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Tuberculosis Vaccines

TAG
Treatment Action Group

Tuberculosis Vaccines

Persistent impatience

By Mike Frick

Comparisons between research and development (R&D) timelines for COVID-19 and tuberculosis (TB) vaccines, while inevitable, are also more than a little unfair. The remarkable pace at which COVID-19 vaccines progressed from concept to clinical trials to commercial manufacture set a world historical record. Headlines in both the academic and lay press framed this achievement in Olympian terms, describing the development of the mRNA vaccines from Pfizer/BioNTech and the U.S. government/Moderna as "a lightning-fast quest" accomplished "in record time."[1,2]

By their nature, world records commemorate nonpareil performances. But they also become benchmarks for judging other similar efforts. In many minds, the exceptional achievement of COVID-19 vaccine R&D is now the expectation for next time. Some vaccine developers are even aiming to do one better: In preparation for the next global pandemic, the Coalition for Epidemic Preparedness Innovations has committed to a "100 days mission" to deliver a vaccine against Pathogen X in a little over three months from first sequencing the genome of a novel viral threat.[3] Where does this leave vaccine development against ongoing pandemics, ones with actual names, ones that existed long before COVID-19 and that will continue to claim millions of lives each year that the world waits for (new) vaccines against them?

TB is one such pandemic. One that claimed 1.5 million lives in the first year of COVID-19, and one that can only be ended with the development of new safe, effective, and affordable vaccines. But the scientists committed to developing new TB vaccines are running a different race than COVID-19 vaccine makers: The course is longer, the hurdles more frequent, the track less straight.[4] As long as this race is measured in COVID-19 time, TB vaccine research risks being discounted or, worse, deprioritized, in favor of easier R&D efforts that promise faster rewards.

That's the other thing about world records: some fall quickly while others last for decades. Records that remain untouched can frustrate as much as they inspire, obscure as much as they enlighten. Long-standing records cast long shadows, shadows that conceal world-class work that deserves to be judged in its own light. And there is a lot of good work happening on TB vaccines that merits the full and unobstructed view of governments and donors. Here is a partial summary, taken from **Tables 1** and **2** that follow:

- The field is mounting multiple phase III trials that will together enroll over **75,000 people**. Not since the large-scale randomized controlled trials of **BCG** in the middle of the 20th century have so many people participated in TB vaccine research at one time.
- These phase III trials will bring TB vaccine science to **over a dozen countries**, building research capacity, generating better knowledge of local TB epidemics, familiarizing TB-affected communities with the idea of preventing TB through vaccination, and sensitizing national regulators and policy makers to promising new prevention tools.
- Investigators will collect **hundreds of thousands of samples**—blood, serum, sputum, urine, etc.—from trial participants that can be analyzed to identify correlates of protection and other biomarkers that will guide next-generation vaccine development and fuel basic science research on TB.
- The ongoing and planned phase II and III trials will collectively enroll **diverse populations** of people at risk of TB, including **PLHIV**, children of all ages (infants, pre-adolescents, teenagers), household contacts of people with TB, people treated for TB disease, and people with **MTB** infection and those without. Still, some groups are missing: The absence of pregnant people is particularly stark. The exclusion of pregnant people from efficacy studies is one of three emergent issues that Treatment Action Group (TAG) urges TB vaccine developers to address; see the conclusion of this report for more on pregnancy inclusion and the two others.

Looking closely at the TB vaccine pipeline on its own terms and not in reference to vaccine research for COVID-19, Pathogen X, or any other disease is not about settling for less, but instead is about facing the real challenges ahead. TB vaccine development is not a 100-day dash; it is an endurance marathon that requires an altogether different kind of stamina from governments, the pharmaceutical industry, and other donors. The field needs patient but persistent investment in quality science—from basic research to clinical trials—and well-placed impatience about the things that can and should go faster. On this last point:

- It should not take 25 years for TB vaccine candidate MTBVAC to travel from discovery work to phase III trials, a story told in a paper by Carlos Martin and colleagues who first started developing MTBVAC at the University of Zaragoza in the 1990s.[5]
- It should not take nearly the same amount of time between when VPM1002 "was constructed in the late 1990s and tested in different animal models" to when its first phase III trial opened in 2017.[6]
- It should not take four years and counting to begin a phase III trial of TB vaccine candidate M72/AS01E following publication of positive results from the primary analysis of its phase IIb trial in 2018.[7]
- A century should not go by between introducing BCG, still the world's only vaccine against TB, in 1921 and developing the new vaccines required to end what many consider to be humanity's oldest epidemic.[8] It took Albert Calmette

BCG = bacille Calmette-Guérin. The only licensed vaccine against TB, BCG is a live attenuated strain of *Mycobacterium bovis*, a close relative of *Mycobacterium tuberculosis* that causes TB in cows.

Countries participating in ongoing phase III trials include Bangladesh, Gabon, Gambia, India, Kenya, Madagascar, Philippines, Russian Federation, Senegal, South Africa, Tanzania, Uganda, and Zambia. More will be named as additional phase III trials open.

PLHIV = people living with HIV.

MTB = *Mycobacterium tuberculosis*. Where text refers to "MTB infection" or "MTB-infected" this refers to infection with MTB as inferred by a positive test for infection (usually a blood-based interferon-gamma release assay [IGRA]).

and Camille Guérin 13 years to create BCG from *Mycobacterium bovis* through a new technique called serial passaging in the early 20th century—and they would have moved more quickly had World War I not halted their progress.[9] Surely TB vaccine science can move faster in the 21st, even if the speed of COVID-19 R&D is the wrong metric to apply.

The Stop TB Partnership's *Global Plan to End TB* voices both persistence and impatience in setting a goal for having a new TB vaccine available by 2025. This is possible, the partnership specifies, if the global community invests $10 billion in TB vaccine R&D from 2023 to 2030, or $1.4 billion a year.[10] This is about 12 times what the world currently spends on TB vaccine R&D each year but is minuscule in comparison to the vast sums of money spent on COVID-19 vaccine research.[11,12]

With persistence and impatience, TAG's 2022 *Tuberculosis Vaccines Pipeline* Report overviews recent progress in TB vaccine development. Two tables summarize notable ongoing, planned, and recently completed trials of 16 vaccine candidates in active clinical development. **Table 1** reviews vaccines in phase III trials, and **Table 2** looks at candidates in phase I and II. Notable updates for some, but not all, candidates in phase III are summarized in the narrative vignettes below. The first candidate discussed, VPM1002, provides a natural starting place as it affords the opportunity to talk about all three of the target use indications guiding late-stage TB vaccine development: **POD**, **POI**, and **POR**.

POD = prevention of disease.

POI = prevention of infection.

POR = prevention of [disease] recurrence (usually either relapse or reinfection).

VPM1002

Developed at the Max Planck Institute for Infection Biology (MPIIB) in Germany, VPM1002 is one of the most advanced candidates in the pipeline with three active phase III trials. In 2004, MPIIB licensed VPM1002 to Vakzine Projekt Management (VPM), which then provided an exclusive sublicense to the Serum Institute of India (SII) in 2012.[13] VPM1002 is a live vaccine based on recombinant BCG (i.e., BCG with purposeful genetic modifications to provide better safety and efficacy). Today, VPM and SII are studying VPM1002 in three phase III efficacy trials, one for each of the primary indications for new TB vaccines: POD, POI, and POR.

VPM1002 **phase III POD trial** with MIP in household contacts CTRI/2019/01/017026

MIP = *Mycobacterium indicus pranii*, a whole-cell TB vaccine candidate also known as Immuvac and originally developed for leprosy.

The **POD phase III trial**, funded by the Indian Council of Medical Research (ICMR), is evaluating the efficacy and safety of VPM1002 and a second vaccine, **MIP**, in preventing TB disease (pulmonary or extrapulmonary) among 12,721 people exposed to TB at home ("**household contacts**"). Enrollment into this study is complete and participant follow-up ongoing. Eligible household contacts include HIV-negative adults, adolescents, and children 6 years and older. These age and HIV status restrictions were likely instituted to justify the trial not providing TB preventive treatment (TPT) to participants. The WHO strongly recommends that PLHIV and child household contacts under age 5 *should receive* TPT and that older, HIV-negative household contacts "*may* be given TB preventive treatment" after clinical evaluation for TB disease "or according to national guidelines"

Household contacts is sometimes abbreviated as HHCs. This term generally refers to people who are exposed to TB because they are close contacts of people with diagnosed pulmonary TB disease, often at home. The definition of household contact may differ by study.

Table 1. TB Vaccines in Phase III Clinical Development

Agent	Type	Sponsor(s) and Major Partners	Status[a]
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. Entries highlighted in pink are appearing in the table for the first time or are substantially changed from previous reports. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence | Rx Vax = therapeutic vaccination*			
MIP	Whole-cell *M. indicus pranii*	ICMR, Cadila Pharmaceuticals	Phase III
POD	Completed enrollment in 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 (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026). (Secondary objectives include efficacy evaluation for POI.) Primary completion: 2022.[β]		
VPM1002	Live rBCG	SII, Vakzine Projekt Management, ICMR, EDCTP, NIH (IMPAACT/HVTN)	Phase III
POD	Completed enrollment in 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 (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026). (Secondary objectives include efficacy evaluation for POI.) Primary completion: 2022.		
POI	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection among 6,940 newborns (HIV-exposed and uninfected eligible) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685). Primary completion: November 2022.		
POR	Undergoing 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 TB in India and Bangladesh (NCT03152903). Primary completion: February 2022.		
Other	Planning for a phase I/II safety/immunogenicity study of VPM1002 or BCG revaccination (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents ages 8–14 with and without MTB infection in South Africa (IMPAACTP2035/HVTN604; LEAP).		
MTBVAC	Live, genetically attenuated MTB	Biofabri, IAVI, TBVI, University of Zaragoza, EDCTP	Phase III
POD	Undergoing a phase III trial to evaluate the efficacy, safety, and immunogenicity of MTBVAC (vs. BCG) in 6,960 HIV-unexposed and HIV-exposed, uninfected infants in South Africa, Senegal, and Madagascar (NCT04975178; MTBVACN3). Primary completion: June 2027.		
	Plans for advanced clinical efficacy studies of MTBVAC in adults and adolescents are under development (source: IAVI and Biofabri).		
Other	Completed a phase IIa dose-defining safety/immunogenicity study of MTBVAC (vs. BCG) in 99 South African infants (NCT03536117). (Informed dose selected for phase POD III trial listed above.) Completion: March 2022.[γ]		
	Planning for a phase Ib safety/immunogenicity study of MTBVAC in PLHIV (including a subgroup of people with advanced HIV disease) is underway. Study initiation is targeted for 2023 (registry number and other details forthcoming. Source: IAVI and Biofabri).		
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 efficacy, safety, and immunogenicity study of GamTBvac (vs. placebo) in preventing primary TB disease among 7,180 HIV-negative, BCG-vaccinated, MTB-uninfected adults aged 18–45 years in the Russian Federation (NCT04975737). Primary completion: November 2025.		

Agent	Type	Sponsor(s) and Major Partners	Status[a]
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. Entries highlighted in pink are appearing in the table for the first time or are substantially changed from previous reports.			
POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence | Rx Vax = therapeutic vaccination			
BCG (re) vaccination	Whole-cell *M. bovis*	Gates MRI, ICMR, Henry M. Jackson Foundation, NIH (IMPAACT/HVTN)	Phase III
POD	Undergoing a phase III efficacy, safety, immunogenicity study of BCG revaccination (vs. TB preventive treatment) among 9,200 BCG-vaccinated, HIV-negative child and adolescent household contacts ages 6 to 18 years in India (NCT05330884; BRiC). Primary completion: June 2025.		
POI	Undergoing a phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in 1,820 BCG-vaccinated, MTB-uninfected adolescents aged 10–18 years in South Africa (NCT04152161). Primary completion: April 2023. Undergoing a phase III trial to evaluate the efficacy and safety of pre-travel vaccination with BCG (vs. placebo) among 2,000 BCG-naïve, MTB-uninfected adults aged 18–65 years, either healthcare workers or long-term travelers to high-TB-burden countries from the United States (NCT04453293). Primary completion: May 2024.		
Other	Planning for a phase I/II safety/immunogenicity study of BCG revaccination or VPM1002 (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents aged 8–14 years with and without MTB infection in South Africa (IMPAACTP2035/HVTN604).		
M72/AS01E	Protein/adjuvant subunit vaccine	Gates MRI, GSK Biologicals (AS01E adjuvant), Wellcome Trust (MESA-TB)	Phase III
POD	Preparing to begin a phase III efficacy, safety, and immunogenicity study of M72/AS01E (vs. placebo) in up to 26,000 people ages 15–44 years. The primary objective will evaluate vaccine efficacy against POD in participants with MTB infection. (Secondary objectives will evaluate POI among participants who enter the study without MTB infection and POD in PLHIV, pending results of MESA-TB study described below.) Expected start: 2023. In preparation for the phase III study, the Gates MRI has begun an epidemiologic study to assess IGRA positivity and TB incidence near potential trial sites with plans to enroll 8,000 adolescents and adults aged 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: January 2024.		
Other	Completed enrollment in a phase II safety/immunogenicity study of M72/AS01E (vs. placebo) in 402 PLHIV ages 16–35 years who are on ART, are virally suppressed, and have previously taken TPT in South Africa (NCT04556981; MESA-TB). (The trial is intended to support inclusion of PLHIV in the phase III POD study listed above.) Primary completion: August 2022.		

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

β. For ongoing/planned studies, "expected completion" date is the "estimated primary completion date" in ClinicalTrials.gov, or the date of final data collection for the primary outcome measure. This is not the date by which results will be available.

γ. 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. 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: AIDS Clinical Trials Group
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
ICMR: Indian Council of Medical Research
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network
M. bovis: Mycobacterium bovis
MIP: *Mycobacterium indicus pranii*
MTB: *Mycobacterium tuberculosis*
NIH: National Institutes of Health (USA)
PLHIV: people living with HIV
rBCG: recombinant bacillus Calmette-Guérin
SII: Serum Institute of India
TB: tuberculosis
TBVI: TuBerculosis Vaccine Initiative
TPT: TB preventive treatment

[italics added].[14] The Indian government's 2021 *Guidelines for Programmatic Management of Tuberculosis Preventive Treatment* state that "all HHCs of pulmonary TB patients, regardless of their age, should be given TPT after ruling out TB."[15] This recommendation was not in place when the study opened in 2018 and points to an important ethical question: How should vaccine trials respond to changing standards of care? Today, a TB vaccine trial among household contacts would have an ethical obligation to offer TPT irrespective of the age or HIV status of participants—especially if that were the recommendation of national guidelines—or to justify the non-provision of TPT on carefully reasoned scientific and ethical grounds.

In its **phase III POI trial**, SII is studying VPM1002 among nearly 7,000 newborns in five African countries. This two-arm study is assessing the efficacy, safety, and immunogenicity of a single dose of VPM1002 compared with BCG. Infant participants must be HIV-negative, but the study is enrolling some HIV-exposed, uninfected infants born to mothers living with HIV. The POI endpoint is defined as **IGRA conversion** from negative to positive at 12 to 36 months after vaccination. Secondary endpoints will measure TB disease and sustained IGRA conversion (read the section on BCG below for more on the meaning of "sustained conversion"). The study is currently enrolling participants.

VPM1002 **phase III POI trial** in infants NCT04351685

IGRA conversion refers to a person initially testing IGRA negative (indicating no MTB infection) subsequently testing IGRA positive, indicating infection with MTB.

The third **phase III trial** of VPM1002 is a **POR study** looking at whether vaccination with a single dose of VPM1002 can prevent disease recurrence (defined as either reinfection or relapse) in adults who have recently completed TB treatment. The study, which is currently enrolling, will randomize 2,000 participants in India and Bangladesh to receive either VPM1002 or placebo and then will follow participants for recurrent disease (pulmonary and/or extrapulmonary) 12 months post vaccination. Notably, all three of these VPM1002 trials indicate 2022 as the "primary completion date," which is the date of final data collection for the primary outcome measure. This means that results from one or more of these studies could be available by **2023** (more likely **2024**),[16] giving the field its first look at efficacy endpoint data since the publication of final results from the phase IIb trial of M72/AS01E in 2019.[17]

VPM1002 **phase III POR** trial NCT03152903

A September 12, 2022 article in India's Deccan Herald paper quoted an unnamed "senior government official" saying that results from the phase III POD trial of VPM10022 and MIP could be available "within a year" (i.e., **2023**).

SII told TAG that results from the POI and POR phase III trials of VPM1002 are expected to be available in **2024**.

MTBVAC

MTBVAC is embarking on one **phase III trial in infants** and is preparing for a second late-stage efficacy study among adolescents and adults. Both trials are POD studies. The infant trial will randomize nearly 7,000 newborns (HIV-unexposed and HIV-exposed, uninfected) in Madagascar, Senegal, and South Africa to receive either one dose of MTBVAC or BCG and follow them for a minimum of 24 months to see how many develop TB disease. The adolescent and adult study, which is still being planned, is a collaboration between Biofabri and IAVI.

Phase III trial of MTBVAC in infants NCT04975178

This work on MTBVAC can only proceed if funders step up to support both trials. The European and Developing Countries Clinical Trials Partnership is funding the infant trial, but financial commitments from additional donors would ensure that both studies proceed on a timeframe that might satisfy the United Nations goal of ending the TB epidemic by 2030. Funding for late-stage studies of MTBVAC is one area where well-placed impatience at the pace of things is warranted.

MTBVAC is the only vaccine in the pipeline based on the MTB organism itself. Weakened and made safe for human use by two gene deletions, MTBVAC is a live vaccine that otherwise contains all the antigens present in MTB. This feature comes with upsides and downsides. On the upside, it suggests that MTBVAC might engender a qualitatively and quantitatively fuller immune response compared with vaccines that present only a handful of antigens or even recombinant BCG vaccines (BCG lost ~100 genes compared with MTB).[18] On the downside, it means that vaccination with MTBVAC will make current tests for TB infection turn positive.[19] (It is also worth examining whether MTBVAC will throw off antigen tests such as the **urine TB LAM** test used to diagnose TB in people with advanced HIV disease). IGRA positivity following vaccination with MTBVAC is not necessarily a problem, but its implications do require consideration. If investigators wish to evaluate whether MTBVAC can prevent TB infection in a POI study—or perhaps as a secondary POI endpoint nested within larger POD trials—they will have to develop novel assays for measuring MTB infection that are unaffected by MTBVAC.[20] Researchers should also examine whether the effect of MTBVAC on IGRA positivity is permanent or transient.

One additional consideration: The live nature of the vaccine raises a potential safety concern about giving MTBVAC to PLHIV. IAVI is in discussions with partners about conducting a phase **Ib safety/immunogenicity study** of MTBVAC in people with HIV to determine whether this key population can be included in the late-stage adolescent and adult trial. These plans are consistent with the consensus report of a workshop on developing TB vaccines for PLHIV—convened by the National Institutes of Health-funded HIV/AIDS clinical trials networks—that "encourage[s] the evaluation of immunogenicity and safety of novel live attenuated vaccines early in development."[21]

Urine TB LAM is an inexpensive, urine-based point-of-care test for TB in people with advanced HIV disease (AIDS).

LAM (lipoarabinomannan) is an antigen and component of the MTB outer cell wall that is shed into urine when MTB enters the kidneys. Read TAG's *An Activist's Guide to the LAM Test* for more information.

The *WHO recommends* the Determine TB LAM Ag test made by Abbott; next-generation LAM tests are under development.

The **phase Ib safety/immunogenicity study** of MTBVAC in PLHIV is aiming for a 2023 start date; other details are forthcoming.

BCG (re)vaccination

Now more than a century old, BCG continues to inspire a range of research endeavors. In August 2022, *Lancet Global Health* published a meta-analysis of BCG effectiveness analyzing patient data from 68,552 TB contacts in 26 cohort studies in 17 countries (all published within the last 20 years). This study-of-studies found an overall effectiveness of BCG against all forms of TB of 18%. BCG offered significant protection against TB in children younger than age 5 (37%) and a striking >80% protection against death, an effect that lasted through age 14.[22] These findings provide further confirmation that BCG provides life-

saving protection to children but does not shield older adolescents or adults from TB. The title of an accompanying editorial summed it up nicely—"Infant BCG vaccination is beneficial, but not sufficient"—and concluded that "A new tuberculosis vaccine strategy . . . is urgently needed."[23]

Oddly enough, BCG remains a contender for that new, better strategy. The pipeline contains three studies evaluating revaccination with BCG (i.e., a second BCG dose after infancy). The farthest along is a **phase IIb trial** sponsored by the Bill & Melinda Gates Medical Research Institute (Gates MRI). This is a POI study looking at whether BCG revaccination prevents MTB infection (defined as **sustained IGRA conversion**); the study is fully enrolled. Essentially, it aims to interrogate the result of an **earlier phase II study** that found BCG revaccination had an estimated vaccine efficacy of 45.4% (95% CI: 6.4–68.1) against sustained IGRA conversion.[24] However, this was a secondary endpoint (meaning the study was not powered to look at it). The current trial seeks to reproduce this finding in a bigger population (1,820 vs. 989 adolescents), representing a slightly wider age range (10–18 vs. 12–17 years) of adolescents drawn from more places (sites across South Africa vs. Worcester in the Western Cape Province) and followed for a longer period (four years vs. two years). The study is also using an updated test for infection (QFT Gold Plus vs. QFT Gold) and is treating sustained IGRA conversation as the primary (not a secondary) endpoint.

Gates MRI **phase IIb trial** of BCG revaccination NCT04152161

Sustained IGRA conversion in this study means an initial conversion from negative to positive (signaling MTB infection) and subsequent positive results upon testing three and six months after the initial conversion.

Earlier phase II study of BCG revaccination NCT02075203

A positive result from this study could spark a policy change recommending a second dose of BCG in adolescence to protect high-risk people from MTB infection. Or it could motivate a phase III POD trial among IGRA-negative people to see if BCG revaccination protects against TB disease.[25] The investigators of the original phase IIa trial had recommended such a study in the *New England Journal of Medicine*: "On the basis of our results ... a trial of BCG revaccination for the prevention of disease in adolescents who do not have *M. tuberculosis* infection is justified in settings with a high incidence of tuberculosis."[26]

The second BCG revaccination trial is a newly announced study by ICMR. This **phase III POD study** will be the first randomized controlled trial to directly compare a TB vaccine to TPT. Over 9,000 BCG-vaccinated, HIV-negative child and adolescent household contacts (ages 6–18 years) will receive either a second BCG vaccination or TPT. Several facets of the trial are designed to respond to the epidemiology of India's TB epidemic. The study will enroll both MTB-infected and uninfected participants with infection documented using the **C-Tb skin test**. Adolescents and children who are contacts of people with either drug-sensitive or drug-resistant TB will be eligible to participate. For those randomized to the TPT arm, contacts of drug-sensitive TB patients will receive either **6H** or **3HP**, while contacts of people with drug-resistant TB will receive 6 months of levofloxacin. Investigators will follow participants for 24 months to record the incidence of TB disease (pulmonary and extrapulmonary). A secondary endpoint will evaluate POI among MTB-uninfected participants who enter the study with a negative C-Tb skin test.

ICMR **phase III POD study** of BCG revaccination NCT05330884

Unlike older tuberculin skin tests, the **C-Tb skin test** does not cross-react with prior BCG vaccination.

6H = six months of daily isoniazid (H) preventive therapy.

3HP = 12 once-weekly doses of rifapentine (P) and isoniazid (H) as preventive treatment.

ICMR is carving out a niche for itself as the leader of TB vaccine trials among household contacts. In addition to this trial of BCG revaccination and TPT, ICMR is also funding a phase III trial of VPM1002 and MIP among people exposed to TB at home. The direct comparison of BCG revaccination to TPT in this population is intriguing and raises several important questions. One is 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). As noted above, India's national guidelines recommend TPT for all household contacts regardless of age or HIV status.[27] Given this recommendation, how can the trial ethically enroll TB-exposed children and adolescents to receive BCG but not TPT?

Equipoise is genuine uncertainty about whether one intervention is better than another and provides an ethical justification for the random assignment of participants to the intervention or control group.

ICMR investigators thought about this question carefully and concluded that it would not be feasible to test the efficacy of BCG revaccination if BCG were given together with TPT, necessitating a direct comparison of the two interventions alone. In justifying this decision, ICMR scientists and ethics committees pointed to the low rates of TPT uptake among child household contacts; the limitations of TPT in this age group (e.g., adherence challenges in adolescence, drug toxicity concerns); and the robust monitoring provided by the trial to ensure participant safety and to refer children who develop TB while in the study to treatment.[28] It is possible that other sponsors may reach a different conclusion about the ethical responsibility to provide TPT in TB vaccine studies conducted among similar groups.

Finally, the third study of BCG revaccination is the LEAP trial sponsored by **IMPAACT** and **HVTN**. This **phase I/II study** is in final stages of protocol development and is expected to open shortly. It will assess the safety and immunogenicity of BCG revaccination or VPM1002 to placebo in 480 pre-adolescents ages 8–14.[29] The study will include participants who are HIV-negative and HIV-positive as well as pre-adolescents with and without MTB infection. Although IMPAACT and HVTN are global clinical trials networks, this study will be limited to sites in South Africa in order to standardize the birth dose of BCG received by participants.

IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trials Network, funded by the U.S. NIH.

HVTN = HIV Vaccine Trials Network, funded by the U.S. NIH.

Phase I/II study of BCG revaccination and VPM1002 in pre-adolescents is IMPAACT2035/HVTN604

M72/AS01E

The Gates MRI is proceeding with preparations for a phase III trial of M72/AS01E. This subunit TB vaccine conferred 49.7% (90% CI: 12.1–71.2) protection against developing bacteriologically confirmed pulmonary TB disease among HIV-negative, MTB-infected adults in a **phase IIb study**, final results of which were published in 2019.[30] As of September 16, 2022, the phase III trial is not registered on ClinicalTrials.gov or similar platforms. The proposed trial intends to enroll an anticipated 26,000 adolescents and adults ages 15–44 and will randomize them 1:1 to receive either two doses of M72/AS01E or placebo.[31] The majority of participants will be IGRA-positive with a smaller subset IGRA-

Phase IIb study of M72/AS01E NCT01755598

negative. Pending favorable safety results of the **MESA-TB trial**, the Gates MRI plans to enroll a cohort of ~2,000 PLHIV to evaluate vaccine safety and immunogenicity in this important population. (The MESA-TB trial is fully enrolled with results expected in early 2023.) The primary analysis will estimate vaccine efficacy for POD (laboratory-confirmed pulmonary TB) among HIV-negative participants who enter the trial IGRA-positive. Secondary endpoints will evaluate vaccine efficacy in preventing infection among the IGRA-negative, HIV-negative subgroup and in preventing disease among PLHIV.[32]

MESA-TB trial of M72/AS01E in PLHIV NCT04556981

The Gates MRI expects to begin the phase III trial in 2023. Like other TB vaccine efficacy trials, the primary analysis is event-driven, meaning that participants will be followed until the number of TB cases needed for the efficacy analysis have accrued. Clinical trial timelines are difficult to predict, but the Gates MRI hopes to enroll all 26,000 participants in 2.5 years and expects to the first efficacy analysis to occur approximately two years after completion of enrollment. That calendar means results could be available as early as 2028.

Preparations for this trial are well underway. A site-level **epidemiology study** to assess IGRA positivity and TB incidence in communities near potential trial sites is ongoing and had enrolled 4,000 participants at 30 sites in eight countries by September 2022. Ultimately, the study will open at up to 50 sites in up to 14 countries.[33] Though billed as laying the groundwork for the phase III trial, this study is itself a massive undertaking and will enroll 8,000 people. The information on local rates of IGRA positivity near trial sites will constitute an invaluable resource—not only for the Gates MRI, but also for other vaccine developers planning phase III trials.

Gates MRI **epidemiology study** NCT05190146

Three Issues to Fix in TB Vaccine Trials

This year's *Pipeline Report* on TB vaccines ends with three cross-cutting issues in TB vaccine R&D that, in TAG's view, require attention from donors, sponsors, and the broader research community.

1. **The larder is nearly empty.** The justifiable excitement about late-stage TB vaccine research risks obscuring the lack of activity in phase I. In fact, phase I of the pipeline contains only three constructs, two of which TAG has listed in this position for **over five years**. The newcomer is the field's first TB vaccine candidate based on mRNA. In September 2022, **BioNTech** registered a phase I study of two investigational mRNA vaccines grouped under the common name BNT164: BNT164a1 and BNT164b1. This phase I safety/immunogenicity study will evaluate three different dose levels of the two vaccines in 96 MTB-uninfected, BCG-naïve adult volunteers ages 18–55. Developers have hinted that other candidates based on novel platforms—e.g., a CMV-vectored TB vaccine (VirBio) and additional vaccines built using mRNA from IAVI/Moderna and the **WHO mRNA vaccine technology transfer hub**—are on their way.[34,35,36]

The two constructs TAG has listed in phase I for **over five years** are AdHu5Ag85A and several candidates based on an influenza platform called TB/FLU. See Table 2 for details.

BioNTech phase I study of BNT164 NCT05537038

In September 2022, Bloomberg reported that the **WHO mRNA hub** in South Africa had started work on an mRNA TB vaccine. Asked about this project on a briefing call with civil society that TAG attended, spokespeople for the hub offered few details.

But for now, phase I sits nearly empty. This raises a real concern that the field will have few "plan B" options ready to work with if the vaccines currently in phase II and III trials do not demonstrate efficacy—or even if they do.[37] The world will likely need multiple new vaccines to end TB for all at-risk populations. The first vaccine to show efficacy in phase III should not be taken as the stopping point for further research. Replenishing the pipeline through a robust program of preclinical and early clinical work is essential to successful TB vaccine development and deserves increased resources and attention.

2. **Left out, again.** The issue is this: Pregnant women get TB, they just never get better ways to treat and prevent it (to borrow a line from the **Gran Fury** AIDS activist art collective). The systematic exclusion of pregnant people from biomedical research is a well-documented phenomenon, one that has resisted reform despite a sea change in thinking about pregnancy research ethics.[38] Traditionally seen as uniquely vulnerable to research-related harms, pregnant people have been "protected" from the risks of research but, as a consequence of this protection, have been left unprotected from real health risks. What is the greater source of "vulnerability" for a pregnant person: participating in a well-designed research study, or contracting TB? If the question feels unanswerable, that may be because it is not asked of the person who can answer it: the pregnant woman herself.

Gran Fury expressed a similar sentiment in a famous poster: "Women don't get AIDS / They just die from it."

In the context of TB vaccine research, the total absence of pregnant study participants from the trials listed in Tables 1 and 2 is troubling given the facts of TB and pregnancy. There are an estimated 215,000 cases of TB in pregnant people each year; pregnant and postpartum women face a higher risk of TB than the general population; a woman's greatest risk of developing TB coincides with her reproductive years; TB during pregnancy threatens the health and life of both mother and fetus.[39,40] A vaccine that could safely and effectively prevent TB disease during pregnancy would offer a major improvement over existing TB preventive treatment regimens, which come with concerns about drug toxicities and are themselves understudied in pregnancy.[41]

Developers who wish to include pregnant people in trials have several options. The easiest to implement would be a combined cross-study effort to collect standardized information on maternal, infant, and pregnancy outcomes among people who become pregnant after enrolling in vaccine studies. Developers can expect to see hundreds if not thousands of pregnancies among the tens of thousands of participants expected to enroll in phase III studies over the coming years. Systematically collecting data on people who become pregnant during studies might induce more progressive regulators and policy makers to approve the use of new TB vaccines in pregnant people based on benefit/risk calculations—as was done for COVID-19 vaccines.[42]

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. Entries highlighted in pink are appearing in the table for the first time or are substantially changed from previous reports. *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, GHIT Fund	Phase IIb
POI	Published results from a phase IIb safety and efficacy trial of DAR-901 (vs. placebo) in preventing MTB infection in about 650 BCG-vaccinated, HIV-negative, MTB-uninfected adolescents ages 13–15 years in Tanzania (NCT02712424). Completion: February 2020.[γ]		
H56:IC31	Protein/adjuvant subunit vaccine	SSI, IAVI, EDCTP, Valneva (IC31 adjuvant)	Phase IIb
POR	Undergoing a phase IIb trial of the efficacy, safety, and immunogenicity of H56:IC31 (vs. placebo) in preventing TB disease recurrence in 900 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.[β]		
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 51adults 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)	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. The trial will be conducted in five countries: Indonesia, Philippines, South Korea, Thailand, and Vietnam. Registry number, expected start date, and other details are forthcoming.[δ]		
POI	Completed 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 healthcare workers ages 19–64 in South Korea (NCT03806686). Completion: April 2021; results via press release.		
Other	Completed 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; results via press release.		
Work on ID93/GLA-SE sponsored by the NIH			
Rx Vax	Planning for a phase IIa/IIb safety/immunogenicity study of ID93/GLA-SE given as a therapeutic adjunct in 1,500 HIV-positive and HIV-negative adults being treated for DS-TB at different time points relative to the start of TB treatment. Protocol number: A5397/HVTN603.[ε]		
Other	Completed a phase I safety/immunogenicity study comparing two vaccine formulations: a single vial of freeze-dried ID93/GLA-SE vs. a two-vial formulation of lyophilized ID93 + liquid GLA-SE among 48 MTB-uninfected adult volunteers in the United States (NCT03722472). Completion: June 2020.		
RUTI	Fragmented MTB	Archivel Farma	Phase IIb
Rx Vax	Undergoing a phase IIb efficacy, safety, and immunogenicity trial of RUTI (vs. placebo) given as a therapeutic adjunct to 140 HIV-negative adults ≥18 years undergoing treatment for drug-susceptible and multidrug-resistant TB in India (NCT04919239). Primary completion: November 2025.		
	Undergoing a phase II safety and immunogenicity trial of RUTI (vs. placebo) given as a therapeutic adjunct to 44 people receiving treatment for drug-sensitive TB in Argentina (NCT05455112; CONSTAN-ARG). Primary completion: February 2023.		
	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.)		
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 immunogenicity of a ChAdOx1 85A prime vaccine followed by MVA85A boost vaccine (vs. BCG revaccination) in 60 adolescents ≥12 years in Uganda (NCT03681860). 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.			

Agent	Type	Sponsor(s) and Major Partners	Status[α]
Notable recently completed, ongoing, and planned clinical trials. Entries highlighted in pink are appearing in the table for the first time or are substantially changed from previous reports. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence | Rx Vax = therapeutic vaccination*			
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 adult volunteers ≥18 years with MTB infection (skin test positive) in China (NCT05284812). (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.) Expected completion: October 2022.			
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.			
BNT164	mRNA	BioNTech	Phase I
Undergoing a phase I dose-defining safety/immunogenicity study of two investigational vaccines under the name BNT164 (BNT164a1 and BNT164b1) vs. placebo in 96 MTB-uninfected, BCG-naïve adult volunteers ages 18–55 (NCT05537038). Expected completion: June 2025.			
TB/FLU-05E (aerosol)	Viral vector	Smorodintsev Research Institute of Influenza, Ministry of Health of the Russian Federation	Phase I
Planning for a phase I safety/immunogenicity study of TB/FLU-05E given intranasally (vs. placebo) in BCG-vaccinated adults ages 18–50 (registry number and other details forthcoming).[ζ]			
TB/FLU-01L & **TB/FLU-04L**	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan; Smorodintsev Research Institute of Influenza, Russian Federation	Phase I
Planning a phase I safety/immunogenicity study of TB/FLU-01L.[ζ]			
Phase IIa study of TB/FLU-04L in MTB-infected adult men not completed (recruitment challenges). Further phase II work pending additional preclinical reproductive toxicology studies.			
Previously completed a phase I safety/immunogenicity study of TB/FLU-04L (vs. placebo) in 44 BCG-vaccinated adults ages 18–50 (NCT02501421) and a phase I safety/immunogenicity study of TB/FLU-01L intranasal vs. sublingual administration among 36 BCG-vaccinated adults ages 18–50 in Kazakhstan (NCT03017378).			
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.			
α. Status indicates the most advanced phase of either ongoing or recently completed trials. β. For ongoing/planned studies, "expected completion" date is the "estimated primary completion date" in ClinicalTrials.gov, or the date of final data collection for the primary outcome measure. This is not the date by which results will be available. γ. For completed studies, "completion" is the "actual study completion date" in ClinicalTrials.gov (or date provided by study sponsor). δ. Yuhwa Choi (Quratis, Seoul, South Korea). Personal correspondence with: Mike Frick (Treatment Action Group, New York, USA). 2022 September 13. ε. Information on the A5397/HVTN603 trial of ID93/GLA-SE provided to TAG by the protocol team. ζ. Marina Stukova (Smorodintsev Research Institute of Influenza, St. Petersburg, Russian Federation). Submission to: Working Group on New TB Vaccines (Stop TB Partnership, Geneva, Switzerland). 2022 July 1. (Submission on file with TAG.) Sources: Information compiled from ClinicalTrials.gov and other clinical trial registries. 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.			
ChAd: chimpanzee adenovirus vector COX-2: cyclooxygenase-2 GHIT Fund: Global Health Innovative Technology Fund IND: investigational new drug application MDR-TB: multidrug-resistant tuberculosis *M. obuense*: *Mycobacterium obuense* MVA: modified vaccinia virus Ankara SSI: Statens Serum Institut For abbreviations and acronyms not listed here, see footnote to Table 1.			

Longer term, TB vaccine developers need to design for inclusion. Not all TB vaccines will be appropriate to study in pregnant people, but many can be with purposive effort to generate supporting evidence. **DART studies** should be completed early enough to enable the inclusion of pregnant people in efficacy trials. The case for including pregnant women in studies would be easier to make with better data on TB incidence and IGRA positivity during pregnancy, so pregnancy should be incorporated into the preparatory epidemiological studies that will precede phase III trials. The **PHASES project** has other practical suggestions for developing a pregnancy-inclusive research agenda.

DART studies refer to development and reproductive toxicology studies and are designed to assess the reproductive safety of new drugs or vaccines.

The **PHASES project** developed guidelines on HIV research in pregnancy, and many of the recommendations are transferable to TB research.

3. **"Trust us, it's taken care of."** The shameful inequities in COVID-19 vaccine access have heightened long-standing concerns that new global health products will remain out of reach of people who need them most. Negotiating the accessibility and affordability of new TB vaccines upfront, during early stages of R&D, is essential to ensuring that affected communities can enjoy the benefits of TB science. Yet when asked about access by advocates, funders and vaccine developers are able to give only vague assurances that access conditionalities are part of funding and licensing agreements. These agreements are negotiated with minimal public oversight and almost always reside outside the public domain. Advocates and community representatives are left to search minimally worded press releases for clues about access terms—an absurd exercise. Take these recent examples (lightly anonymized here but cited to the original sources):

   > Vaccine developer A and company B "join forces to develop, manufacture and market a new TB vaccine in more than 70 countries in Southeast Asia and sub-Saharan Africa."[43] How many countries? Which ones? At what price will the vaccine be sold, and how will this price be determined?
   >
   > –or–
   >
   > Agreement between nonprofit vaccine developer X and for-profit pharmaceutical company Y is "paving the way for continued development and potential use of the vaccine candidate in low-income countries with high TB burdens."[44] What about middle-income countries, where the global burden of TB is concentrated? Does this include low-income countries with low TB burdens? Does the list of countries reflect income levels at the time of the agreement or at the time the vaccine will be approved for use?

–or–

> Biotech A "concluded an exclusive license agreement with [nonprofit research institute B] for a tuberculosis vaccine . . . Following the phase 2 clinical trials, the company plans to establish a GMP plant for the production of its vaccine . . . in order to gain a foothold for establishing both local and global markets."[45] Which markets? Does the license cover technology transfer? Are the rights limited to certain geographic jurisdictions or to particular components of the vaccine technology?

Such basic questions deserve clear answers. For a field almost totally reliant on public and philanthropic funding,[46] the more rational approach would entail open, transparent licenses with clear access conditions governing price, technology transfer, national regulatory filings, commercial space, and other issues. Those who argue that such agreements cannot be made except behind the closed doors of total confidentiality will need to explain how their opaque approach will avoid the "vaccine apartheid" that created deadly delays in access to COVID-19 vaccines among Global South countries, many of which are the same places that will contribute to TB vaccine clinical trials. To return to the opening metaphor of this *Pipeline Report* chapter: Run a race in the dark and expect to stumble.

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