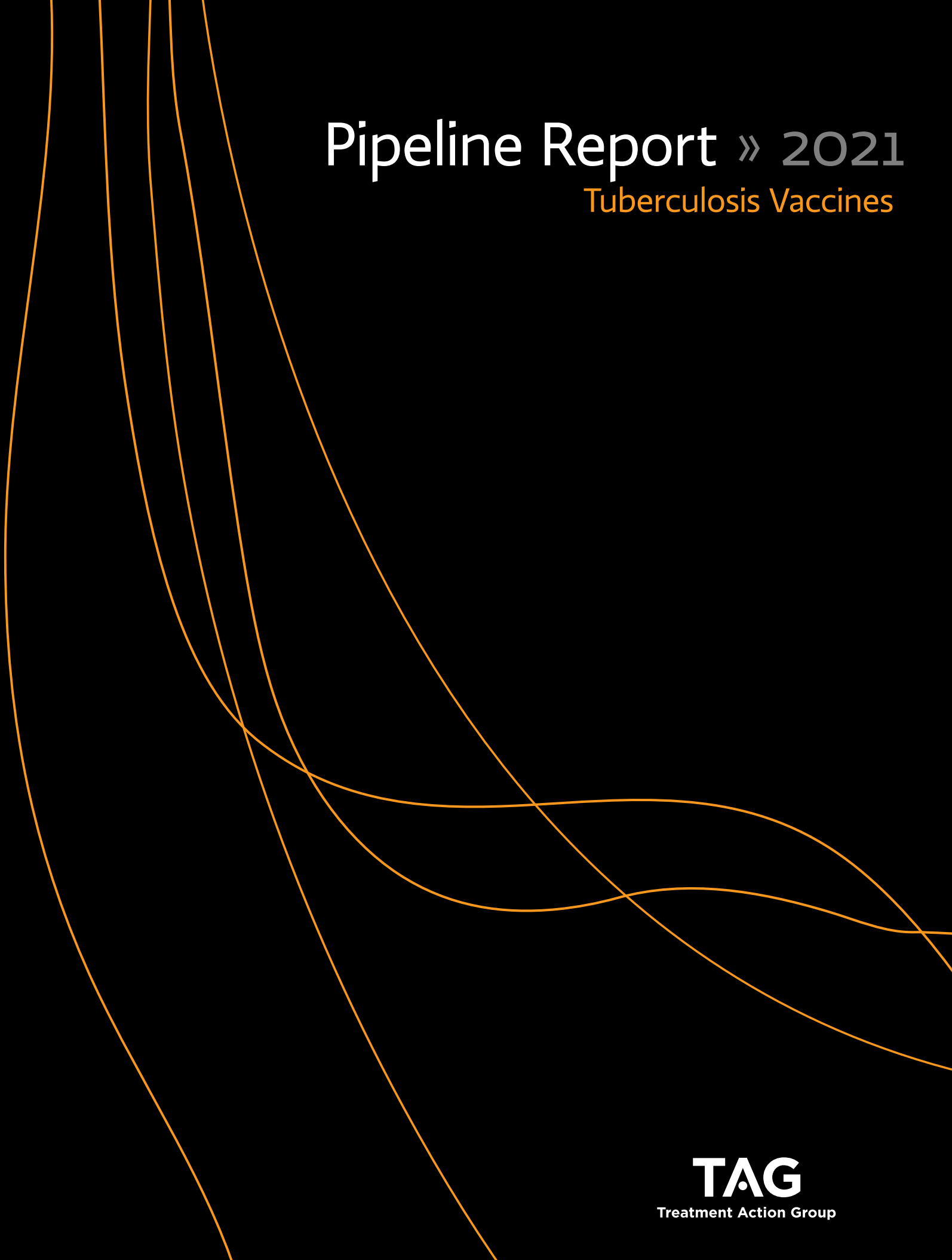
Pipeline Report » 2021

Tuberculosis Vaccines



TAG
Treatment Action Group

Tuberculosis Vaccines

Running a different race

By Mike Frick

What is there left to say about the importance of vaccine research and access? If the first year of the COVID-19 pandemic will be remembered for the stunning pace and success of vaccine development, the grave injustice of inequitable vaccine access will surely define the second. The fight to ensure everyone, everywhere can receive the protection of COVID-19 vaccines (and it is a fight) has eclipsed the unprecedented scientific achievements that have delivered 20 vaccines to date with likely more on the way.[1] One could easily forget that such a timeline for vaccine development is neither a guarantee for future pandemics nor the reality of ongoing ones. For tuberculosis (TB)—a disease which killed one billion people in the 19th and 20th centuries and one that has claimed over a million lives each year of the 21st[2]—the search for a new vaccine is measured not in years, or even decades, but now centuries.

On July 18, 2021, bacille Calmette-Guérin (BCG), the only existing vaccine against TB, turned 100 years old. One hundred years ago on that day, an infant in Paris, France received BCG after being born to a mother who died from TB soon after delivery.[3] For those who marked this year's centennial milestone, the day was neither a birthday party for BCG nor its funeral, neither a celebration of BCG nor its send-off into desuetude, but an altogether stranger occasion. It was an anniversary that asked its witnesses to do many things: nod to the continued importance of BCG for the lives it saves in preventing the most severe forms of childhood TB. Recognize the enduring inspiration it gives TB researchers (alternate routes of BCG administration and revaccination with BCG are central TB vaccine development strategies). And acknowledge its myriad contributions to health over and beyond TB. For example, BCG as a bladder cancer treatment or its association with lower rates of all-cause mortality among young children.[4] Just weeks before BCG's 100-year anniversary, the *Lancet Infectious Diseases* published a study illustrating the heterologous protection BCG confers infants against non-TB infectious disease.[5] The 101st year of BCG promises to bring even more data on such non-specific immunological effects with results anticipated from a slew of clinical trials evaluating whether BCG vaccination protects healthcare workers and the elderly against severe disease or death from COVID-19.[6] Surprisingly, the last five years have generated more data on BCG than the previous five decades.

Nonspecific effects may represent heterologous immunity (protection against one pathogen provides cross protection against others) and/or trained immunity (i.e., BCG alters gene expression related to pathogen recognition and immune response).

So, 100 years after its first human use, BCG is suddenly everywhere. Nowhere to be found is the tool that would reduce TB incidence in time to realize the World Health Organization's vision of eliminating TB by 2030: a new vaccine (or multiple vaccines) that protects adolescents and adults against TB. The confluence of the BCG centenary and the advent of COVID-19 vaccines begs the question: why are there no new vaccines against TB? Quick comparisons between TB and COVID-19 vaccine development reveal the answer. To take just one area of comparison, money. Governments spent an estimated US$90 billion on COVID-19 vaccine research and development (R&D) in the first 11 months of the pandemic, or nearly 82 times the US$1.1 billion the world spent on TB vaccine research in the last 11 years.[7] At one virtual event after another, across conference panels and keynote lectures, the question "why are there no new vaccines against TB?" transformed into the searching reflection: "What can we learn from COVID-19 vaccine development to change this?"

Whoever the speaker, answers generated a common list of ingredients, obvious but worth repeating: more funding, political will, scientific resources, advocacy, and public awareness of the problem and the prospects of solving it. A greater sense of urgency and outrage, starting with those closest to the issue (scientists, TB survivors, communities affected by TB) and spreading outward to policymakers and the public. A willingness among funders and developers to do things differently in order to move forward vaccine research more quickly.

Many of these prescriptions looked inward to focus on changes to be taken by individuals and institutions already working on TB vaccines. Sometimes lost in these discussions was a recognition that TB vaccine research and development (R&D) is up against some serious structural barriers that actions by individual scientists and institutions alone cannot overcome. Since there is a tendency to talk about vaccine development as a race—against time, transmission, deaths, and commercial competitors—a metaphor borrowed from track and field helps to summarize the situation: the 400-meter dash is not the same race as the 400-meter hurdles. A world-class runner sprinting down an open track will nearly always post a faster time than if asked to clear successive hurdles over the same distance. And what if the distance is longer and the hurdles remain?

For COVID-19 vaccine development, governments removed obstacles to ensure development could proceed apace. The United States, European Union, and other governments de-risked investment by pharmaceutical companies via advanced market purchase commitments. Regulators issued emergency use authorizations to expedite vaccine approvals and worked closely with developers so that trials that usually occur in stepwise phases took place in parallel.[8] Previous investments in HIV vaccine development created the clinical trial networks, laboratory infrastructure, and human capacity that allowed experimental COVID-19 vaccines to enter clinical testing without delay.[9] Backing all these interventions

were decades of public spending on basic science, much of it not appreciated as directly applicable at the time (see the story behind mRNA vaccines).[10,11]

These efforts to remove hurdles to success were not perfect in their execution. In their haste to clear the way, governments gave up the leverage they would need to ensure that vaccines, once developed, would be available to all.[12] Some of the same governments worked to maintain certain obstacles by defending a maximalist approach to intellectual property (IP) protection even as inequitable vaccine rollout, in part a consequence of global IP rules, abetted the unchecked spread of new variants.[13,14] Although the track record of COVID-19 vaccines is imperfect, the lesson for TB vaccine R&D is clear: access and innovation run hand-in-hand.

A series of linked statements by the World Health Organization (WHO) put TB and COVID-19 vaccines into the same conversation. "Vaccine equity is the challenge of our time," WHO Director-General Tedros Adhanom Ghebreyesus has repeated on many occasions.[15] Tereza Kasaeva, director of the WHO Global TB Programme, followed one such statement by saying: "WHO's call for vaccine equity is important as we work in parallel on research and development for new TB vaccines."[16] Kasaeva's remark points to the importance of thinking about vaccine accessibility alongside *availability*. In the human rights framework, availability refers not just to the quantity of health goods, but also to whether they exist at all. Many of the tools needed to end TB, such as new vaccines, are unavailable because they have not yet been created by R&D.[17] The fact that the world has multiple vaccines for some diseases but not for others is itself an inequity and the product of greater inequalities by which some pandemics spark the political, financial, and societal resolve to bring about their end and others last for hundreds of years.

If there is agreement that the next five to ten years of TB vaccine development need to be run faster than the last 100, then the field needs to start directing questions outward by asking governments and other powerful institutions what concrete actions they will take to remove the hurdles that have slowed discovery and development and may later impinge on access.

As the TB vaccine field takes stock of the course ahead at this moment of historical resonance, Treatment Action Group's *2021 Tuberculosis Vaccines Pipeline Report* shows where the field currently stands. Three tables review 15 vaccines under development by listing candidate vaccines above summaries of ongoing, planned, and recently completed clinical trials. Table 1 tallies vaccines in phase III trials, table 2 looks at candidates that have reached phase II, and table 3 summarizes phase I work. Major updates or changes in position for some, but not all, candidates are summarized in the bullet points below.

This year's *Pipeline Report* does not provide a detailed overview of M72/AS01E, the candidate that has generated the most excitement among observers. The 2019 and 2020 *Pipeline Reports* provided in-depth discussions of the M72/AS01E phase IIb trial results, access and benefit sharing concerns surrounding the AS01E adjuvant, and phase III clinical trial plans led by the Gates Medical Research Institute (GMRI).[18,19] The GMRI continues to plan for a phase III trial of M72/AS01E and in doing so has embraced an admirably open and consultative approach by holding far-reaching scientific consultations as well as community dialogues over 2021. Over the next year, the GMRI will make final decisions about endpoint definitions, enrollment inclusion and exclusion criteria, the role of TB preventive treatment in the study, site selection, regulatory strategy, community engagement, and other design elements. The phase III study is targeting a 2023 start date and will follow a preparatory epidemiological study to define TB incidence at potential trial sites.[20] In addition, results of the ongoing phase II MESA-TB study of M72/AS01E in people living with HIV (PLHIV) will inform whether PLHIV on stable antiretroviral treatment can join the phase III trial. MESA-TB is fully enrolled with an estimated primary completion date of 2022.[21]

MESA-TB, phase II trial of M72/AS01E in PLHIV NCT04556981

Also not reviewed here are recent advances in the preclinical space, though there is a lot to look forward to, including: vaccines using the same mRNA platform that proved so successful for COVID-19 vaccines;[22] DNA-based vaccines;[23] experimental vaccines that harness vectors such as cytomegalovirus, human parainfluenza virus, or Listeria monocytogenes;[24,25,26] and, yes, even some recombinant BCG candidates that innovate on the now-century-old original.[27] Don't look away—with the right interventions by governments and other funders, the next few years of R&D could ensure that BCG will not reach its next significant milestone alone.

An mRNA TB vaccine developed by BioNTech with Gates Foundation funding could enter human clinical trials as early as 2022, according to BioNTech CEO Ugur Sahin as quoted in the Wall Street Journal.

The company plans to support TB and malaria vaccine manufacturing in Africa, likely in Rwanda and Senegal, according to reporting by Fierce Pharma.

Table 1. TB Vaccines in Phase III Clinical Development

Agent	Type	Sponsor(s) and Major Partners	Status*
Notable recently completed, ongoing, and planned clinical trials. The abbreviations appearing in red boxes give the indication for which a vaccine is being developed. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence*			
MIP	Whole-cell *M. indicus pranii*	ICMR, Cadila Pharmaceuticals	Phase III
POD	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of MIP and VPM1002 (vs. placebo) in preventing TB disease 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.) Expected completion: 2022.**		
VPM1002	Live rBCG	SII, Vakzine Projekt Management, EDCTP, ICMR, IMPAACT, HVTN	Phase III
POD	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 and MIP (vs. placebo) in preventing TB disease 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.) Expected 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 newborn infants (HIV-exposed and uninfected eligible) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685). Expected completion: July 2023.		
POR	Undergoing a phase II/III trial evaluating efficacy, safety, and immunogenicity of VPM1002 (vs. placebo) in preventing TB disease recurrence in 2,000 HIV-negative adults aged 18–65 years successfully treated for TB in India and Bangladesh (NCT03152903; CTRI/2017/03/008266). Expected completion: June 2023.		
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 (each of four arms stratified by HIV and MTB infection status). Protocol number: IMPAACTP2035/HVTN604.		
M72/AS01E	Protein/adjuvant subunit vaccine	GMRI, GSK Biologicals (AS01E adjuvant)	Phase III
POD	Planning for a phase III efficacy, safety, and immunogenicity study in up to 20,000 individuals aged 16–34 years with and without MTB infection. (Secondary objectives will evaluate POI among participants who enter study without MTB infection.) Study population, locations, and other details still being determined. Expected start: 2023.		
Other	Undergoing a phase II safety/immunogenicity study in 400 PLHIV aged 16–35 years on ART and virally suppressed in South Africa (NCT04556981). (Known as MESA-TB, the trial is intended to support inclusion of PLHIV in the phase III POD study listed above.) Expected completion: July 2022.		
MTBVAC	Live, genetically attenuated MTB	Biofabri, IAVI, TBVI, University of Zaragoza, EDCTP	Phase III
POD	1. Undergoing a phase III trial to evaluate the efficacy, safety, and immunogenicity of MTBVAC (vs. BCG) in 6,960 HIV-unexposed and HIV-exposed infants in South Africa, Senegal, and Madagascar (NCT04975178). Expected completion: September 2027. 2. Planning for a phase III trial to evaluate the efficacy, safety, and immunogenicity of MTBVAC in adults and adolescents (source: IAVI and Biofabri July 2021 press release).		
Other	1. Completed a phase IIa dose-defining safety/immunogenicity study in 99 South African infants (NCT03536117). (Informed dose selected for phase POD III trial listed above.) Completion: March 2021; results forthcoming 2022. 2. Completed a phase Ib/IIa dose-defining safety/immunogenicity study in 144 adults with and without MTB infection in South Africa (NCT02933281). Completion: September 2020; results forthcoming 2022.		

Agent	Type	Sponsor(s) and Major Partners	Status*
Notable recently completed, ongoing, and planned clinical trials. The abbreviations appearing in red boxes give the indication for which a vaccine is being developed. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence*			
BCG (re) vaccination	Whole-cell *M. bovis*	GMRI, IMPAACT, Henry M. Jackson Foundation	Phase III
POI	1. Undergoing a phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in 2,150 BCG-vaccinated, MTB-uninfected adolescents in South Africa (NCT04152161). Expected completion: April 2023. 2. 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). Expected 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 (each of four arms stratified by HIV and MTB infection status). Protocol number: IMPAACTP2035/HVTN604.		
GamTBvac	Protein/adjuvant subunit vaccine	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). Expected completion: November 2025.		
Other	Published results from a phase IIa safety/immunogenicity study of GamTBvac (vs. placebo) in 180 BCG-vaccinated, MTB-uninfected adult volunteers aged 18–49 years in Russia (NCT03878004). Completion: December 2019.		

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

**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.

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.

ART: antiretroviral treatment

BCG: bacillus Calmette-Guérin

EDCTP: European and Developing Countries Clinical Trials Partnership

GMRI: Gates Medical Research Institute

GSK: GlaxoSmithKline

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

PLHIV: people living with HIV

rBCG: recombinant bacillus Calmette-Guérin

SII: Serum Institute of India

TB: tuberculosis

TBVI: TuBerculosis Vaccine Initiative

Entering phase III:

- **MTBVAC:** BCG was not the only TB vaccine that celebrated a major anniversary in 2021—TB vaccine candidate MTBVAC marked its 25th year of research with the announcement that it will soon begin a phase III trial among nearly 7,000 HIV-exposed and unexposed infants in South Africa, Madagascar, and Senegal.[28] MTBVAC is a live-attenuated form of *Mycobacterium tuberculosis* weakened by the strategic deletion of two virulence genes (*phoP* and *fadD26*). Work on MTBVAC began with an unusual outbreak of multidrug-resistant *Mycobacterium bovis* that killed more than 100 individuals with HIV in Spain in the early 1990s. From that outbreak, researchers at University of Zaragoza identified the *phoP* gene as central to MTB virulence.[29] Phase I trials began in 2012 followed by multiple phase II studies in both infants and adults.[30] Now, the phase III trial in infants will evaluate the efficacy, safety, and immunogenicity of MTBVAC in preventing TB disease compared to BCG. The study is sponsored by the Spanish biotech company Biofabri and co-funded by the EDCTP. Biofabri and IAVI have also announced plans for a future phase III POD trial of MTBVAC in adolescents and adults.[31]

MTBVAC phase III trial in infants NCT04975178

MTB is *Mycobacterium tuberculosis*. Where text refers to "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]).

POD = prevention of disease.

- **GamTBvac:** Russia's Gamaleya Research Institute of Epidemiology and Microbiology announced a phase III trial of the subunit TB vaccine candidate GamTBvac in July 2021. The trial will assess the efficacy, safety, and immunogencitiy of two doses of GamTBvac versus placebo in preventing TB disease among 7,180 adults. Participants in the study must be HIV-negative, BCG-vaccinated, and MTB-uninfected. This last requirement is curious for late-stage POD trials, most of which target enrollment toward participants with a positive test for MTB infection to take advantage of higher TB disease rates in this population. The focus on individuals without MTB infection satisfies a request by Russian health authorities to conduct the phase III trial among the same population in which vaccine safety was demonstrated in prior phase I and II trials.[32] The phase III trial follows a recently published phase IIa study that found two-doses of GamTBvac were safe and well-tolerated among 180 adults and elicited antigen-specific CD4+ T-cell and antibody (IgG) responses.[33] Investigators at Gamelaya are planning to conduct an additional efficacy and safety study of GamTBvac among persons with MTB infection and/or exposure in the future.[34]

GamTBvac phase III trial NCT04975737

- **BCG:** A phase III trial of a century-old vaccine? Yes, indeed—the Henry M. Jackson Foundation for the Advancement of Military Medicine has registered a phase III trial to evaluate the efficacy, safety, and immunogenicity of pre-travel vaccination with BCG. The trial will enroll 2,000 long-term travelers and healthcare workers preparing to work outside of the United States. Participants must be BCG-naïve and uninfected with MTB, meaning that participants randomized to the experimental arm will receive BCG for the first time before travel (BCG vaccination at birth is not routine practice in the United States). This is a POI trial that seeks to evaluate whether primary BCG vaccination prevents infection measured by IGRA conversion post-travel and sustained conversion four to six months after return to the United States. This is different from the phase IIb trial of BCG revaccination among South African adolescents sponsored by the Gates Medical Research Institute that takes sustained IGRA conversion as a primary endpoint.

Pre-travel BCG phase III trial NCT04453293

POI = prevention of infection.

IGRA = interferon-gamma release assay. These blood-based tests detect cell-mediated immune responses to MTB antigens (but do not measure MTB infection directly).

BCG revaccination phase IIb trial NCT04152161

Table 2. TB Vaccines in Phase II Clinical Development

Agent	Type	Sponsor(s) and Major Partners	Status*
Notable recently completed, ongoing, and planned clinical trials. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence*			
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 650 BCG-vaccinated, HIV-negative, MTB-uninfected adolescents aged 13–15 years in Tanzania (NCT02712424). Completion: February 2020.**		
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 aged 18–60 years who have completed at least five months of drug-susceptible TB treatment in South Africa and Tanzania (NCT03512249). Expected completion: July 2023.		
Other	Completed a phase I safety/immunogenicity study of H6:IC31 given with and without COX-2 inhibitors as a therapeutic adjunct in 39 adults aged 18–70 years being treated for TB disease in Norway (NCT02503839). Completion: September 2019; results forthcoming.		
ID93/GLA-SE (QTP101)	Protein/adjuvant subunit vaccine	Quratis, ACTG, HVTN	Phase IIb
Work on QTP101 sponsored by Quratis			
POD	Planning for a phase IIb/III dose exploration and efficacy, safety, and immunogenicity evaluation of ID93/GLA-SE in up to 4,500 BCG-vaccinated, MTB-infected adults and adolescents aged 14–44 years. Study locations and other details still being determined. Expected start: late 2021.		
Other	1. 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 aged 19–64 years in South Korea (NCT03806686). Completion: March 2020; results via press release. 2. Completed a phase I safety/immunogenicity study of low-dose or high-dose ID93/GLA-SE (vs. placebo) in 36 BCG-vaccinated, MTB-negative adolescents aged 14–18 years in South Korea (NCT03806699). Completion: September 2020; results via press release.		
Work on ID93/GLA-SE sponsored by the NIH			
POR	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 people being treated for DS-TB. Five enrollment groups will receive ID93/GLA-SE at progressively earlier timepoints in TB treatment. Protocol number: A5397/HVTN603.1		
Other	1. Completed 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 in the United States (NCT03722472). Completion: June 2020; results forthcoming.		

Agent	Type	Sponsor(s) and Major Partners	Status*
Notable recently completed, ongoing, and planned clinical trials. *POD = prevention of disease | POI = prevention of infection | POR = prevention of recurrence*			
RUTI	Fragmented MTB	Archivel Farma	Phase IIb
1. 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). Expected completion: September 2023. 2. Undergoing a phase IIa safety/immunogenicity study of RUTI given as a therapeutic adjunct in 27 adults being treated for MDR-TB in the Netherlands (NCT02711735). Indication: therapeutic vaccination. Expected completion: July 2020.			
ChAdOx1 85A + MVA85A	Viral vector	Oxford University	Phase IIa
1. 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) aged 18–55 years in Switzerland (NCT04121494). Completion: August 2020; results forthcoming. 2. Undergoing a phase I/II dose escalation and age de-escalation safety study of ChAdOx1 85A in 12 adults and adolescents in Uganda. This will be followed by a phase IIa study comparing the immunogenicity of an intervention of ChAdOx1 85A prime and followed by MVA85A boost (vs. BCG revaccination) in 60 adolescents ≥12 years in Uganda (NCT03681860). Expected completion: January 2022.			

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

**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.

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. Information on QTP101 phase III trial plans comes from press releases (5/31/2021, 7/20/2021) and personal communication between TAG and the company facilitated by Seemoon Choi.

ACTG: AIDS Clinical Trials Group

ChAd: chimpanzee adenovirus vector

COX-2: cyclooxygenase-2

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.

Making progress in phase II:

- **H56:IC31:** Developed at the Statens Serum Institute of Denmark, the subunit TB vaccine candidate H56:IC31 has started a phase IIb efficacy, safety, and immunogenicity study in South Africa and Tanzania. This is a POR study that will assess whether vaccination with two doses of H56:IC31 at the end of TB treatment can prevent recurrent TB disease (defined as either reinfection with TB or relapse). The trial will enroll 900 HIV-negative adults nearing the end of treatment for drug-susceptible TB, randomize them to receive either H56:IC31 or placebo, and then follow them for a year after the second vaccine dose to observe rates of relapse or reinfection. The long-term goal of this clinical development program is to determine whether vaccination with H56:IC31 improves TB treatment outcomes—for drug-susceptible and drug-resistant TB—or can even reduce the duration of TB treatment. Five previous clinical trials have tested the safety and immunogenicity of H56:IC31 in a variety of populations (adolescents/adults, MTB-infected/un-infected) and at different time points in TB treatment.[35] One group not included in the current phase IIb study is PLHIV. Anticipating the question, the ClinicalTrials.gov entry explains: "As this is a proof-of-concept TB vaccine study, HIV positive individuals have been excluded as it is not yet known what effect HIV infection may have on the immune response to the vaccine. However, HIV positive individuals are an important population to include in future studies should efficacy be demonstrated in this study."[36]

Phase IIb POR trial of H56:IC31 NCT03512249

POR = prevention of recurrence.

- **DAR-901:** In late 2020 a consortium of researchers led by Dartmouth College published results of a phase IIb trial of DAR-901, a vaccine comprised of inactivated, whole-cell *M. obuense*. Known as DAR-PIAT, this phase IIb POI trial enrolled 650 HIV-negative, MTB-uninfected Tanzanian adolescents aged 13–15 years, randomized them to receive either three doses of DAR-901 or placebo, and followed them for IGRA conversion over three years.[37] The primary endpoint was time to IGRA conversation (negative to positive, measured using Oxford Immunotec's T-SPOT.TB test). In the end, the trial did not demonstrate a difference in time to IGRA conversion between participants who received DAR-901 (19 conversions) as opposed to placebo (18 conversions).[38] DAR-901 was manufactured from the master cell bank of the earlier TB vaccine candidate SRL172, which was evaluated in the DarDar trial. SRL172 reduced the primary endpoint of the DarDar study (disseminated TB) and a secondary endpoint (definite TB), but only the efficacy measure against the secondary endpoint was statistically significant.[39] With the SRL172 experience in mind, investigators at Dartmouth have questioned what the negative result of the recent DAR-PIAT study means for the strategy of using smaller POI studies in phase II to select candidates to advance to larger POD efficacy evaluations in phase III.[40] The question is important, but extracting a generalizable lesson about whether prevention of infection predicts prevention of disease (or stated a different way: whether a vaccine must prevent infection in order to prevent disease) will require looking at results across many different trials. The Dartmouth team has shared their intention to conduct a enhanced dose study (comparing the 1 mg dose used in DAR-PIAT to higher doses of 3 and 5 mg) followed by a phase III POD trial. Commenting on the phase III plans, Ford von Reyn of

Phase IIb POI trial of DAR-901 NCT02712424

Mycobacterium obuense (*M. obuense*) is a type of non-tuberculosis mycobacteria.

DAR-901 is broth-grown, a more scalable production method than the agar-grown SRL172.

The DarDar trial (NCT00052195) ran in Tanzania between 2001 and 2008 and enrolled PLHIV (97% not on ART).

Dartmouth emphasized the need for phase III trials to test multiple candidate vaccines at once given the field's limited resources, a strategy of "taking two shots on goal."[41]

Getting back on track:

- **ID93/GLA-SE:** The overnight dissolution of the Seattle-based Infectious Disease Research Institute's (IDRI's) TB program (described in last year's *Pipeline Report*) threw the fate of TB vaccine candidate ID93/GLA-SE into doubt.[42] After more than a year of sorting through the confusion with IDRI and other relevant parties, investigators at the AIDS Clinical Trials Group and HIV Vaccine Trials Network are ready to move forward A5397/HVTN603, a phase IIa/IIb trial in late-stage protocol development. The study will evaluate the safety, immunogenicity, and efficacy of ID93/GLA-SE versus placebo when given as a therapeutic adjunct to people undergoing treatment for rifampicin-susceptible TB.[43] The trial aims to enroll 1,500 participants into one of five groups (group 5 is the largest with 1,100 individuals and constitutes the bulk of the phase IIb component of the trial). Participants across the five groups will receive two doses of ID93/GLA-SE spaced two months apart at progressively earlier timepoints in TB treatment. Results from the earlier groups will determine the timing of vaccination for group 5. The efficacy hypothesis is that investigators will observe fewer bacteriologically-confirmed unfavorable TB treatment outcomes among individuals in the ID93/GLA-SE group compared to participants who receive placebo at 18 months after the start of TB treatment.

- **QTP101, or ID93/GLA-SE by another name:** South Korean biotech Quratis owns rights to develop ID93/GLA-SE under the name QTP101 in 17 Asian countries.[44] Quratis has completed two early-stage safety/immunogenicity studies of ID93/GLA-SE in South Korea: a phase II trial in 107 BCG-vaccinated, MTB-uninfected healthcare workers and a phase I trial among 36 South Korean adolescents. A press release in Korean noted that three doses of QTP101 had a favorable safety profile in both trials and "strong cellular and humoral immune responses compared to placebo."[45] The release quotes Yu Hwa Choi, clinical director at Quratis, saying that a "global late-stage clinical trial" will follow. Dr. Choi shared an overview of those plans with TAG, describing a phase IIb/III dose exploration and efficacy, safety, and immunogenicity evaluation of QTP101 in up to 4,500 BCG-vaccinated, MTB-infected adults and adolescents aged 14–44 years. Quratis hopes to open the trial before the end of 2021.[46] The company has the capacity to manufacture enough vaccine for a phase III trial and potentially commercial supply. In August 2020, the company completed construction of a GMP manufacturing facility at the Osong Medical Complex in Cheongju. The Osong site will produce both antigen (ID93) and adjuvant (GLA-SE) for liposomal and lyophilized (freeze-dried) formulations of QTP101.[47] Interestingly, this same plant will serve as the manufacturing site for Quratis's mRNA vaccine against COVID-19. Called QTP104, the product is a collaboration between Quratis, HDT Bio Corp (USA), and Gennova Biopharmaceuticals (India). A phase I trial of QTP104 received the greenlight from Korea's Ministry of Food and Drug Safety in July.[48]

The 17 countries where Quratis has rights to ID93/GLA-SE are Brunei, Cambodia, China, East Timor, Indonesia, Laos, Macao SR, Malaysia, Mongolia, Myanmar, North Korea, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam.

QTP101 healthcare worker phase II trial NCT03806686

QTP101 adolescent phase I trial NCT03806699

Moving down and out:

- **TB/FLU-04L:** TAG has downgraded TB/FLU-04L from phase II to phase I due to the lack of a registered phase II clinical trial of either TB/FLU-04L or related candidate TB/FLU-01L. Each of these viral vectored vaccines is constructed using a replication deficient influenza A virus vector; both have completed phase I trials. A study among 36 participants compared the safety and immunogenicity of TB/FLU-01L administered intranasally vs. sublingually. In the phase I study of TB/FLU-04L, 44 volunteers received either TB/FLU-04L or placebo. This trial was first registered to ClinicalTrials.gov in July 2015 and last updated in August 2020 to report the total number of participants enrolled. A phase IIa trial of TB/FLU-04L in IGRA-positive adults, first announced at the 4th Global Forum on TB Vaccines in 2018,[49] was not completed due to difficulties enrolling men into the study.[50] Investigator Marina Stukova shared with TAG that further phase II work is on hold pending the completion of additional preclinical reproductive toxicology studies that would allow women to join future studies. In the meantime, the involved research institutes in Russia and Kazakhstan have been busy pursuing a similar flu-vectored vaccine against COVID-19.[51]

Phase I studies of TB/FLU-01L (NCT03017378) and TBFLU-04L (NCT02501421)

- ***M. vaccae*:** TAG has listed TB vaccine candidate ***M. vaccae*** in phase III since the 2013 *Pipeline Report*. Sponsored by Chinese conglomerate Anhui Zhifei Longcom, the phase III trial of *M. vaccae* evaluated the efficacy and safety of six doses of vaccine versus placebo in preventing TB disease among 10,000 adolescents and adults with MTB infection. Anhui Zhifei Longcom already holds China State Food and Drug Administration approval to market *M. vaccae* as immunotherapy for people with TB disease. The phase III trial sought to update the product's indication to include prevention of disease among MTB-infected individuals. Since 2018, TAG has reported the trial complete and results as forthcoming. Four years later and still waiting for results to be published or publicly presented, TAG has removed *M. vaccae* from table 1. Pu Jiang, CEO of Anhui Zhifei Longcom, shared with TAG that based on a review of the phase III trial data, China's National Medical Products Administration added an indication to *M. vaccae's* marketing label on June 8, 2021. The vaccine can now be used in China to prevent TB disease among people with MTB infection in addition to its earlier approved use as immunotherapy.[52] Anhui Zhifei Longcom is also the sponsor for TB vaccine candidate AEC/BC02, which is completing a second phase I study. AEC/BC02 is a subunit vaccine consisting of MTB antigen Ag85B and an ESAT6/CFP10 fusion protein paired with the BC02 adjuvant (BCG-derived CpG and aluminum salt).[53]

M. vaccae phase III trial NCT01979900

AEC/BCO2 phase I study NCT04239313

TAG thanks the TB vaccine sponsors and scientists who provided or reviewed information for this report.

Table 3. TB Vaccines in Phase I Clinical Development

Agent	Type	Sponsor(s) and Major Partners	Status*
Notable recently completed, ongoing, and planned clinical trials.			
BCG (aerosol)	Whole-cell *M. bovis*	University of Oxford	Phase I
1. Completed a phase I safety/immunogenicity study of BCG challenge at different doses delivered via aerosol or intradermal vaccination (vs. placebo) in 46 BCG-naïve adult volunteers aged 18–50 years in the United Kingdom (NCT02709278). Completion: May 2019;** results forthcoming. 2. Undergoing a phase I safety/immunogenicity study of BCG challenge at different doses delivered via aerosol (vs. placebo) in 65 BCG-vaccinated, MTB-uninfected adult volunteers aged 18–50 years in the United Kingdom (NCT03912207). Expected completion: June 2022. 3. Undergoing a phase I safety, immunogenicity, and dose-escalation study of BCG challenge delivered via aerosol in 12 historically BCG-vaccinated adults volunteers aged 18–50 years in the United Kingdom (NCT04777721). Expected completion: March 2023.			
AdHu5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
Completed a phase I safety/immunogenicity study of high- and low-dose AdHu5Ag85A (aerosol vs. intramuscular vaccination) in 36 BCG-vaccinated adult volunteers aged 18–55 years in Canada (NCT02337270). Completion: September 2021; results forthcoming.			
AEC/BC02	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase I
1. Undergoing a phase Ib safety/immunogenicity study of freeze-dried, low-dose AEC/BC02 vaccine and adjuvant (vs. placebo) in 30 adult volunteers aged 18–45 years in China (NCT04239313). Expected completion: July 2021. 2. Completed a phase I safety and dose-defining study of AEC/BC02 vaccine and adjuvant (vs. placebo) in 25 adult volunteers China (NCT03026972). Completed: September 2018.			
TB/FLU-01L & TB/FLU-04L	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan; Research Institute of Influenza, Russian Federation	Phase I
1. Phase IIa study of TB/FLU-04L in MTB-infected adult men not completed (recruitment challenges). Further phase II work pending additional preclinical studies. 2. Previously completed a phase I safety/immunogenicity study of TB/FLU-04L (vs. placebo) in 44 BCG-vaccinated adults aged 18–50 years (NCT02501421) and a phase I safety/immunogenicity study of TB/FLU-01L intranasal vs. sublingual administration among 36 BCG-vaccinated adults aged 18–50 years in Kazakhstan (NCT03017378).			

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

**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.

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.

For abbreviations and acronyms, see footnotes to Tables 1 and 2.

Endnotes

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