiving both vaccine doses at two subsequent time points for longitudinal immunological analyses.
- **MTB infection testing:** The trial is not testing all participants for MTB infection, but participants at three sites in Chennai, Delhi, and Hyderabad will receive a TST at screening. Those who are **TST** negative will have a repeat TST at month six. This information will inform a secondary POI endpoint.

TST = tuberculin skin test. TST is a type of test for MTB infection but different from the IGRAs used in most POI trials.

- **Radiography:** The study involves significant radiography with chest X-ray for all participants at screening, two months following the first vaccine dose, and thereafter once every year for the three-year follow-up period.

The phase III POD trial run by ICMR is not the only VPM1002 study keeping the field in suspense. SII completed a **phase III POR trial** of VPM1002 among 2,000 adults treated for TB disease in India and Bangladesh. Representatives of SII presented results at the TBVI annual meeting in Les Diablerets, Switzerland, on January 28–29, 2025, but the findings have not been presented to wider audiences and were not known to TAG at the time of writing. The company told TAG that results will be published soon.[40] A third phase III trial evaluating VPM1002 for **POI in infants** in five African countries completed enrollment in June 2022; since then, investigators have been following participants waiting

Phase III POR trial of VPM1002 NCT03152903.

Phase III trial evaluating VPM1002 for POI in infants NCT04351685.

to observe the number of endpoints ("incident cases of QFT [IGRA] conversion, indicating MTB infection") required for the primary analysis.[41] Whether the trial will accrue sufficient endpoints remains to be seen; on February 10, 2025, SII updated the registry entry for the study to change the study's status from "active, not recruiting" to "complete." Last year's *Pipeline Report* discussed the drawbacks of the study's noninferiority design and choice of a POI endpoint to compare VPM1002 to BCG (other infant trials with an active BCG comparator arm are designed as superiority trials with a primary outcome of POD).[42]

QTP101 (ID93/GLA-SE)

QTP101 is a subunit vaccine also known as ID93/GLA-SE.

If VPM1002 kept the field waiting for results, the candidate known as **QTP101** has sparked anticipation about when it will start a phase IIb/III trial announced by its developer, the South Korean company Quratis. Initially developed by the Infectious Disease Research Institute (reborn as Access to Advanced Health Institute), ID93/GLA-SE was licensed to Quratis in 2017, where it picked up the name QTP101 (a story covered by TAG in previous *Pipeline Report* issues). Since receiving the license, Quratis has completed two clinical trials of QTP101: a **phase II study** in 107 IGRA-negative South Korean healthcare workers (ages 19–64) and a **phase I study** in 36 IGRA-negative adolescents (ages 14–18).[43]

QTP101 phase II study in healthcare workers NCT03806686.

QTP101 phase I study in adolescents NCT03806699.

Quratis confirmed with TAG that the company is moving ahead with plans for a phase IIb/III POD trial in adolescents and adults ages 14–55. The company has now secured regulatory approval for the study from the South Korean Ministry of Food and Drug Safety (in July 2022) and from the Philippines Food and Drug Administration (in November 2024).[44] Additionally, Quratis has obtained ethics approval from five sites in South Korea and one in the Philippines. Quratis plans to conduct the trial in two stages. The first stage consists of a phase IIb study in 288 participants (BCG vaccinated, HIV negative, IGRA negative, and IGRA positive). This will be followed by the second stage, a phase III POD trial in 8,778 participants (BCG vaccinated, HIV negative, and IGRA positive).[45] Quratis expects to open stage one of the study in 2025; a clinical trial registry is forthcoming.

In addition to the planned phase IIb/III trial, Quratis registered a phase I study of QTP101 in **older adults** (ages 55–74 years) in January 2025 supported by the Korean Ministry of Health and Welfare. According to a company spokesperson: "The results will inform the potential inclusion of older adults in the future phase 3 trial."[46] The studies of QTP101 sponsored by Quratis are evaluating the vaccine given as three intramuscular injections spaced 28 days apart at a dose of 10 µg ID93 + 5 µg GLA-SE. Studies of this candidate undertaken by other sponsors — for example, a **phase IIb/III trial** of ID93/GLA-SE given as a therapeutic vaccine during TB treatment funded by the U.S. NIH — are studying the vaccine using a different dose and schedule.[47]

Phase I study of QTP101 in older adults NCT06714513.

The U.S. NIH-funded phase IIb/III trial of ID93/GLA-SE given as a therapeutic vaccine (NCT06205589) is administering the vaccine as two injections at a dose of 2µg ID93 and 5µg GLA-SE.

In addition to work on QTP101, Quratis is pursuing preclinical development of a novel subunit vaccine as well as work to develop mRNA vaccines against TB.

Embarking on new efficacy trials

M72/AS01E

The most watched ongoing study is the **phase III trial** of M72/AS01E, which opened to enrollment in March 2024. The field has looked forward to an efficacy trial of M72/AS01E ever since positive results from an earlier **phase IIb trial** were shared in 2018. In that study, which was conducted among 3,575 HIV-negative, IGRA-positive adults, M72/AS01E offered ~50% protection against developing bacteriologically confirmed pulmonary TB compared with placebo (vaccine efficacy = 49.7% [95% confidence interval 12.1–71.2]) over three years.[48]

M72/AS01E **phase III trial** NCT06062238.

Phase IIb trial of M72/AS01E NCT01755598.

Previous *Pipeline Reports* have described the design of the M72/AS01E phase III trial, but by the time the study opened in March 2024, the Gates MRI had made several important modifications. Most notable, the sample size decreased from 26,000 to 20,000 individuals. The Gates MRI made this change in response to site-level epidemiological data suggesting a higher TB incidence rate in the areas where the trial is enrolling than the assumed rate used in the initial sample size estimation.[49] The reduction in sample size affects all three participant cohorts in the study.

The largest cohort will enroll 18,000 (instead of 20,000) adolescents and adults ages 15–44 who are HIV negative and who enter the study with MTB infection (IGRA positive). This IGRA-positive cohort will provide data for the primary efficacy analysis, the case definition for which remains the same as previously described: laboratory-confirmed pulmonary TB disease not associated with HIV, presenting with one or more TB symptoms, and with at least two positive TB test results (culture and/or Xpert) from the same or different sputum samples collected before initiation of TB treatment.

The trial will also enroll an IGRA-negative cohort of 1,000 (instead of 4,000) participants who enter the study uninfected with MTB. This cohort will inform two secondary outcomes. One, a POI endpoint looking at the number of participants with sustained IGRA conversion. Two, a POD endpoint assessing the number of people who enter the trial IGRA negative and then develop TB disease. This cohort will also contribute data on vaccine safety in people without MTB infection. The goal here is to ensure M72/AS01E can be licensed and recommended for use without an accompanying requirement to first test people for MTB infection, which would add complexity and cost to vaccination campaigns.

The third cohort includes 1,000 (instead of 2,000) people living with HIV (PLHIV) of any IGRA status who have been taking antiretroviral therapy for at least three months, have a viral load <200 copies/mL, have a CD4 T-cell count of ≥200 cells/mL, and have taken TB preventive treatment in the past (based on self-report). A secondary outcome will assess whether the vaccine prevents TB disease among participants with HIV. This cohort is also contributing safety and immunogenicity

data. The inclusion of PLHIV follows favorable results from a **phase II study** the Gates MRI completed in 402 PLHIV in South Africa that showed M72/AS01E is safe and immunogenic in this population.[50,51]

Phase II study of M72/AS01E in PLHIV NCT04556981.

Preparations for the M72/AS01E phase III trial included a noninterventional epidemiological study to assess IGRA test positivity at 45 sites in 14 countries. At the 7th Global Forum, Alemnew Dagnew of the Gates MRI shared results for baseline IGRA status (the study re-tested participants after one year of follow-up; those results are forthcoming). As one would expect, IGRA positivity varied by country and by sites within a country. When analyzed by age, the odds of having a positive IGRA test were higher among the older age group (25–34 years).[52] The Gates MRI used the epidemiology study to help select and prepare sites for the phase III trial and target site-level recruitment strategies.

If the pace of enrollment into the phase III trial is any indication, this preparatory work paid off. As of March 4, 2025, the study had enrolled 18,818 of 20,000 participants at sites in **five countries**. The primary efficacy analysis will occur after investigators observe 110 incident cases of TB disease; there is no pre-planned interim analysis. The Gates MRI expects to have results by 2028 (if not sooner).[53]

The five countries participating in the M72/AS01E phase III trial are Indonesia, Kenya, Malawi, South Africa, and Zambia.

MTBVAC

The other vaccine candidate embarking on a much-anticipated efficacy trial is **MTBVAC**. Initially developed at the University of Zaragoza and now with Biofabri, a Spanish biotech company belonging the **Zendal Group**, MTBVAC has attracted the involvement of many partners. When it comes to clinical trials, there are three main partnerships.

MTBVAC is a live attenuated vaccine created from an isolate of MTB with two virulence gene deletions.

The Zendal Group contains eight biopharma companies, including Biofabri, and is named after Spanish nurse Isabel Zendal, who in 1803 set off on a "vaccination mission" sponsored by the Spanish crown that vaccinated half a million people against smallpox.

- The first is a globally focused partnership in which Biofabri is collaborating with IAVI on a phase IIb POD trial funded by Open Philanthropy, the Gates Foundation, and the German government.[54]
- The second is an India-focused partnership between Biofabri and Bharat Biotech International Limited (BBIL), enabled by a 2022 licensing deal between the two companies giving BBIL the rights to develop, manufacture, and market the vaccine in more than 70 countries in Asia and Africa.[55]
- Under the third partnership, which predates the first two, Biofabri is completing a **phase III POD trial** of MTBVAC in newborns with funding from the EDCTP. Last year's *Pipeline Report* discussed the infant trial, which continues to enroll participants in South Africa, Senegal, and Madagascar and has a primary completion date of December 2028. This study received a funding boost in 2024 when **HERA** announced it would provide €12.5 million to Biofabri and TBVI to "fast-track phase 3 clinical trials [of MTBVAC] in neonates across several African countries."[56]

Phase III POD trial of MTBVAC in newborns NCT04975178.

HERA = Health Emergency Preparedness and Response Authority, a directorate-general of the European Commission focused on pandemic preparedness.

First looking at the global partnership: on February 19, 2025, the first participants were vaccinated in a **phase IIb POD trial** of MTBVAC called **IMAGINE** sponsored by IAVI in collaboration with Biofabri.[57] The trial will enroll and randomize 4,300 adolescents and adults ages 14–45 to receive either one dose of MTBVAC or placebo. Participants must be HIV negative and have evidence of MTB infection based on a positive IGRA at screening. The study is enrolling at 15 sites in Kenya (2), South Africa (12), and Tanzania (1). The primary endpoint is prevention of bacteriologically confirmed pulmonary TB disease with a similar primary case definition to the one used in the M72/AS01E phase III trial: clinical suspicion of TB disease (i.e., symptoms) and diagnosis based on at least two positive diagnostic tests from sputum collected before TB treatment initiation. The primary analysis will occur after investigators observe 35 participants develop TB. IAVI expects to have results by 2029.

Phase IIb POD trial of MTBVAC NCT0627812.

IMAGINE = Investigation of MTBVAC toward Accelerating Global Immunization for a Neglected Epidemic.

A cohort of 660 participants will form a safety cohort followed for solicited adverse events, and 90 participants will contribute data for immunogenicity assessments. IAVI is also collecting and biobanking samples for correlates of immune protection analyses. The study will be the first late-stage trial to include an exploratory endpoint assessing vaccine efficacy against asymptomatic TB (formerly called subclinical TB and referring, most simply, to people with TB disease who do not report classic symptoms).[58] IAVI has signaled its desire to expand the study to include two other populations. Additional funding would allow IAVI to enroll a cohort of MTB-uninfected (IGRA-negative) participants to generate safety data in this population. The inclusion of PLHIV depends on favorable results from an ongoing **phase IIa study** run by the U.S. NIH-funded **HVTN** and **ACTG**. That trial is evaluating the safety and immunogenicity of MTBVAC and BCG in 276 HIV-negative and HIV-positive adolescents and adults in South Africa.

Phase IIa study of MTBVAC in PLHIV funded by the **HVTN** (HIV Vaccine Trials Network) and **ACTG** (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections) NCT05947890.

Turning to the India-focused partnership: in March 2024, Biofabri and Bharat Biotech announced the start of safety and immunogenicity trials of MTBVAC. Per a Zendal Group press release, these early-stage studies are building toward an eventual "safety, immunogenicity, and efficacy trial [in India] planned to start in 2025."[59] The first trial is a **phase I safety/immunogenicity study** of MTBVAC in 30 IGRA-negative adults. The trial has already completed enrollment. The second study is a **phase IIa safety/immunogenicity study** comparing MTBVAC to BCG in 164 IGRA-positive and IGRA-negative adolescents and adults ages 12–65 years.[60] To a certain extent, these studies reproduce **earlier phase I and II trials** completed years ago but conducted outside of India. In comments to India's The Tribune paper, ICMR chief Rajiv Bahl alluded to the requirement for local clinical trial data to use a vaccine in India:

> "We are constantly testing for new TB vaccines. One candidate is a Spanish-developed vaccine which we are testing in the Indians in collaboration with Bharat Biotech which has received technology transfer from the Spanish firm. Unless we do a full evaluation of safety and efficacy we cannot use a vaccine in our programme. Our condition is to make the TB vaccine in India."[61]

Phase I safety/ immunogenicity study of MTBVAC In India NCT06438978.

Phase IIa safety/ immunogenicity study of MTBVAC in India CTRI/2024/07/070928.

Earlier phase I and II trials of MTBVAC were conducted in 2013 (NCT02013245) and in 2015 (NCT02729571), followed by a phase Ib/ IIa trial (NCT02933281) in MTB-infected and uninfected adults.

Divining the future

The positive vibe and scientific optimism that buoyed spirits in the TB vaccine R&D field in 2024 already feels an era removed from the harsher political realities of early 2025. In the span of weeks, the new U.S. presidential administration acted against laws, norms, and all procedural safeguards to freeze foreign aid spending and upend the foundations of global health research. Moves to fire staff at USAID and terminate nearly all funding awards will hobble the largest source of bilateral assistance for TB elimination efforts. Bedrock programs such as PEFPAR that innovators relied on to implement and scale new tools are now in serious jeopardy. Staff at funding agencies such as the U.S. NIH have been prohibited from communicating with outside scientists and the public. And dozens of clinical trials have been halted or delayed, in many cases putting scientists in an impossible ethical bind of either complying with stop-work orders or caring for trial participants.[62] Clinical trials of new TB vaccines — funded largely via large philanthropies and European Union donors — have not borne the brunt of these actions, so far. But TB vaccine science will not emerge unchallenged or unscathed. The trust of communities in high-TB-burden countries, who have been asked to participate in study after study of new tools to fight TB, HIV, malaria, and related infections, will not be easily rebuilt following such a sudden rupture. Nor will it be quick to repair the multilateralism required to coordinate an activity as complex as developing new vaccines to address the world's leading cause of death from an infectious disease. It is impossible to divine the future, but the task at hand is clear: advocates, researchers, developers, and funders must band together to protect the scientific promise of the TB vaccine pipeline through what will be a turbulent few years.

Table 2. TB Vaccines in Phase I/II Clinical Development

Agent	Type	Sponsor(s) and Major Partners	Status[α]
Notable recently completed, ongoing, and planned clinical trials. The abbreviations appearing in red boxes give the primary indication for which a vaccine is being studied. **POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence | Rx Vax = therapeutic vaccination**			
DAR-901	Inactivated whole-cell *M. obuense*	Dartmouth College, St. Louis University	Phase IIb
POI	Planning to follow-up results from a phase IIb trial evaluating the efficacy and safety of DAR-901 (vs. placebo) in preventing MTB infection in 625 BCG-vaccinated, HIV-negative adolescents ages 13–15 in Tanzania (NCT02712424). Completion: February 2020.[β]		
ID93/GLA-SE (QTP101)	Protein/adjuvant subunit vaccine	Quratis, NIH (ACTG/IMPAACT/HVTN), AAHI, Oxford University	Phase IIb
Work on QTP101 sponsored by Quratis			
POD	Preparing to open a phase IIb/III efficacy, safety, and immunogenicity trial of QTP101 (vs. placebo) in preventing TB disease among 9,066 adolescents and adults ages 14–55. The trial will have two stages. Stage one: a phase IIb study in 288 participants (BCG vaccinated, HIV negative, MTB infected and uninfected). Stage two: a phase III study in 8,778 participants (BCG vaccinated, HIV-negative, MTB infected). Quratis received regulatory approval for the study from the South Korean Ministry of Food and Drug Safety (in July 2022) and from the Philippines Food and Drug Administration (in November 2024) as well as ethics approval from five South Korean study sites and one in the Philippines. Expected start: stage one will open in 2025 (clinical trial registry forthcoming).		
POI	Published results from a phase IIa safety, immunogenicity, and efficacy study of low-dose or high-dose ID93/GLA-SE (vs. placebo) in 107 BCG-vaccinated, MTB-uninfected health care workers ages 19–64 in South Korea (NCT03806686). Completion: April 2021.		
Other	Undergoing a phase I safety and immunogenicity study of QTP101 at two dose levels (vs. placebo) in 144 BCG-vaccinated, HIV-negative, MTB-infected and uninfected older adults ages 55–74 in South Korea (NCT06714513). Primary completion: September 2026.		
	Announced results (via press release) from a phase I safety/immunogenicity study of low-dose or high-dose ID93/GLA-SE (vs. placebo) in 36 BCG-vaccinated, MTB-uninfected adolescents ages 14–18 in South Korea (NCT03806699). Completion: May 2021.		
Other work on ID93/GLA-SE			
Rx Vax	Preparing to open a phase IIa/IIb trial evaluating the safety, immunogenicity, and therapeutic efficacy of ID93/GLA-SE given as a therapeutic adjunct in 1,500 HIV-positive and HIV-negative adults ages 18–60 in South Africa being treated for DS-TB at different time points relative to the start of TB treatment (NCT06205589). Expected start: April 2025. Primary completion: October 2029.		
Other	Undergoing a phase Ib challenge trial of the safety and immunogenicity of ID93/GLA-SE in BCG-vaccinated and BCG-naive adult volunteers using an aerosol BCG challenge model. Forty-eight MTB-uninfected, HIV-negative adults ages 18–55 in the United Kingdom will be randomized based on BCG vaccination status to receive either ID93/GLA-SE prior to BCG aerosol challenge or receive BCG aerosol challenge without ID93/GLA-SE (NCT0667055). Primary completion: June 2027.		
	Planning for a phase IIa safety and immunogenicity study of ID93/GLA-SE (vs. placebo) in 168 pre-adolescents ages 9–14 living with and without HIV and with and without MTB infection in South Africa (Registry number forthcoming; IMPAACT/HVTN LEAP-2).		

Agent	Type	Sponsor(s) and Major Partners	Status[a]
RUTI	Fragmented MTB	Archivel Farma	Phase IIb
Rx Vax	Undergoing a phase IIb trial evaluating the efficacy and safety of RUTI (vs. placebo) given as a therapeutic adjunct to 140 HIV-negative adults ≥18 years undergoing treatment for DS-TB and MDR-TB in India (NCT04919239). Primary completion: March 2025. (RUTI will be given one week and one month after starting DS-TB and MDR-TB treatment, respectively.)		
	Undergoing a phase II trial evaluating the safety and change in early bactericidal activity of giving RUTI (vs. placebo) as a therapeutic adjunct to 44 HIV-negative adults ≥18 years receiving treatment for DS-TB in Argentina (NCT05455112). Primary completion: August 2024. (RUTI will be given on the day TB treatment starts.)		
ChAdOx1 85A + MVA85A	Viral vector	Oxford University	Phase IIa
Published results from a phase I/II dose escalation and age de-escalation safety study of ChAdOx1 85A in 12 adults and adolescents in Uganda, followed by a phase IIa study comparing the safety and immunogenicity of a ChAdOx1 85A prime vaccine followed by MVA85A boost vaccine (vs. BCG revaccination) in 60 adolescents ≥12 years in Uganda (NCT03681860; EmaBS TB). Completion: May 2021.			
AEC/BC02	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase IIa
Suspended a phase IIa safety, immunogenicity, and dose-ranging study of freeze-dried AEC/BC02 (vs. placebo) in 200 MTB-infected, HIV-negative adult volunteers ≥18 years in China (NCT05284812). Primary completion: June 2024. The suspended label on ClinicalTrials.gov is dated November 2023 and notes: "It is planned to restart the clinical study after the completion of the clinical trial protocol modification."			
BNT164a1 BNT164b1	mRNA	BioNTech	Phase IIa
Undergoing a phase I safety, immunogenicity, and dose-defining study of two investigational vaccines BNT164a1 and BNT164b1 (vs. placebo) in 120 MTB-uninfected, BCG-naïve adult volunteers ages 18–55 in Germany (NCT05537038). Primary completion: June 2025.			
Undergoing a phase Ib/IIa safety, immunogenicity, and dose-defining study of BNT164a1 and BNT164b1 in 732 participants: BCG-vaccinated, HIV-negative, MTB-infected and uninfected adults (phase Ib) plus HIV-negative and HIV-positive adults (phase IIa) ≥18 years in Mozambique and South Africa (NCT05547464). Primary completion: June 2026.			
TB/FLU-05E (aerosol)	Viral vector	Smorodintsev Research Institute of Influenza, Ministry of Health of the Russian Federation	Phase I
Completed a phase I safety, reactogenicity, and immunogenicity study of intranasal TB/FLU-05E (vs. placebo) in 51 BCG-vaccinated, HIV-negative, MTB-uninfected adult volunteers ages 18–50 in the Russian Federation (NCT05945498). Completion: September 2023.			
H107e/CAF10b (incl. aerosol)	Protein/adjuvant subunit vaccine	Statens Serum Institut	Phase I
Undergoing a phase Ia dose-finding study of H107e (unadjuvanted), CAF10b adjuvant, and H107e/CAF10b at low- and full-adjuvant doses followed by a phase Ib safety, reactogenicity, and immunogenicity study of H107e/CAF10b, H107e/CAF10b + BCG, BCG, and placebo in 140 adult volunteers ages 18–45 in South Africa (NCT06050356). Both phases of the trial incorporate intranasal aerosol doses of H107e. Primary completion of phase Ib: third quarter of 2026.			

Agent	Type	Sponsor(s) and Major Partners	Status[a]
Ad5-105K (aerosol)	Viral vector	CanSino Biologics, PT Etana Biotechnologies Indonesia	Phase I
Undergoing a phase I safety, immunogenicity, and dose-finding study of Ad5-105K (vs. placebo) administered via nebulized inhalation through the mouth in 36 BCG-vaccinated, MTB-infected, HIV-negative adult volunteers ages 18–49 in Indonesia (NCT06732583). Primary completion: August 2025.			
RH119	mRNA	Wuhan Ruiji Biotechnology	Phase I
Undergoing a phase I safety, immunogenicity, and dose-ranging study of RH119 (vs. placebo) among 56 HIV-negative, MTB-uninfected adult volunteers ages 18–59 in China (ChiCTR2400094049). Primary completion: unknown.			

α Status indicates the most advanced phase of either ongoing or recently completed trials.

β For ongoing/planned studies, "primary completion" is the "estimated primary completion date" in ClinicalTrials.gov or the date of final data collection for the primary outcome measure. For completed studies, "completion" is the "actual study completion date" in ClinicalTrials.gov (or date provided by study sponsor).

Sources: Information compiled from ClinicalTrials.gov and other clinical trial registries as of 2025 February 28. Information checked against pipeline information collected by the Stop TB Partnership Working Group on New TB Vaccines and supplemented with information provided to TAG by sponsors.

AAHI: Access to Advanced Health Institute

ChAd: chimpanzee adenovirus vector

DS-TB: drug-sensitive tuberculosis

IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network

MDR-TB: multidrug-resistant tuberculosis

M. obuense: Mycobacterium obuense

MVA: modified vaccinia virus Ankara

Other abbreviations are listed in Table 1.

Endnotes

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