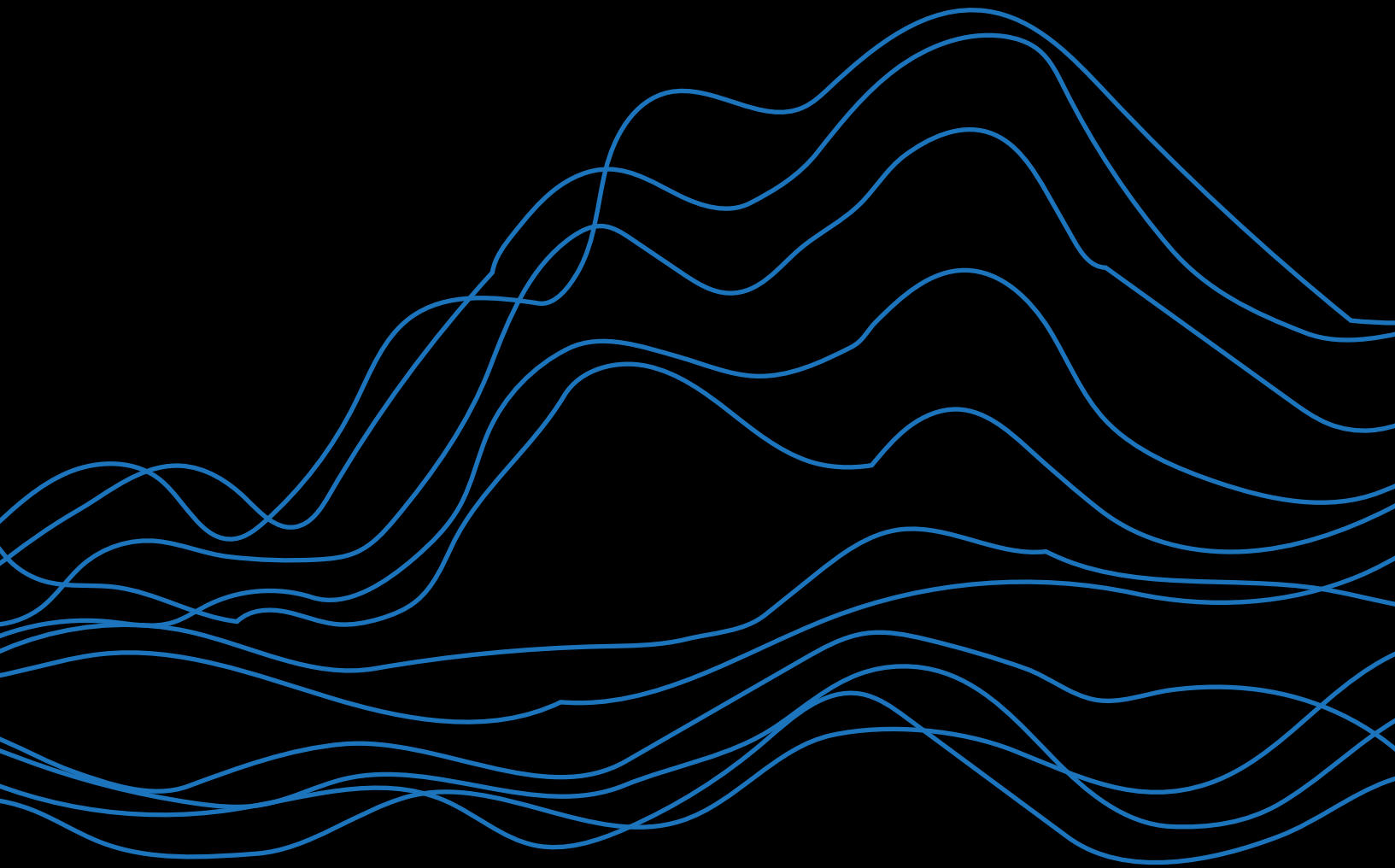


Pipeline Report » 2023

Tuberculosis Vaccines



TAG

Treatment Action Group

Tuberculosis Vaccines

In Anticipation

By Mike Frick

Anticipation is the overriding emotional state of most people involved in tuberculosis (TB) vaccine development (this author included). Its peculiar dualisms of excitement and anxiety, expectation and regret, impatience and forbearance describe how it feels to wait: for funding to arrive, for clinical trials to start, for results to be announced, for governments to take notice, for the pharmaceutical industry to reverse its retreat, for new TB vaccines to enter a world ready to receive them. To wait in anticipation is not passive. TB vaccine development may be slow – especially compared to COVID-19 – but it is an active field of discovery and getting busier across the board, from preclinical development to clinical trials to policymaking. Anticipation for new TB vaccines has even sparked a new set of activities called “vaccine preparedness” meant to smooth the transition from clinical development to implementation. Collective anticipation is a productive space: it generates agitation, which if channeled in the right ways pays off.

Finally, there is some payoff coming in for TB vaccines – literally, speaking of money. The year 2023 opened with news that Open Philanthropy will give \$40 million to the Bill and Melinda Gates Foundation “to fund grantees who are advancing a new vaccine through efficacy trials against tuberculosis in adults.”¹ This award was part of a larger “regranting challenge” designed to add money to high impact programs at other foundations. (Although Open Philanthropy has yet to name the vaccine candidate its money will support, the pipeline of late-stage candidates is small enough, and there are enough clues in the press release, to make an **educated guess**.) Later in the year, the Gates Foundation teamed up with a third philanthropy, Wellcome Trust, to commit a combined **\$550 million** to underwrite the long-awaited phase III trial of M72/AS01E.² One week later, the **German government** announced its contribution of €9.2 million to IAVI over five years to take forward the late-stage development of MTBVAC.³

Much like the quality of anticipation, these funding commitments reveal both positive and negative dynamics about TB vaccine research. On the positive side, this nearly \$600 million in pledged funding represents around four times the \$143 million spent on TB vaccines in 2022.⁴ By any previous measure, 2023 will be remembered as a banner fundraising year. But on the negative side, the fact that most of this money comes from the charity sector raises an uncomfortable question: why have governments not come forward with equal or greater pledges, particularly in a year when advocates set the stage for them do so by organizing a second High-Level Meeting on TB at the United Nations?

Developing new vaccines against the world’s deadliest infectious disease is not an endeavor that should be left to charity. It is a responsibility that should be borne by governments, acting in concert with philanthropies, industry, and each

TAG’s **educated guess** is that Open Philanthropy’s \$40 million will support MTBVAC.

Added to the **German government** money awarded through the German Federal Ministry of Education and Research and KfW Development Bank, this would mean \$50 million raised for MTBVAC.

Of the **\$550 million** for M72/AS01E, Wellcome will provide up to \$150 million with the remaining \$400 million coming from the Gates Foundation.

other to fulfill their obligations to protect the human rights to health and scientific progress. This responsibility has been articulated but not yet fulfilled. The political declaration endorsed at the TB High-Level Meeting contains a commitment to develop “vaccines for all forms of tuberculosis for people of all ages” by “working with the private sector and academia, [to] accelerate the research, development, [and] roll-out of safe, effective, affordable and accessible pre and post exposure vaccines, preferably within the next 5 years.”⁵

This language on vaccines is an improvement from the first TB political declaration, passed in 2018, which mentioned vaccines in a lineup of new tools needed to address TB without attending to this area as a priority.⁶ But a close read of the declaration tempers any excess excitement in this respect. Governments acknowledged the imperative to develop new TB vaccines but backed away from committing the necessary funding. Where Stop TB Partnership and TB activists called for \$5 billion a year for TB research and development (R&D), including at least \$1.25 billion for TB vaccine research,⁷ UN member states **watered down** this figure by expressing \$5 billion not as an annual minimum expectation but instead as a stretch goal to reach for over time. Put another way: governments created a ceiling out of what was meant to be a floor. It is embarrassing that billionaires and their tax-exempt legacy endowments have raised more money for TB vaccines in a year when the spotlight shined so expectantly on governments.

Although UN member states shared few concrete plans for how they will accelerate the development and delivery of new vaccines, anticipation around candidate vaccines in the pipeline continues to build:

- Several phase III clinical trials of VPM1002 have completed enrollment and could report results in the coming year. However, even if one or more of these studies is successful, their translation into global policy is not straightforward (more on this below).
- The Gates Medical Research Institute (Gates MRI) and Wellcome expect to open the M72/AS01E phase III trial in early 2024, ending a 5–6 year wait since positive results of an earlier **phase IIb trial** were published on the eve of the 2018 UN High-Level Meeting on TB. Safety and initial immunogenicity results from the MESA-TB study of M72/AS01E in **PLHIV** will be presented before the end of 2023.
- A phase III trial of MTBVAC in infants continues to enroll and will soon be joined by a study of MTBVAC in adolescents and adults living with HIV, setting the stage for a larger phase IIb efficacy trial in adolescents and adults in African countries to come. Developer Biofabri has also shared plans for a phase I/II safety and immunogenicity study of MTBVAC in adults in India.⁸
- The study of MTBVAC in PLHIV is one of the first large TB vaccine trial protocols taken forward by the **HIV/AIDS Clinical Trials Networks** at the U.S. National Institutes of Health (NIH), which have added serious clinical trials muscle to TB vaccine R&D and are close to opening two additional studies described below.

The political declaration **watered down** the \$5 billion R&D funding target by stating it as:

“Further commit to mobilize adequate, predictable and sustainable financing for tuberculosis research and innovation especially to high burden countries *towards reaching 5 billion United States dollars a year by 2027*” (para. 68; italics added).

Phase IIb trial of M72/AS01E NCT01755598.

PLHIV = people living with HIV.

Three NIH-funded **HIV/AIDS Clinical Trials Networks** are now active in TB vaccine R&D:

HIV Vaccine Trials Network (HVTN)

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

International Maternal Pediatric Adolescent AIDS Clinical Trials network (IMPAACT).

- Sponsored by BioNTech, the first-ever TB vaccine constructs based on mRNA entered phase I testing in 2023. BioNTech may soon be joined by other developers working on mRNA and TB, including the mRNA Technology Transfer Hub in South Africa, Moderna/IAVI in the United States, Popvax in India, and Quratis in South Korea.
- Two subunit vaccines out of Statens Serum Institute in Denmark are approaching major milestones. A phase IIb **POR** trial assessing whether H56:IC31 prevents disease recurrence in adults treated for drug-susceptible TB has completed all participant study visits and expects to report results in the first quarter of 2024.⁹ A new subunit vaccine called **H107/CAF10b** is expected to begin its first phase I clinical trial before the end of the year.¹⁰
- Now 102 years old, the world's only existing vaccine against TB, **BCG**, will once again make news when the Gates MRI publishes results of a phase II trial assessing whether revaccination with BCG protects adolescents against sustained **MTB** infection. The Gates MRI expects to share findings in early 2024. Several other groups are testing BCG revaccination in different populations, including household contacts of people with TB and preadolescents.
- Not to be overlooked, two complex **collaborations** to identify immune correlates of protection using samples from two **successful phase II studies** are finally up and running at participating labs. This initiative is an effort to untangle the ultimate catch-22 of TB vaccine development: a biomarker (or set of biomarkers) that reliably correlates with protection against TB would simplify and accelerate clinical trials, and allow for more informed, iterative vaccine design, but such a marker cannot be validated until a vaccine demonstrates protective efficacy.¹¹

POR = prevention of recurrence (defined as either reinfection or relapse).

First phase I study of **H107/CAF10b** [NCT06050356](#).

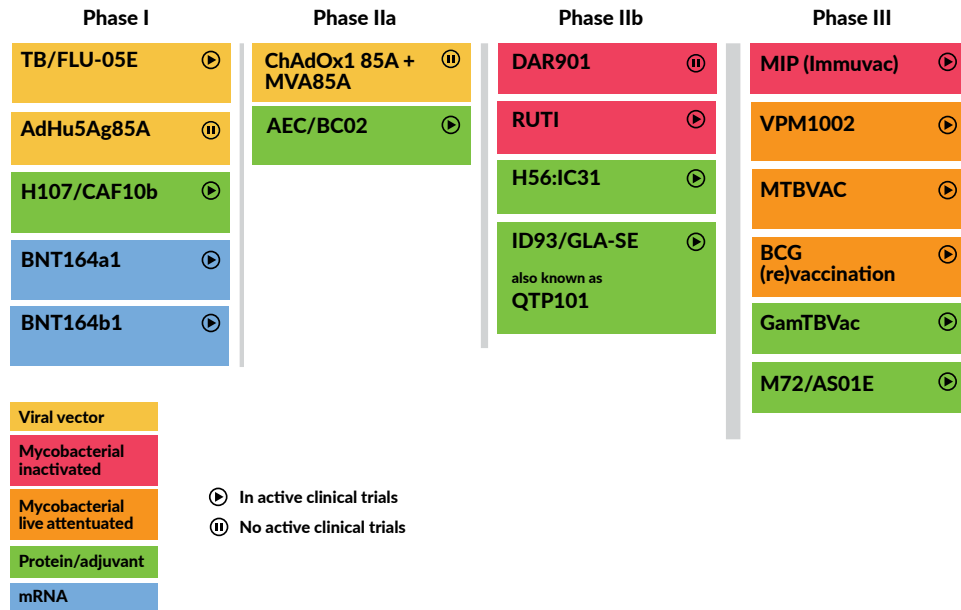
BCG = bacille Calmette-Guérin. BCG is a live attenuated strain of *Mycobacterium bovis*, a close relative of *Mycobacterium tuberculosis* (**MTB**), which causes TB in cows.

The BCG Correlates and M72 Correlates **collaborations** are using specimens from the **successful phase II studies** of M72/AS01E ([NCT01755598](#)) and BCG revaccination ([NCT02075203](#)).

To sum things up: the near horizon is crowded with clinical trial openings and closings. There is a lot to look forward to, but anticipation is not the same thing as prediction. It is likely that some of the trials highlighted above and in the tables that follow will report results before this *Pipeline Report* is published or soon after. Treatment Action Group (TAG) will cover important findings in next year's report. The challenge of writing about a field on the cusp of change is a good problem to have and is a more joyful position to occupy than covering the years of quieter anticipation when big events were fewer and farther between.

With joy in the anticipation of more to come, this 2023 *Tuberculosis Vaccines Pipeline Report* provides updates on the clinical development of 17 candidate vaccines in the pipeline (Figure 1). Table 1 reviews vaccines that have reached phase III trials, and Table 2 summarizes candidates in phase I and II. Notable updates for some, but not all, candidates are discussed in the narrative vignettes below, grouped not by candidate but by population of interest.

Figure 1: The TB Vaccine Pipeline



Building a Better BCG for Children: Two Phase III Trials, Two Different Paths

BCG does a lot for young children. It keeps kids safe from the most severe forms of TB and protects them against death (one recent meta-analysis of BCG observed a >80 percent protection against death, an effect that lasted through age 14).¹² And its benefits extend beyond TB in the form of nonspecific effects that appear to confer protection against non-TB infectious disease.¹³ BCG is a bulwark for child survival, but its limitations are well documented. The modest protection it provides wanes over time and does not shield adolescents or adults, who account for most TB disease and transmission. Because BCG is a live vaccine, it can cause disseminated BCG disease in PLHIV and immunocompromised individuals. Commercialized over a hundred years ago, BCG’s method of manufacture is outdated and inefficient, which has contributed to recurring shortages in recent years.¹⁴ For these reasons, WHO has included “developing an affordable TB vaccine for neonates and infants with improved safety and efficacy as compared to BCG” among the two strategic goals for TB vaccine development in its *Preferred Product Characteristics for New TB Vaccines (PPC)*.¹⁵

Two candidate vaccines are in phase III clinical trials designed with this strategic goal in mind. The first, VPM1002, is a live, genetically modified version of BCG (i.e., recombinant BCG) designed to provide better safety and efficacy than the original. Initially created at the Max Planck Institute of Infection Biology in Germany, VPM1002 is now being developed by Serum Institute of India (SII) under a sublicense from German biotech **Vakzine Projekt Management**.¹⁶ The second, MTBVAC, is a live version MTB itself with two gene deletions

In September 2023, **Vakzine Projekt Management** changed its name to Serum Life Science Europe, a change that nods to SII as its “main shareholder since 2018.”

to attenuate the organism’s virulence and make it safe for human use as a vaccine. MTBVAC was developed at the University of Zaragoza and is now owned by the Spanish company Biofabri, which has partnered with Indian manufacturer Bharat Biotech.¹⁷

On the surface, these two candidates share a lot in common: both are based on live mycobacteria, both are single dose vaccines, both were developed at European universities, both are now sponsored by European small biotech companies with large Indian commercial partners, and both are being tested in infants in phase III trials funded by the **EDCTP** to see if they might replace BCG – but each is pursuing its own path toward this end.

The **VPM1002 phase III trial** started in 2020 and has completed enrollment of 6,940 newborns (0–14 days old) in Gabon, Kenya, South Africa, Tanzania, and Uganda. Also known as the priMe study, this is a **POI** trial that will compare VPM1002 to BCG in terms of safety, immunogenicity, and efficacy against MTB infection. The primary outcome measure is “incident cases of QFT conversion, indicating MTB infection” 12 to 36 months after vaccination. QFT refers to QuantiFERON, a type of **IGRA** test used to indicate infection with MTB. Conversion here means QFT turning from negative, indicating no infection, to positive, suggesting MTB infection. SII told TAG that results from this study will be available by 2026 (later than the 2024 timeline given last year).¹⁸

POI is a surprising primary endpoint for a phase III trial that aims to “build a successor to BCG” by “revealing whether a promising alternative to BCG is safe and effective for use in newborn infants,” to quote the EDCTP information page on the trial.¹⁹ Informal consensus in the field has framed POI studies as a steppingstone to larger efficacy trials powered on **POD** endpoints.²⁰ This consensus arises from the notion that regulators are more likely to license new TB vaccines based on evidence that they prevent disease but may hesitate to grant approval based on POI alone. This is because existing tests for infection have drawbacks, the foremost being that they do not test for MTB infection directly. In addition, repeat IGRA testing can produce variable results – for example, an initial conversion that reverts to negative later – which could signal biological changes (e.g., transient MTB infection that the body clears) or test performance. For this reason, most POI trials in the field have started using a more stringent primary endpoint: **sustained infection**, interpreted as persistent MTB infection.²¹ But in the VPM1002 infant trial, sustained infection is a secondary, not primary, endpoint.

Moreover, the priMe study was designed as a **noninferiority trial**. This means that instead of answering the question, Is VPM1002 superior to BCG at preventing infection with MTB? it asks, Is VPM1002 no worse than BCG by a prespecified allowance? It is doubtful whether a noninferiority trial with a POI primary endpoint can generate the evidence required to change global BCG vaccination policy.

EDCTP = European and Developing Countries Clinical Trials Partnership.

VPM1002 phase III trial in infants (NCT04351685).

POI = prevention of infection.

IGRA = interferon-gamma release assay, a blood-based test that detects cell-mediated immune responses to MTB antigens.

POD = prevention of disease.

Sustained infection means an initial conversion from negative to positive (signaling MTB infection) and subsequent positive results upon retesting at later time points – in this case, at two time points six months apart.

Most simply, **noninferiority trials** aim to show that an intervention is not worse than the comparator by more than a specified margin.

On this point, the WHO PPC document expresses a preference for superiority designs: “Clear evidence of superiority would likely drive policy change, but demonstrating only marginally improved characteristics may not support global implementation as a BCG replacement.”²² SII told TAG that if noninferiority is demonstrated, an assessment of superiority will follow.²³

The **phase III trial of MTBVAC** has taken a different approach by adopting a POD primary endpoint. The study opened in 2022 and plans to enroll 7,120 newborns within their first seven days of life in South Africa, Senegal, and Madagascar.²⁴ Infants will be randomized to receive one dose of either MTBVAC or BCG and then followed for a minimum of 24 months to see how many develop TB disease. Secondary endpoints will assess safety as well as immunogenicity with samples stored for future immunology and biomarker discovery efforts. Biofabri shared December 2028 as the study’s “primary completion date,”²⁵ meaning that results from the VPM1002 trial will be available before those on MTBVAC. It will be interesting to see how regulators, global policymakers, and national governments respond to each study, if successful, and whether the different primary endpoints lead to different policy decisions. For its part, SII has said that if results are positive, it will file VPM1002 for prequalification at WHO.²⁶

MTBVAC phase III infant trial
[NCT04975178](#).

TB Vaccine Trials: Places Where PLHIV Belong

One positive quality of both the VPM1002 and MTBVAC phase III trials is that babies born to women with HIV on antiretroviral therapy (ART) are eligible to enroll. These “HIV exposed, uninfected infants” are an important population to include if the goal is to develop safer alternatives to BCG. PLHIV of all ages should be a priority group for TB vaccine development given their much higher risk of TB. But aside from a few **earlier trials in PLHIV** that concluded more than five years ago, the inclusion of PLHIV in TB vaccine R&D has not been treated as a normative expectation until recently. PLHIV should be included in TB vaccine trials – not as an afterthought, and not merely as a small, underpowered subgroup. A TB vaccine trial is a place where PLHIV belong if it is safe to include them.

Earlier trials in PLHIV
included vaccine candidates M72/AS01E (NCT01262976), MVA85A (NCT01151189), and DAR-901 (NCT00052195; then called SRL-172).

PLHIV are not an afterthought at the NIH HIV/AIDS Clinical Trials Networks. The increased activity on TB vaccines at HVTN, ACTG, and IMPAACT has already increased the representation of PLHIV in TB vaccine research. As articulated by an expert consensus statement the three networks published on the topic: “Trials of tuberculosis vaccine candidates should include people with HIV with careful consideration of safety, immunogenicity, and efficacy specific to people with HIV.”²⁷ The consensus paper recommends when and how to study different types of vaccines in PLHIV – live vaccines required the most careful risk/benefit consideration – and establishes some basic rules, including: “All people with HIV participating in tuberculosis vaccine trials must be on ART,” and “Tuberculosis vaccine trial participants with HIV should either previously have completed a course of tuberculosis preventive treatment (TPT) before enrolment or be offered TPT during the study.”²⁸

Table 1. TB Vaccines in Phase III Clinical Development

Agent	Type	Sponsor(s), Major Partners and Funders	Status ^a
<p>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.</p> <p>POD = prevention of disease POI = prevention of infection POR = prevention of recurrence Rx Vax = therapeutic vaccination</p>			
MIP	Whole-cell <i>M. indicus pranii</i>	ICMR, Cadila Pharmaceuticals	Phase III
POD	Results anticipated from a phase III trial evaluating the efficacy, safety, and immunogenicity of MIP and VPM1002 (vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) among 12,721 household contacts (≥six years old, HIV negative) of people with pulmonary TB in India (CTRI/2019/01/017026). Primary completion: 2022. ^β		
VPM1002	Live rBCG	SII, Vakzine Projekt Management, ICMR, EDCTP, NIH (IMPAACT/HVTN)	Phase III
POD	Results anticipated from a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 and MIP (vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) among 12,721 household contacts (≥six years old, HIV negative) of people with pulmonary TB in India (CTRI/2019/01/017026). Primary completion: 2022.		
POI	Completed enrollment in a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection among 6,940 newborns 0–14 days old (HIV-exposed/HIV-negative eligible) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685; priMe). Expected completion: 2026.		
POR	Completed enrollment in 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 years successfully treated for pulmonary TB in India and Bangladesh (NCT03152903). Primary completion: February 2024.		
Other	Undergoing a phase I/II safety/immunogenicity study of VPM1002 and BCG revaccination (vs. placebo) in 480 HIV-positive and HIV-negative preadolescents ages 8–14 with and without MTB infection in South Africa (NCT05539989; IMPAACT 2035/HVTN 604). Primary completion: October 2026.		
MTBVAC	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, and immunogenicity of MTBVAC (vs. BCG) in preventing TB disease in 7,120 infants within their first seven days of life (HIV-exposed/HIV-negative eligible) in South Africa, Senegal, and Madagascar (NCT04975178; MTBVACN3). Primary completion: December 2028.		
	Planning for a phase IIb trial evaluating the efficacy, safety, and immunogenicity of MTBVAC (vs. placebo) in preventing TB disease in around 4,300 MTB-infected, HIV-negative adults and adolescents in Africa. Expected start: 2024 (clinical trial registry forthcoming). Source: IAVI and Biofabri.		
Other	Completed a phase IIa safety, immunogenicity, and dose-defining study of MTBVAC (vs. BCG) in 99 infants ages 0–4 days in South Africa (NCT03536117). (Informed dose selected for phase III POD trial listed above.) Completion: March 2022.		
	Results expected by 2024 from a phase IIa safety, immunogenicity, and dose-defining study of MTBVAC (vs. BCG) in 144 HIV-negative adults ages 18–50 with and without MTB infection in South Africa (NCT02933281). Completion: September 2021.		
	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: November 2024.		
	Planning for a phase Ib/IIa trial evaluating the safety and immunogenicity of MTBVAC (vs. placebo) in adults in India. Expected start: December 2023 (clinical trial registry forthcoming). Source: Biofabri.		

Agent	Type	Sponsor(s), Major Partners and Funders	Status ^α
<p>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.</p> <p>POD = prevention of disease POI = prevention of infection POR = prevention of recurrence Rx Vax = therapeutic vaccination</p>			
BCG (re)vaccination	Whole-cell <i>M. bovis</i>	ICMR, Gates MRI, Fiocruz, Henry M. Jackson Foundation, NIH (IMPAACT/HVTN)	Phase III
POD	Plans on hold for a phase III trial evaluating the efficacy, safety, immunogenicity of BCG revaccination (vs. TPT) in preventing TB disease (pulmonary or extrapulmonary) among 9,200 BCG-vaccinated, HIV-negative child and adolescent household contacts ages 6–18 years in India (NCT05330884; BRiC). Primary completion: June 2025.		
POI	Results expected by 2024 from a phase IIb trial evaluating the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in preventing sustained MTB infection in 1,820 BCG-vaccinated, MTB-uninfected, HIV-negative adolescents aged 10–18 years in South Africa (NCT04152161). Primary completion: September 2025.		
	Undergoing a phase III trial evaluating the efficacy and safety of pretravel BCG vaccination (vs. placebo) in preventing MTB infection among 2,000 BCG-naïve, MTB-uninfected adults aged 18–65 years, either health care workers or long-term travelers to high-TB-burden countries from the United States (NCT04453293). Primary completion: May 2025.		
	Registered a phase IV trial evaluating the efficacy and safety of BCG revaccination (vs. no intervention) in preventing MTB infection in 760 adult male inmates in prisons in Brazil (NCT05541952). Primary completion: July 2023.		
Other	Undergoing a phase I/II safety/immunogenicity study of BCG revaccination or VPM1002 (vs. placebo) in 480 HIV-positive and HIV-negative preadolescents ages 8–14 with and without MTB infection in South Africa (NCT05539989; IMPAACT 2035/HVTN 604). Primary completion: October 2026.		
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 pulmonary TB disease among 7,180 HIV-negative, BCG-vaccinated, MTB-uninfected adults ages 18–45 years in the Russian Federation (NCT04975737). Primary completion: November 2025.		
M72/AS01E	Protein/adjuvant subunit vaccine	Gates MRI, Wellcome Trust, GSK Biologicals (AS01E adjuvant)	Phase III
POD	Preparing to begin a phase III trial evaluating the efficacy, safety, and immunogenicity of M72/AS01E (vs. placebo) in 26,000 people ages 15–44 years in Indonesia, Kenya, Malawi, Mozambique, South Africa, Vietnam, and Zambia. The primary objective will evaluate vaccine efficacy for POD in participants with MTB infection. (Secondary objectives will evaluate POI among participants who enter the study without MTB infection and safety/immunogenicity in PLHIV.) Expected start: 2024 (clinical trial registry forthcoming).		
	In preparation for the phase III study, the Gates MRI is conducting an epidemiologic study to assess IGRA positivity and TB incidence at 45 potential trial sites and has completed enrollment of 7,200 adolescents and adults ages 15–34 years in Bangladesh, Brazil, Democratic Republic of Congo, Gambia, India, Indonesia, Kenya, Mozambique, Peru, Philippines, South Africa, Uganda, Vietnam, and Zambia (NCT05190146). Primary completion: September 2024.		
Other	Results expected by 2024 from a phase II safety/immunogenicity study of M72/AS01E (vs. placebo) in 402 adults living with HIV ages 16–35 years who are on ART, are virally suppressed, and have previously taken TPT in South Africa (NCT04556981; MESA-TB). Primary completion: August 2022.		
<p>^α Status indicates the most advanced phase of either ongoing or recently completed trials.</p> <p>^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).</p> <p>Sources: Information compiled from ClinicalTrials.gov and other clinical trial registries as of 2023 September 25. 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.</p> <p>Abbreviations defined at bottom of Table 2.</p>			

The Networks are preparing to begin three large TB vaccine trials, each of which includes PLHIV alongside HIV-negative trial participants as a matter of course:

- **IMPAACT 2035/HVTN 604** is a phase I/II safety and immunogenicity study of BCG revaccination and VPM1002 – each compared to placebo – in 480 HIV-positive and HIV-negative preadolescents ages 8–14 in South Africa. The trial will enroll adolescents with and without MTB infection. This is one of the only studies that includes preadolescents, an age group that usually falls through the demographic gap between infant trials and studies in older adolescents and adults (the other such study is a trial in household contacts in India discussed in the next section).
- **ACTG 5397/HVTN 603** is a phase IIa/IIb efficacy, safety, and immunogenicity study of ID93/GLA-SE given as a therapeutic vaccine to 1,500 participants with drug-sensitive TB at different timepoints in TB treatment. The main idea is to see whether vaccination with ID93/GLA-SE improves TB treatment outcomes (treatment failure, TB recurrence, death due to TB). Exploratory endpoints will assess lung health during and after treatment. The phase IIa component will be conducted in four participant groups and test giving the vaccine at progressively earlier timepoints in TB treatment. The phase IIb portion will evaluate therapeutic efficacy of the vaccination schedule selected by investigators to move forward. Enrollment is open to PLHIV who are receiving ART, are virally suppressed, and have a minimum CD4 count of 250 cells/mm³. The ACTG and HVTN expect to open the study in early 2024.
- **ACTG 5421/HVTN 605**, a second joint undertaking by the HVTN and ACTG, is a phase IIa study that will test the safety and immunogenicity of MTBVAC and BCG revaccination in 276 HIV-negative and HIV-positive adolescents and adults living with HIV in South Africa. The trial is noteworthy for studying two live attenuated vaccines in PLHIV. All participants with HIV must be taking ART and have completed TPT in the past. More notable is the inclusion of a subgroup enrolling people who have **advanced HIV disease** at screening. This is the first study identified by TAG to enroll people with advanced HIV disease (earlier trials in PLHIV did not require ART but had higher CD4 cutoffs for enrollment).

IMPAACT 2035/HVTN 604 phase I/II trial of BCG revaccination and VPM1002 [NCT05539989](#).

ACTG 5397/HVTN 603 phase IIa/IIb study of ID93/GLA-SE did not have a clinical trial registry number at time of publication.

ACTG 5421/HVTN 605 phase IIa study of MTBVAC and BCG revaccination [NCT05947890](#).

Also called AIDS, **advanced HIV disease**, is defined by WHO as a CD4 count less than 200 cells/mm³.

The HIV/AIDS Clinical Trials Networks are not alone in including PLHIV in TB vaccine trials. The Gates MRI recently completed **MESA-TB**, a phase II safety/immunogenicity study of M72/AS01E in 402 adults with HIV in South Africa. Safety and initial immunogenicity results from MESA-TB will be presented at the 2023 Union World Conference on Lung Health and are expected to support plans to enroll a cohort of 2,000 PLHIV in the phase III trial that will begin in 2024. At the March 2023 WHO Strategic Advisory Group of Experts on Immunization (SAGE) meeting, the Gates MRI shared that MESA-TB “safety data [are] available (no safety signal detected).”²⁹ Detailed immunogenicity results will be published in early 2024.

MESA-TB phase II safety/immunogenicity study of M72/AS01E in PLHIV [NCT04556981](#).

QTP101 Making Money Moves

The ID93/GLA-SE candidate being studied by the HVTN and ACTG is also under development by a different name: QTP101. The developer in this case is Korean biotech Quratis, which in 2017 received an exclusive license and technology transfer to develop ID93/GLA-SE from **IDRI** (now **AAHI**) in South Korea and other countries in Asia.³⁰ ID93/GLA-SE is a subunit vaccine that combines a fusion protein of four MTB antigens with the GLA-SE adjuvant.

Quratis previously announced plans to conduct a phase IIb/III POD trial of QTP101 in over 9,000 adolescents and adults and received approval of the clinical trial plan from the South Korea Ministry of Food and Drug Safety in July 2022.³¹ That trial is slated to start in Korea in December 2023. Quratis has identified a **CRO** to oversee future clinical trials in Indonesia and the Philippines.³²

In May of this year, Quratis published results from a **phase IIa study** that compared the safety and immunogenicity of high-dose versus low-dose QTP101 among 107 Korean health care workers who were BCG vaccinated but MTB uninfected.³³ Both doses were safe, well tolerated, and generated similar ID93 antigen-specific antibody and cellular immune responses that held up over 12 months. Researchers concluded that “10 µg ID93 + 5 µg GLA-SE [the higher dose] is desirable for further studies including efficacy evaluation in the future.”³⁴

The announcement of phase IIa results and early signaling about the phase IIb/III trial were part of the build-up to something unusual for the TB vaccine field: an initial public offering (IPO). In June 2023, Quratis completed an IPO that raised KRW14 billion (~\$11 million) at a public offering price of KRW4,000 (\$3) per share, below the target band of KRW6,500–8,000 (\$5–6).³⁵ Quratis is now listed on the KOSDAQ exchange. The company has stated that “the money raised will be used to conduct [the] phase 2b/3 clinical trial of QTP101.”³⁶

In statements to the press, Quratis has set an ambitious goal of commercializing QTP101 by 2025 and entering 44 countries with a focus on Indonesia and China, where it has signed partnerships with two state-owned outfits:³⁷ In Indonesia, with Bio Farma PT;³⁸ in China, with Shandong Lukang Hao Li You, cofounded by Orion Holdings and a Chinese state-owned pharmaceutical company.³⁹ Based in Yongsan, South Korea, **Orion Holdings** invested KRW42.7 billion in Quratis in a 2021 private equity funding round.^{40,41}

The timeline of market entry by 2025 is not realistic – a phase III POD trial of 9,000 participants cannot be completed in less than two years. (Most phase III POD trials are designed with around five years of follow-up to observe enough TB disease endpoints to estimate vaccine efficacy.⁴²) Still, Quratis raising \$11 million for TB vaccine R&D is noteworthy in a year when most biotech companies worldwide are struggling to raise money and in which similar Korean biotech IPOs yielded disappointing results.⁴³ In addition to QTP101, Quratis is pursuing preclinical and clinical development of **other vaccines** against TB and additional diseases. Furthest along is QTP104, a self-amplifying mRNA vaccine against COVID-19.

IDRI, the Infectious Disease Research Institute, initially developed ID93/GLA-SE but closed abruptly in 2019 and entered a receivership. It emerged again in 2022 as the Access to Advanced Health Institute (AAHI) with a board chaired by South African billionaire Patrick Soon-Shiong.

CRO = contract research organization.

Phase IIa study of QTP101 [NCT03806686](#).

Orion Holdings is best known as the maker of the Choco Pie, a line of snack cakes created in 1974.

Other vaccines in development at Quratis include a vaccine against schistosomiasis (QTP105) and several vaccines against TB including QTP102, QTP106 (an mRNA TB vaccine), and QTP109 (a TB vaccine billed for the elderly).

Prevention at Home: Studying New TB Vaccines in Household Contacts

For a long time, young children and PLHIV were the focus of TB prevention programming and research. This narrow lens widened to include “**household contacts**” when the 2018 TB High-Level Meeting political declaration set a target for UN member states to provide TPT to 20 million household contacts by 2022. By the end of 2021, only 600,000 close contacts had received TPT, leaving 97 percent of the target unmet.⁴⁴ As household contacts have drawn more attention from TPT programs, they have also moved closer to the center of prevention research, including vaccine research.

One of the largest active clinical trials is directing enrollment toward household contacts. Funded by **ICMR**, this **phase III POD trial** is evaluating the efficacy and safety of VPM1002 and MIP (each compared to placebo) among 12,721 household contacts six years of age and older. MIP is an inactivated, whole-cell vaccine created from *Mycobacterium indicus pranii*. Originally developed as a leprosy vaccine, MIP is made by Cadila Pharmaceuticals under the name Immuvac. This study is being conducted at six sites across India and is fully enrolled. The POD endpoint includes the prevention of both pulmonary and extrapulmonary TB. The protocol indicates plans for an interim analysis after investigators observe 80 incident cases of TB (or the trial reaches 50 percent enrollment); results from this analysis have not been shared. The final analysis will occur after 160 trial participants develop TB or when the trial reaches the end of its 38-month follow-up period, whichever occurs first. Results are expected in 2024.

In addition to the POD primary endpoint, the trial contains a secondary POI endpoint, defined as “the number of participants developing LTBI [MTB infection]” six months after vaccination. This analysis will use data collected at three of the six sites.

The second ICMR study among household contacts is a **phase III POD trial** comparing BCG revaccination to TPT among 9,200 HIV-negative child and adolescent household contacts ages 6–18 years. When first announced in 2022, this trial stood out for being the first to use TPT as an active comparator in place of placebo (or BCG in infant trials). ICMR informed TAG that plans for the trial have been “suspended as the proposal is undergoing significant revisions” in response to India’s national TB guidelines. The substance of these revisions is not known to TAG (at the time of publication, the trial registration page on ClinicalTrials.gov had not been updated since July 2022).

The changes may relate to the how the trial approaches TPT. As described last year, investigators had planned to randomize participants to receive either BCG revaccination or TPT and follow each group for 24 months to compare the incidence of TB disease (pulmonary or extrapulmonary). Children exposed to drug-sensitive TB would have received either **6H** or **3HP**; those exposed to

Household contacts (HHC) refers to people exposed to or at risk of TB because they have had close contact with someone with the disease.

ICMR = Indian Council of Medical Research.

Phase III POD trial of VPM1002 and MIP in household contacts [CTRI/2019/01/017026](https://www.clinicaltrials.gov/ct2/show/study/NCT019017026).

Phase III POD trial of BCG revaccination vs. TPT [NCT05330884](https://www.clinicaltrials.gov/ct2/show/study/NCT05330884).

6H = six months of isoniazid preventive therapy taken daily.

3HP = 12 weeks of isoniazid, and rifapentine taken once a week for 12 weeks.

drug-resistant TB would have received **six months of levofloxacin**. Participants could have taken TPT in the past, but they could not have received preventive treatment within six months of enrollment and “they should be current HHC.” In last year’s *Pipeline Report*, TAG expressed concern about “whether a study clinician could truly be in equipoise about randomizing a 6-year-old child exposed to TB to receive either TPT (a known effective intervention) or a second dose of BCG (an unproven intervention).”⁴⁵ As more clinical trials enroll household contacts and other high-risk populations, it will be important for researchers to establish ethical consensus on how to incorporate TPT into TB vaccine trials.

Two trials evaluating **six months of levofloxacin** as TPT for people exposed to drug-resistant TB will report results this year: TB CHAMP (ISRCTN92634082) and V-QUIN (ACTRN12616000215426).

One perspective on this issue (coauthored by the present writer) argues that TPT should be seen as part of the “standard of prevention” for TB and therefore made available to trial participants who are indicated to receive it.⁴⁶ The high effectiveness of TPT, however, will make it more difficult to demonstrate the efficacy of vaccines given on top of or alongside it by reducing the number of trial participants who develop TB – and therefore pushing trials to larger sample sizes and longer periods of follow-up at greater financial cost. To address this dilemma, the perspective piece sketches four trial designs that borrow from how HIV vaccine developers have incorporated pre-exposure prophylaxis for HIV into vaccine trials. The bottom line: there are ways to ethically conduct TB vaccine efficacy trials without either withholding TPT in the face of guidelines recommending it or disallowing the participation of people who should receive it.

Another notable facet of the original study design was the inclusion of both well-nourished and malnourished children. This is significant because the WHO attributes one in five incident cases of TB to poor nutrition.⁴⁷ In 2023, a landmark trial funded by ICMR called RATIONS showed that offering nutritional supplementation to household contacts resulted in a 39–48 percent reduction in TB incidence over two years, leading some observers to call food “the TB vaccine we already have.”⁴⁸ The **RATIONS trial** provides strong evidence that food supplementation is another irreplaceable part of the TB “standard of prevention,” one that should be provided to participants alongside TPT.⁴⁹ It will be interesting to see how the original clinical trial design evolves in relation to TPT, nutritional supplementation, and other changes to India’s national guidelines on TB prevention.

RATIONS trial of nutritional supplementation for prevention CTRI/2019/08/020490.

Studying TB Vaccines in Pregnant People

This section is intentionally left blank because there are no TB vaccine clinical trials that include pregnant people among eligible participants. For a discussion of why developers should make concerted efforts to include pregnant people in TB vaccine studies, please read the section of last year’s *Pipeline Report* titled “Three issues to fix in TB vaccine trials.”⁵⁰

Twenty-six Thousand People Strong: The M72/AS01E Phase III Trial

The most anticipated event on the horizon is the long-awaited opening of the M72/AS01E phase III trial. At the beginning of 2023, the expectation was that the study would start late this year, but by late March, when the Gates MRI presented the phase III trial plans to **SAGE**, the timeline had been moved to early 2024.

As of September 25, 2023, the trial does not have a clinical trials registry entry and known details about the study design remain similar to those reported by TAG in previous *Pipeline Reports*. To recap: the trial will enroll around 26,000 adolescents and adults ages 15–44 years in **seven countries**. The trial is not targeting enrollment to particular groups selected for their high risk of TB such as household contacts; instead, participants will come from the “general population” of people who live in areas where there is documented high risk of TB infection. A **preparatory epidemiological study** assessing IGRA positivity and TB incidence in communities from which potential phase III trial sites intend to enroll is helping the Gates MRI to identify these areas. The epidemiological study is fully enrolled (7,200 participants at 45 sites in 14 countries in Africa, South America, and South and Southeast Asia) and will continue follow-up into 2024.⁵¹

The primary endpoint of the phase III trial is the efficacy of M72/AS01E in preventing bacteriologically confirmed pulmonary TB disease among HIV-negative participants who enter the study with MTB infection (IGRA-positive). This cohort will be the largest in the study at 20,000 participants. The primary case definition in the phase III trial matches the one used for a sensitivity analysis of the primary outcome measure in the phase IIb study. This more stringent definition required bacteriologic confirmation of TB on at least two positive sputum tests and resulted in a higher estimated vaccine efficacy (68.0%, 95% CI [25.1 – 86.3]) than the first case definition, which required only one positive sputum test (49.7%, 95% CI [2.1 – 74.2]).⁵²

Secondary endpoints will evaluate vaccine efficacy in preventing MTB infection (sustained IGRA conversion) among 4,000 HIV-negative participants who are MTB-uninfected (IGRA-negative) at screening and in preventing disease among a cohort of 2,000 PLHIV (any IGRA status). Other secondary endpoints will assess safety, reactogenicity, and immunogenicity. The immunogenicity analysis will be performed on samples from four hundred participants in each of these three cohorts.

The assessable period for the efficacy analysis for each participant will begin one month after receiving the second dose of M72/AS01E and last until the end of study (up to five years after the last participant is enrolled). The Gates MRI hopes to fully enroll the study within 2.5 years. Like nearly all TB vaccine efficacy trials, the primary analysis is event driven and will occur once investigators observe 150 cases of lab-confirmed pulmonary TB among HIV-negative, baseline IGRA-positive participants in the per-protocol analysis.⁵³ Trial simulations run by the Gates MRI indicate that that could happen as early as two years after completing enrollment,

SAGE = Strategic Advisory Group of Experts on Immunization. SAGE is the body at WHO responsible for advising the agency on global vaccination policy.

The **seven countries** in the M72/AS01E phase III trial are Indonesia, Kenya, Malawi, Mozambique, South Africa, Vietnam, and Zambia.

Preparatory epidemiological study for the M72/AS01E phase III trial [NCT05190146](https://www.clinicaltrials.gov/ct2/show/study/NCT05190146).

which would mean results could be available in 2028 – just in time for the next UN High-Level Meeting on TB and two years ahead of the **SDG** deadline of 2030.

Time delayed in starting the trial is not necessarily time lost, and the Gates MRI and Wellcome have used this preparatory period to lay the groundwork for vaccine access and implementation should the trial prove successful. An important piece of work has involved courting potential commercial partners who can manufacture the antigen component of the vaccine (GSK retains rights to supply the AS01E adjuvant) and serve as the marketing authorization holder. Identifying a commercial partner requires discussing issues like technology transfer, cost of goods, pricing, and regulatory strategy. On this last point, the Gates MRI has indicated that it would support a first registration of the vaccine with **SAHPRA** and then seek WHO prequalification (if the eventual commercial partner and marketing authorization holder agrees).⁵⁴ This approach is admirable in bringing the first review to a regulatory agency in a high-TB-burden country – one expected to contribute a substantial number of the 26,000 trial participants – rather than taking the usual road to the **FDA** in Silver Spring or **EMA** in Amsterdam. South Africa will also host the study's central lab where sites will ship sputum samples collected for the primary analysis.

Anticipating Success: Get Ready to Stay Ready

Recognizing that the TB vaccine pipeline is weighted toward late-stage trials – studies that have the potential to deliver long-awaited new TB vaccines but will take years to complete – funders, developers, normative agencies, and civil society actors are thinking about what can be done today to prepare for results tomorrow, whether positive or negative. In some ways, success is more difficult to plan for than failure. Like any field of medical research, TB vaccine R&D has had its share of clinical trial disappointments. Success has proven more elusive. A positive efficacy finding in a phase III trial would trigger a new set of regulatory decisions, research questions, commercial outlays, policy actions and, most importantly, community- and individual-level choices about whether to take a new TB vaccine or not.

Anticipating success, TB vaccine stakeholders have embarked on a forward-looking set of activities known as “vaccine preparedness.” These activities have started to bring work on downstream factors related to supply, distribution, demand, and hesitancy into the upstream space of clinical development. Rather than wait for trials to conclude, the idea is to act in anticipation of successful results so that new TB vaccines enter a world prepared to approve them, manufacture them, distribute them, and implement them without delays and in equitable ways. Already, the preparedness conversation has recast the image of the TB vaccine pipeline as containing not one, but two streams of activity: a scientific pipeline composed of candidate vaccines under study and, running alongside it, a policy pipeline leading to vaccine introduction.

Sustainable Development Goal (**SDG**) 3 sets a goal to end the TB epidemic by 2030.

SAHPRA = South African Health Products Regulatory Authority.

FDA = Food and Drug Administration.

EMA = European Medicines Agency.

The Gates MRI has also expressed interest in taking advantage of EU-M4All, a cooperative program of the EMA and WHO in which the EMA grants a positive opinion on a medicine or vaccine for use outside of Europe that can serve as the basis of applying for WHO prequalification.

This vaccine preparedness theme is new enough to the TB field that many conversations have started by comparing definitions: does preparedness start with addressing supply concerns related to availability, manufacturing, and procurement? Or should activities begin with building demand for and confidence in new TB vaccines, and at what level: among politicians, immunization program decisionmakers, or communities? Or is it about doing all things at once? These questions are being considered by WHO, which is preparing a global framework “to prepare the pathway for rapid introduction, coverage scale-up, and impact of new TB vaccines.”⁵⁵ Other key efforts include a TB vaccine demand forecast and market analysis commissioned by Wellcome, a TB vaccine policy partnership envisioned by the Gates Foundation, and vaccine readiness research funded under **SMART4TB**.

The COVID-19 experience looms large behind all these initiatives.⁵⁶ Today’s focus on vaccine preparedness not only reflects the mature state of the TB vaccine pipeline – it also responds to the unforgivable failures of the second year of the pandemic when efforts to vaccinate the world faltered on the inequitable distribution of limited vaccine supply, a prolonged injustice of unequal availability and unmet demand that contributed to vaccine hesitancy and cost millions of lives.

Against the backdrop of this collective shame, preparedness has become a refrain in global health, one borrowed from fields permanently oriented toward crisis response. The floods, fires, and famines of “disaster preparedness” and “emergency preparedness” now sit alongside COVID-19 and the future plagues addressed by “pandemic preparedness.” When attached to another word in this way, preparedness completes the thought, creating a new term that stands in for a set of different activities, as in vaccine preparedness. But if repeated too often, preparedness risks becoming just another inert buzzword. Even the construction of the word itself hedges the urgency to act. The last two syllables blunt the direct imperative of the first two alone: “pre·pare.” Get ready. Act now. It’s the first half of the word that TB vaccine stakeholders should take to heart.

SMART4TB is a five-year investment of up to \$200 million in TB research funded by USAID and led by Johns Hopkins University and a consortium of partners (including TAG).

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

Agent	Type	Sponsor(s), Major Partners and Funders	Status ^a
Notable recently completed, ongoing, and planned clinical trials. POD = prevention of disease POI = prevention of infection POR = prevention of recurrence Rx Vax = therapeutic vaccination			
DAR-901	Inactivated whole-cell <i>M. obuense</i>	Dartmouth College, St. Louis University	Phase IIb
POI	Published 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 years in Tanzania (NCT02712424; DAR-PIA). Completion: February 2020. ^b		
H56:IC31	Protein/adjuvant subunit vaccine	SSI, IAVI, EDCTP, Valneva (IC31 adjuvant)	Phase IIb
POR	Results expected by 2023 from a phase IIb trial evaluating the efficacy, safety, and immunogenicity of H56:IC31 (vs. placebo) in preventing TB disease recurrence in 831 HIV-negative adults ages 18–60 years who have completed at least five months of drug-susceptible TB treatment in South Africa and Tanzania (NCT03512249). Primary completion: July 2023.		
Other	Published results from a phase I/II safety/immunogenicity study of H56:IC31 given with and without COX-2 inhibitors as a therapeutic adjunct in 51 adults ages 18–70 being treated for TB disease in Norway (NCT02503839). Completion: March 2020.		
ID93/GLA-SE (QTP101)	Protein/adjuvant subunit vaccine	Quratis, NIH (ACTG/HVTN), AAHI	Phase IIb
Work on QTP101 sponsored by Quratis			
POD	Planning for phase IIb/III dose exploration and efficacy, safety, and immunogenicity evaluation of QTP101 in up to 9,066 BCG-vaccinated, MTB-infected and -uninfected adults and adolescents ages 14–55. These plans include a phase IIb study in 288 participants (BCG-vaccinated, MTB-infected and -uninfected, HIV-negative) followed by a phase III study in 8,778 participants (BCG-vaccinated, MTB-infected, HIV-negative). Quratis received IND approval from South Korea's Ministry of Food and Drug Safety in July 2022. The trial will start in South Korea and may expand to other countries. Expected start: December 2023 (clinical trial registry forthcoming).		
POI	Published results from a phase II 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	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.		
Work on ID93/GLA-SE sponsored by the NIH and AAHI			
Rx Vax	Planning for 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. Protocol number: ACTG 5397/HVTN603 (clinical trial registry forthcoming).		
Other	Published results from a phase I safety/immunogenicity study comparing two vaccine formulations: a single vial of lyophilized ID93/GLA-SE vs. a two-vial formulation of lyophilized ID93 + liquid GLA-SE among 48 MTB-uninfected adult volunteers ages 18–55 in the United States (NCT03722472). Completion: June 2020.		

Agent	Type	Sponsor(s), Major Partners and Funders	Status ^a
<p>Notable recently completed, ongoing, and planned clinical trials. POD = prevention of disease POI = prevention of infection POR = prevention of recurrence Rx Vax = therapeutic vaccination</p>			
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: November 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 efficacy and safety of RUTI (vs. placebo) given as a therapeutic adjunct to 44 HIV-negative adults ≥18 years receiving treatment for drug-sensitive pulmonary TB in Argentina (NCT05455112; CONSTAN-ARG). Primary completion: December 2023. (RUTI will be given on the day TB treatment starts; efficacy will be evaluated as early bactericidal activity.)		
	Terminated a phase IIa safety/immunogenicity study of RUTI given as a therapeutic adjunct to 27 adults being treated for MDR-TB in Ukraine (NCT02711735). (Termination noted on June 30, 2022 for lack of recruitment; nine of an anticipated 27 participants had enrolled.)		
ChAdOx1 85A + MVA85A	Viral vector	Oxford University	Phase IIa
Completed 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/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.			
Completed a phase I safety, immunogenicity, and dose-escalation study of ChAdOx1 85A (aerosol versus intramuscular vaccination) in 39 adult volunteers (both BCG-vaccinated and BCG-naïve) ages 18–55 in Switzerland (NCT04121494). Completion: August 2020.			
AEC/BC02	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase II
Undergoing a phase II safety, immunogenicity, and dose-ranging study of freeze-dried AEC/BC02 (vs. placebo) in 200 MTB-infected, HIV-negative adult volunteers in China (NCT05284812). Primary completion: June 2024. (In addition to the placebo and intervention groups, the study contains a group that will receive the BC02 adjuvant alone and a control group of MTB-negative individuals.)			
Completed a phase Ib safety/immunogenicity study of freeze-dried, low-dose AEC/BC02 vaccine and adjuvant (vs. placebo) in 30 MTB-uninfected adult volunteers ages 18–45 in China (NCT04239313). Completion: June 2022.			
BNT164a1 BNT164b1	mRNA	BioNTech	Phase I
Undergoing a phase I safety, immunogenicity, and dose-defining study of two investigational vaccines BNT164a1 and BNT164b1 (vs. placebo) in 96 MTB-uninfected, BCG-naïve adult volunteers ages 18–55 in Germany (NCT05537038). Primary completion: August 2025.			
Undergoing a phase I safety, immunogenicity, and dose-defining study of two investigational vaccines BNT164a1 and BNT164b1 in 144 BCG-vaccinated, HIV-negative adult volunteers (MTB-infected and uninfected both eligible) ages 18–55 in South Africa (NCT05547464). Primary completion: October 2024.			

Agent	Type	Sponsor(s), Major Partners and Funders	Status ^α
Notable recently completed, ongoing, and planned clinical trials. POD = prevention of disease POI = prevention of infection POR = prevention of recurrence Rx Vax = therapeutic vaccination			
TB/FLU-05E (aerosol)	Viral vector	Smorodintsev Research Institute of Influenza, Ministry of Health of the Russian Federation	Phase I
Undergoing a phase I safety/immunogenicity study of TB/FLU-05E given intranasally (vs. placebo) in 51 BCG-vaccinated, HIV-negative, MTB-uninfected adult volunteers ages 18–50 in the Russian Federation (NCT05945498). Primary completion: June 2023.			
AdHu5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
Published results from a phase I safety/immunogenicity study of high- and low-dose AdHu5Ag85A (aerosol vs. intramuscular vaccination) in 36 BCG-vaccinated adult volunteers ages 18–55 in Canada (NCT02337270). Completion: September 2021.			
H107/CAF10b	Protein/adjuvant subunit vaccine	SSI	Phase I
Undergoing a phase Ia dose-finding study followed by a phase Ib safety/immunogenicity study of H107/CAF10b, H107/CAF10b + BCG, BCG, and placebo in 140 adult volunteers ages 18–45 in South Africa (NCT06050356). Primary completion: May 2026.			
<p>α Status indicates the most advanced phase of either ongoing or recently completed trials.</p> <p>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).</p> <p>Sources: Information compiled from ClinicalTrials.gov and other clinical trial registries as of 2023 September 25. 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.</p>			
AAHI: Access to Advanced Health Institute ACTG: Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections ART: antiretroviral treatment BCG: bacillus Calmette-Guérin ChAd: chimpanzee adenovirus vector COX-2: cyclooxygenase-2 EDCTP: European and Developing Countries Clinical Trials Partnership Gates MRI: Gates Medical Research Institute GHIT Fund: Global Health Innovative Technology Fund HVTN: HIV Vaccine Trials Network ICMR: Indian Council of Medical Research IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network		IND: investigational new drug application M. bovis: <i>Mycobacterium bovis</i> MDR-TB: multidrug-resistant tuberculosis MIP: <i>Mycobacterium indicus pranii</i> M. obuense: <i>Mycobacterium obuense</i> MTB: <i>Mycobacterium tuberculosis</i> MVA: modified vaccinia virus Ankara NIH: National Institutes of Health (USA) PLHIV: people living with HIV rBCG: recombinant bacillus Calmette-Guérin SII: Serum Institute of India SSI: Statens Serum Institute TB: tuberculosis TBVI: TuBerculosis Vaccine Initiative TPT: TB preventive treatment	

Endnotes

1. Open Philanthropy. Announcing the awardees for our \$150M regrating challenge [Internet]. 2023 January 12 (cited 2023 August 22). <https://www.openphilanthropy.org/research/announcing-the-awardees-for-our-150m-regrating-challenge/>.
2. Bill & Melinda Gates Foundation (Press Release). Wellcome and the Gates Foundation to fund late-stage development of a tuberculosis vaccine candidate that could be the first in 100 years if proven effective. 2023 June 28 (cited 2023 September 12). <https://www.gatesfoundation.org/ideas/media-center/press-releases/2023/06/funding-commitment-m72-tb-vaccine-candidate>.
3. IAVI (Press Release). Germany issues award to IAVI to support development of the MTBVAC tuberculosis vaccine candidate. 2023 July 6 (cited 2023 September 12). <https://www.iavi.org/news-resources/press-releases/2023/germany-issues-award-to-iavi-to-support-development-of-the-mtbvac-tuberculosis-vaccine-candidate>.
4. Treatment Action Group. Far off track: funding for TB research, 2018–2022. New York: Treatment Action Group; 2023. <https://www.treatmentactiongroup.org/publication/far-off-track-funding-for-tb-research-2018-2022/>
5. President of the General Assembly. Political declaration on the High-Level Meeting on the Fight Against Tuberculosis: PGA text as of 1 September 2023 [Internet]. 2023 September 1(cited 2023 September 28). <https://www.un.org/pga/77/2023/09/01/letter-from-the-president-of-the-general-assembly-health-related-processes-political-drafts/>
6. United Nations General Assembly. Political declaration of the High-Level Meeting of the General Assembly on the Fight Against Tuberculosis [A/RES/73/3]. New York: United Nations; 2018. <https://digitallibrary.un.org/record/1645268?ln=en>.
7. Stop TB Partnership. UN HLM key asks from TB stakeholders. 2023 April 27 (cited 2023 August 31). <https://www.stoptb.org/news/launched-key-asks-tb-stakeholders-un-high-level-meeting-tb>.
8. Ingrid Murillo Jelsbak (Biofabri, Pontevedra, Spain). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
9. POR TB Consortium. POR-TB: last participant last visit [Internet]. 2023 April 18 (cited 2023 August 31). <https://www.porconsortium.org/news/2023/por-tb-last-participant-last-visit>.
10. Alvaro Borges (Statens Serum Institut, Copenhagen, Denmark). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 August 31.
11. Nemes E, Fiore-Gartland A, Boggiano C, et al. The quest for vaccine-induced correlates of protection against tuberculosis. *Vaccine Insights*. 2022;1(3):165–181. doi: 10.18609/vac/2022.027.
12. Martinez L, Cords O, Liu Q, et al. Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis. *Lancet Glob Health*. 2022;10(9):e1307–16. doi: 10.1016/S2214-109X(22)00283-2.
13. Moorlag SJ, Arts RJ, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin Microbiol Infect*. 2019;25(12):1473–1478. doi: 10.1016/j.cmi.2019.04.020.
14. UNICEF Supply Division. Bacillus Calmette-Guérin vaccine supply and demand update – August 2019. New York: UNICEF; 2019. <https://www.unicef.org/supply/reports/bacillus-calmette-gu%C3%A9rin-bcg-supply-and-demand-update>.
15. World Health Organization. Preferred product characteristics for new TB vaccines. Geneva: World Health Organization; 2018. <https://apps.who.int/iris/rest/bitstreams/1140948/retrieve>.
16. Nieuwenhuizen N, Kulkarni P, Shaligram U, et al. The recombinant Bacille Calmette-Guérin vaccine VPM1002: ready for clinical efficacy testing. *Front Immunol*. 2017;8:1147. doi: 10.3389/fimmu.2017.01147.
17. Martin C, Marinova D, Aguiló N, Gonzalo-Asensio J. MTBVAC, a live TB vaccine poised to initiate efficacy trials 100 years after BCG. *Vaccine*. 2021;39(50):7277–7285. doi: 10.1016/j.vaccine.2021.06.049.
18. Sajjad Desai (Serum Institute of India). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
19. EDCTP. Better TB protection for newborns [Internet]. n.d. (cited 2023 August 29). <https://publications.edctp.org/international-partnerships-against-infectious-diseases/mtbvac-newborns>.
20. Garcia-Basteiro A, White R, Tait D, et al. End-point definition and trial design to advance tuberculosis vaccine development. *Eur Respir Rev*. 2022;31(164):220044. doi: 10.1183/16000617.0044-2022.
21. Ibid.
22. World Health Organization. Preferred product characteristics.

23. Sajjad Desai (Serum Institute of India). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
24. Ingrid Murillo Jelsbak (Biofabri, Pontevedra, Spain). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
25. Ibid.
26. Sajjad Desai (Serum Institute of India). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
27. Miner M, Hatherill M, Mave V, et al. Developing tuberculosis vaccines for people with HIV: consensus statements from an international expert panel. *Lancet HIV*. 2022;9(11):e791–e800. doi: 10.1016/S2352-3018(22)00255-7.
28. Ibid.
29. Alex Schmidt. Investigational TB vaccine M72/AS01E-4. Presentation at: Meeting of the Strategic Advisory Group of Experts on Immunization; 2023 March 20–22; Geneva, Switzerland. https://www.who.int/news-room/events/detail/2023/03/20/default-calendar/sage_meeting_march_2023.
30. Quratis (Press Release). Quratis teams with IDRI on TB vaccine. 2017 August 30 (cited 2023 August 29). <https://www.tbonline.info/posts/2017/9/6/quratis-teams-idri-tb-vaccine/>.
31. Yuhwa Choi (Quratis, Seoul, South Korea). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2022 September 13.
32. Tae Gyun Park (Quratis, Seoul, South Korea). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 7.
33. Chang Marianne. Quratis' novel TB vaccine confirms safety, immunogenicity in phase 2 study. *Korea Biomedical Review*. 2023 May 22 (cited 2023 August 29). <https://www.koreabiomed.com/news/articleView.html?idxno=21160>.
34. Choi YH, Kang YA, Park KJ, et al. Safety and immunogenicity of the ID93 + GLA-SE tuberculosis vaccine in BCG-vaccinated healthy adult: a randomized, double-blind, placebo-controlled phase 2 trial. *Infect Dis Ther*. 2023;12(6):1605–1624. doi: 10.1007/s40121-023-00806.
35. Seo Yoon-Seok. Quratis, the public offer price of 4,000 won has been confirmed..” The public offer price is below the below the band. *Biospector*. 2023 June 2 (cited 2023 August 29). <https://www.newsdirectory3.com/quratis-the-public-offer-price-of-4000-won-has-been-confirmed-the-public-offer-price-is-below-the-band/>.
36. N.A. Quratis to pursue IPO in June..” Aim to commercialize adult and adolescent tuberculosis vaccine by 2025...Plan to enter 44 countries. *The Stock*. 2023 May 26 (cited 2023 August 29). <https://www.newsdirectory3.com/quratis-to-pursue-ipo-in-june-aim-to-commercialize-adult-and-adolescent-tuberculosis-vaccine-by-2025-plan-to-enter-44-countries-by-the-stock/>.
37. Ibid.
38. Kim J. Quratis sells TB vaccine worth \$1.1 billion to Indonesia's state-run company. *BioWorld*. 2019 December 17 (cited 2023 August 29). <https://www.bioworld.com/articles/431846-quratis-sells-tb-vaccine-worth-11b-to-indonesias-state-run-company?v=preview>.
39. Quratis. History [Internet]. n.d. (cited 2023 August 29). <http://www.quratis.com/en/about/history.php>.
40. Ha Soo-Jung. Orion enters China's vaccine market with tuberculosis plant in Jining. *KED Global*. 2022 July 13 (cited 2023 August 29). <https://www.kedglobal.com/bio-pharma/newsView/ked202207130015>.
41. Crunchbase.com. Quratis [Internet]. n.d. (cited 2023 August 29). https://www.crunchbase.com/organization/quratis/company_financials.
42. Hill P, Cobelens F, Martinez L, et al. An aspiration to radically shorten phase 3 TB vaccine trials. *J Infect Dis*. 2023;jjad356. doi: 10.1093/infdis/jiad356.
43. Lee Han-Soo. These biopharma firms eye IPO in 2023 despite headwinds. *Korea Biomedical Review*. 2023 January 6 (cited 2023 August 29). <https://www.koreabiomed.com/news/articleView.html?idxno=20184>.
44. World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>.
45. Frick M. Tuberculosis vaccines pipeline report. New York: Treatment Action Group; 2022. <https://www.treatmentactiongroup.org/resources/pipeline-report/2022-pipeline-report/>.
46. Rangaka M, Frick M, Churchyard G, et al. Clinical trials of tuberculosis vaccines in the era of increased access to preventive antibiotic treatment. *Lancet Respir Med*. 2023;11(4):380–390. doi: 10.1016/S2213-2600(23)00084-X.

47. World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>.
48. Sinha P, Mehta S. Food: the tuberculosis vaccine we already have. *Lancet*. 2023;402(10402):588–590. doi: 10.1016/S0140-6736(23)01321-1.
49. Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomized, controlled trial. *Lancet*. 2023;402(10402):627–640. doi: 10.1016/S0140-6736(23)01231-X.
50. Frick M. Tuberculosis vaccines pipeline report. New York: Treatment Action Group; 2022. <https://www.treatmentactiongroup.org/resources/pipeline-report/2022-pipeline-report/>.
51. Alex Schmidt (Gates Medical Research Institute, Boston, MA). Personal communication with: Mike Frick (Treatment Action Group, New York, NY). 2023 September 14.
52. Tait D, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *N Engl J Med*. 2019;381(25):2429–2439. doi: 10.10156/NEJMoa1909953.
53. Alex Schmidt. Investigational TB vaccine M72/AS01E-4. Presentation at: Meeting of the Strategic Advisory Group of Experts on Immunization; 2023 March 20–22; Geneva, Switzerland. https://www.who.int/news-room/events/detail/2023/03/20/default-calendar/sage_meeting_march_2023.
54. Ibid.
55. World Health Organization. A global framework to prepare for country introduction of new TB vaccines for adolescents and adults [Draft for public consultation]. Geneva: World Health Organization; 2023. <https://www.who.int/publications/m/item/a-global-framework-to-prepare-for-country-introduction-of-new-tb-vaccines-for-adults-and-adolescents>.
56. Leach M, MacGregor H, Akello G, et al. Vaccine anxieties, vaccine preparedness: perspectives from Africa in a COVID-19 era. *Soc Sci Med*. 2022;298:114826. doi: 10.1016/j.socscimed.2022.114826.