

# Pipeline Report » 2020

Tuberculosis Vaccines

**TAG**

Treatment Action Group

# TUBERCULOSIS VACCINES

Mike Frick

## Introductory Note

“Open a window” is an old tuberculosis (TB) prevention adage, one that remains good advice for preventing TB in the household and, now, SARS-CoV-2/COVID-19 too.<sup>1</sup> While I was writing this year’s *TB Prevention Pipeline Report* at home in New York City—a time spent mostly indoors due to the COVID-19 pandemic—my open window and its view of a small square of dirt with a ginkgo tree, standing solitary yet resilient amid a stretch of concrete, reminded me that prevention can arise from the simplest of natural things: a breeze, a patch of soil, the trunk and foliage of a tree. The nature metaphors invoked throughout this year’s *TB Prevention Pipeline Report* are not incidental. Like so much of medical science, recent advances in TB preventive therapy (TPT) and TB vaccines originate in the natural world. Rifapentine and rifampicin, the drugs at the center of shorter TPT regimens, were first synthesized from a compound discovered in a soil sample taken from the pine forests of southern France.<sup>2</sup> A key component of the M72/AS01E TB vaccine candidate—the QS-21 molecule—comes from the soapbark tree, a medicinal resource recognized in the traditional knowledge of Indigenous Andean peoples.<sup>3</sup>

Tracing things back to their source is instructive for demonstrating how much a field has grown from its roots. In recent years, TB prevention science has traveled by leaps. Researchers developing new TPT regimens are processing a bounty of data from recently concluded clinical trials that have established a new standard of care (reviewed in a separate chapter available [here](#)). For TB vaccine developers, successful phase II studies have tilled the ground for larger efficacy trials, most notably a phase III trial of M72/AS01E (reviewed in this chapter). Whatever our vantage point, it is a good time to watch the TB prevention pipeline closely, keeping our gaze on where prevention science is going without forgetting where it all began.

## The TB Vaccine Pipeline

*“Farmers begin every year with a vision of perfection. And every year, in the course of the seasons and the work, this vision is relentlessly whittled down to a real result.”*

—Wendell Berry<sup>4</sup>

The last two TB vaccine *Pipeline Reports* published by TAG each reviewed a pivotal clinical trial in depth. Last year’s focused on the phase IIb trial of TB vaccine candidate M72/AS01E. A phase IIa study of BCG revaccination occupied the spotlight the year before. Each trial exceeded the modest expectations set for it by a field conditioned to a scarcity of good news; together, these studies have changed the direction of TB vaccine development indelibly. Optimism is in the air. Scientists, vaccine developers, and funders are planting seeds that they hope will germinate into a long-sought new vaccine against TB. For M72/AS01E, the groundwork is being laid for a phase III efficacy trial to confirm the signal of protection observed in the phase IIb study and generate the data to support product licensure. For BCG, the next step entails a follow-on study to see if a larger population of adolescents than the one included in the phase IIa trial experience fewer sustained TB infections after revaccination with BCG, a vaccine normally given to infants.

Like the farmer described by the American writer Wendell Berry, the clinical trialist must believe that today’s careful planning will yield tomorrow’s scientific fruits. It will take years of hard work and investment to turn the “vision of perfection” contained in the study protocols of the next M72/AS01E and BCG revaccination trials into results that, if all goes well, will give the world new options for preventing TB. Sagely, the TB vaccine field is not taking the eventual success of either M72/AS01E or BCG revaccination for granted. **Table 1** reviews the pipeline of TB vaccine candidates under clinical development and lists ongoing, planned, and recently completed clinical trials for each. In all, the field contains 16 vaccine candidates or constructs at various clinical development stages.

The clinical trials listed in Table 1 and discussed below are progressing alongside renewed efforts to coordinate and align research efforts globally. Plans abound. The EDCTP is developing a *Global Roadmap for the Research and Development of New Tuberculosis Vaccines* in collaboration with the WHO, which itself obtained member state endorsement of its broader *Global Strategy for TB Research and Development*.<sup>5,6</sup> At the U.S. National Institutes for Health (NIH), the Division of AIDS HIV Clinical Trials Networks are developing a *Roadmap for TB Vaccine Trials in People Living with HIV*. The Collaboration for TB Vaccine Discovery, supported by the Bill & Melinda Gates Foundation, is implementing a version 2.0 of its own roadmap to translate basic discovery into next-generation vaccine candidates.<sup>7</sup> Several such candidates may enter the pipeline soon: two novel vaccine concepts supported by the Gates Foundation are poised to enter clinical development in coming years. One is based on a messenger RNA (mRNA) delivery platform held by a company called BioNTech. The second is a cytomegalovirus-based vaccine (rCMV) developed at the University of Oregon and licensed to VirBio.

First introduced in 1921, bacillus Calmette–Guérin (BCG) is given to infants and prevents severe forms of childhood TB but offers little and variable protection against TB disease to adults.

The EDCTP is the European and Developing Countries Clinical Trials Partnership, which in 2018 was the third largest funder of TB vaccine research with expenditures of over \$13 million.

The profusion of roadmaps is a direct response to the scientific progress made over the past two years. It signals that this moment in TB vaccine research and development (R&D) is about making plans and following through on them relentlessly to arrive at results that seemed remote and unattainable just a few years ago. However, this is no ordinary season: the COVID-19 pandemic has upended TB research efforts and may impose lasting damage if funders do not shore up support for ongoing and planned projects. Yet, in the middle of the disarray caused by COVID-19, the value of TB vaccine research has never shone more clearly. The considerable overlap between TB vaccine and COVID-19 vaccine development, reviewed at the end of this chapter, demonstrates that investing in R&D for new TB vaccines carries **broad benefits** for the COVID-19 response and medical research at large.

### ***Now introducing to the pipeline: mRNA!***

For as long as TAG has tracked TB vaccine R&D, the pipeline has contained three types of candidate technologies: viral-vectored vaccines, subunit vaccines, and whole-cell mycobacterial vaccines (either live or inactivated/killed). Missing were so-called ‘next-generation’ vaccine constructs based on either DNA or RNA. That absence may end in coming years thanks to recently initiated preclinical work on the field’s first **mRNA** vaccine candidates. In 2019, the Gates Foundation inked a \$55 million equity investment in German vaccine developer BioNTech.<sup>8</sup> Today, most people know BioNTech for its partnership with Pfizer to develop **mRNA vaccines against COVID-19**.<sup>9</sup> Originally, BioNTech specialized in developing mRNA vaccines for cancer. The Gates Foundation’s investment will support BioNTech in establishing a preclinical development program for TB and HIV vaccines (the company also cites the potential to receive up to \$100 million from the Gates Foundation via future grant funding to support clinical evaluations of the resulting candidates). Under the agreement, BioNTech “will retain rights for commercialization of the vaccine candidates in the developed world, while providing affordable access to the candidates in developing countries.”<sup>10</sup> But first the technology needs to pass preclinical development and enter clinical testing.

Barring the possible approval of an mRNA-based COVID-19 vaccine, no stringent regulatory authority has ever licensed an mRNA vaccine against any disease. Essentially, mRNA vaccines harness regular cellular machinery to produce antigenic proteins that prepare the immune system for future encounters with disease-causing pathogens. They do this by introducing an mRNA sequence into the body; the sequence encodes a disease-specific antigen that, once taken up and produced by cells, is recognized by the immune system, which is left more prepared to recall and respond to the pathogen itself.<sup>11</sup> To be effective, mRNA vaccines need a vehicle to deliver mRNA to the cell; left unaccompanied in the body, free RNA is quickly degraded. For this reason, mRNA sequences are often packaged in liposomes, lipid bilayers, or nanoparticle suspensions.<sup>12</sup> Part of the excitement behind mRNA vaccines stems from the idea that they lend themselves to quicker development and swifter, more efficient manufacturing at scale.

The **broad benefits** of TB research—or how TB research infrastructures, concepts, and constructs are benefitting COVID-19 R&D—are reviewed in a [TAG policy brief](#).

**mRNA** stands for messenger RNA. Most simply, mRNA is the molecule that tells cells what to build; it is the intermediate step between the translation of protein-encoding DNA and the production of proteins by ribosomes.

TAG’s [COVID-19 Vaccine Pipeline Report](#) reviews **COVID-19 mRNA vaccines** under development, including BioNTech/Pfizer’s BNT162b2 candidate and Moderna’s mRNA-1273.

At this stage, there are few publicly available details on the mRNA vaccines that BioNTech will pursue for TB. But the company’s entry into the field has brought a novel approach that, if it demonstrates proof of concept, will introduce a new type of vaccine into the pipeline.

**ID93/GLA-SE: the best-laid plans**

*ID93/GLA-SE is a subunit TB vaccine composed of a fusion of four Mycobacterium tuberculosis (MTB) antigens (Rv3619, Rv3620, Rv2608, Rv1813) and the GLA-SE adjuvant. The adjuvant contains a synthetic TLR4 agonist glucopyranosyl lipid (GLA) formulated in a squalene-in-water emulsion (SE).*

In the last edition of the *Pipeline Report*, ID93/GLA-SE stood out among other candidates for having the most listed clinical trial activity, as judged by the number of recently completed, ongoing, and planned clinical trials. (Figure 1 reproduces the ID93/GLA-SE entry from last year’s pipeline table.<sup>13</sup>) That indication of activity belied deeper problems ailing the vaccine’s sponsor, **IDRI**, which without warning announced the dissolution of its TB drug and vaccine discovery programs in November 2019. The news shocked everyone, most of all IDRI scientists working on TB, who learned of their lab’s closure one day before the U.S. Thanksgiving holiday.<sup>14</sup> In total, one-third of IDRI staff lost their jobs and a prominent TB vaccine developer shuttered its programs—literally overnight.

The *Infectious Disease Research Institute (IDRI)* is a nonprofit biomedical research institute based in Seattle working “to create vaccine platforms and technologies to combat the world’s most devastating infectious diseases.”

**Figure 1: 2019 pipeline entry for ID93/GLA-SE before IDRI TB program closure**

ID93/GLA-SE	Protein/adjuvant subunit vaccine	Infectious Disease Research Institute, Quratis, Gennova Biopharmaceuticals	Phase II
<ol style="list-style-type: none"> <li>1. Published results of a phase IIa safety/immunogenicity study in 60 HIV-negative adults successfully treated for DS-TB in South Africa (NCT02465216)</li> <li>2. Undergoing a phase IIa POI trial in 107 BCG-vaccinated, MTB-uninfected healthcare workers in South Korea (NCT03806686). Expected completion: March 2020</li> <li>3. Undergoing a phase I safety and age de-escalation study in 36 MTB-negative adolescents 14–18 years old in South Korea (NCT03806699). Expected completion: September 2020. Following this, Quratis is planning a phase IIb POI trial in 1000 BCG-vaccinated, MTB-negative adolescents and adults in South Korea, Indonesia, the Philippines, Thailand, and China.</li> <li>4. Planning for a phase IIa POR safety/immunogenicity study in 60 HIV-negative adults being treated for DS-TB (TBVTC-204) in India (no clinical trials record available). Expected start: Q4 2019<sup>1</sup></li> <li>5. Planning for a phase IIb POR study in 270 HIV-negative adults being treated for DS- and DR-TB in India (TBVTC-205) (no clinical trials record available). Expected start: 2020<sup>1</sup></li> <li>6. Planning for a phase IIb POR study among 720 DS-TB patients at high risk for treatment failure in South Africa with the U.S. National Institutes of Health AIDS Clinical Trials Group and HIV Vaccine Trials Network<sup>1</sup></li> <li>7. Under consideration for a possible POI or POR trial in children with the U.S. NIH International Maternal Pediatric Adolescent AIDS Clinical Trials Network<sup>1</sup></li> </ol>			

The institute cited “financial difficulties,” specifically the perennial nonprofit challenge of raising enough grant funding to cover overhead costs. Reporting by the New York Times pointed to tensions between IDRI’s founder, Steve Reed, and its board.<sup>15</sup> The timing seemed off, and not only because of its proximity to a holiday. The decision to close the TB labs came shortly after IDRI received a seven-year NIH grant for TB research. The award intended to establish IDRI as one of several “new centers for immunology research to accelerate progress in tuberculosis vaccine development” under the NIH’s flagship **IMPACT-TB** program.<sup>16</sup> Whatever the cause, IDRI’s abrupt retreat from TB vaccine R&D left one of the field’s most promising subunit vaccine candidates in limbo.

As usual in global health, the murkiness of ID93/GLA-SE’s current situation originates in opaque licensing agreements between technology holders and commercial partners. In 2017, the South Korean biotech company **Quratis** entered an exclusive licensing agreement with IDRI to develop and market ID93/GLA-SE in South Korea (and perhaps other Asian countries; the agreement is not in the public domain).<sup>17</sup> In an August 2017 announcement, **Quratis** indicated that the agreement included “domestic technology transfer” and plans to “establish a GMP plant to manufacture tuberculosis vaccine in the future and lay the groundwork for establishing domestic vaccine sovereignty and advancing into the global market.”<sup>18</sup> This suggests that IDRI’s woes will not stop **Quratis** from **manufacturing** the vaccine for clinical trials in jurisdictions covered by the license. A month after the TB program closure at IDRI, **Quratis** signed a \$1.1 billion deal with Indonesia’s state-run vaccine manufacturer Bio Farma PT “to develop and commercialize **Quratis**’ tuberculosis (TB) vaccine, **QTP-101**, for adults and adolescents.”<sup>19</sup> **Quratis** will lead clinical trials, funded by Bio Farma PT via milestone-based payments, in exchange for exclusive supply rights in Indonesia following regulatory approval. Intriguingly, a statement by **Quratis** managing director Yuhwa Choi hints that similar arrangements in other countries may follow: “We will accelerate the TB vaccine’s global marketing throughout approximately 40 countries, including Korea and Indonesia. Currently, we are discussing licensing and exclusive marketing rights with some vaccine companies in Russia and Thailand and hope to announce good news in the near future.”<sup>20</sup>

Where does that leave trials of ID93/GLA-SE in other parts of the world? The NIH-funded ACTG is interested in pursuing work on ID93/GLA-SE and has drawn up plans for a phase IIa/IIb study evaluating the vaccine as a therapeutic adjunct to TB therapy in people with rifampicin-susceptible TB.<sup>21</sup> The IMPAACT Network at NIH is also considering studying ID93/GLA-SE in a multi-arm pediatric TB vaccine trial alongside BCG revaccination and TB vaccine candidate VPM1002.<sup>22</sup> The NIH-funded networks are currently in discussions with IDRI about accessing sufficient supply of ID93/GLA-SE for the clinical trials, which may require IDRI to manufacture the ID93 antigen and/or GLA-SE adjuvant for purchase.<sup>23</sup>

Immune Mechanisms of Protection Against *Mycobacterium tuberculosis* (**IMPACT-TB**) is a new NIH program to accelerate TB immunology and vaccine research at several centers of excellence.

It is not clear whether **Quratis** has rights to **manufacture** both the ID93 antigen and GLA-SE adjuvant. Additionally, it is unclear whether **Quratis** has rights to the lyophilized (freeze dried) formulation of ID93/GLA-SE. *One report* suggests the company’s production facility in Osong, South Korea will include lines for both the antigen and adjuvant in liposomal and lyophilized formulations.

**Quratis** statements refer to ID93/GLA-SE by the name **QTP101**.

**Table 1. TB Vaccines in Clinical Development**

Agent	Type	Sponsor(s) and Major Partners	Status*
<i>Notable recently completed, ongoing, and planned clinical trials.</i>			
<b>M. vaccae</b>	Whole-cell <i>M. vaccae</i>	Anhui Zhifei Longcom	Phase III
1. Completed a phase III trial in 10,000 MTB-infected, HIV-negative adults (aged ≥15 years) in China in 2017 (NCT01979900). Indication: POD. Results still not published.			
<b>MIP</b>	Whole-cell <i>M. indicus pranii</i>	ICMR, Cadila Pharmaceuticals	Phase III
1. Undergoing a phase III trial evaluating the safety, efficacy, and immunogenicity of MIP and VPM1002 (vs. placebo) in preventing TB disease among 12,000 household contacts (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026). Indication: POD. Expected completion: 2022.**			
<b>VPM1002</b>	Live rBCG	SII, Vakzine Projekt Management, ICMR, IMPAACT	Phase III
1. Completed a phase II safety/immunogenicity study in 416 BCG-naïve, HIV-exposed and HIV-unexposed newborn infants in South Africa (NCT02391415). Results not yet published.			
2. Undergoing a phase III POD trial among 12,000 household contacts (≥6 years old) of people with TB in India (see above entry for MIP; CTRI/2019/01/017026).			
3. Undergoing a phase II/III trial evaluating efficacy, safety, and immunogenicity of VPM1002 (vs. placebo) in preventing TB disease recurrence in 2000 HIV-negative adults successfully treated for DS-TB in India (NCT03152903). Indication: POR. Expected completion: February 2022.			
4. Planning for a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection among 6,940 newborn infants in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685). Indication: POI (sustained QFT conversion). Expected completion: July 2023.			
5. Planning for a phase IIa safety/immunogenicity study of VPM1002, BCG revaccination, and ID93/GLA-SE in HIV-unexposed and HIV-exposed children aged 8–14 years. Protocol number: CAP 555. <sup>1</sup>			
<b>M72/AS01E</b>	Protein/adjuvant subunit vaccine	Gates Medical Research Institute, GlaxoSmithKline (AS01E adjuvant)	Phase IIb
1. <u>Published final analyses</u> from a phase IIb efficacy, safety, and immunogenicity study of M72/AS01E (vs. placebo) in 3575 HIV-negative, MTB-infected adults in Kenya, South Africa, and Zambia (NCT01755598). Indication: POD.			
2. Undergoing a phase II safety/immunogenicity study in 400 PLHIV aged 16–35 years in South Africa (NCT04556981). Expected completion: April 2022.			
3. Planning for a phase III efficacy, safety, and immunogenicity study in up to 20,000 QFT- positive and QFT-negative individuals aged 16–35 years; inclusion of PLHIV contingent on above phase II study. Indication: POD (overall population and QFT-positive participants) and POI (QFT-negative participants). Expected completion: 2028.			
<b>DAR-901</b>	Inactivated whole-cell nontuberculosis mycobacterium	Dartmouth University, Global Health Innovative Technology Fund	Phase IIb
1. <u>Published results</u> 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 13- to 15-year-old adolescents in Tanzania (NCT02712424). Indication: POI (T-spot IGRA conversion). Results expected 2020.			

Agent	Type	Sponsor(s) and Major Partners	Status*
<i>Notable recently completed, ongoing, and planned clinical trials.</i>			
<b>H56:IC31</b>	Protein/adjuvant subunit vaccine	SSI, IAVI, EDCTP, Valneva—IC31 adjuvant	Phase IIb
<ol style="list-style-type: none"> <li>1. <b>Published results</b> from a phase Ib safety/immunogenicity study of H6:IC31 (and H4:IC31 and BCG revaccination) in 84 MTB-uninfected, HIV-negative adolescents in South Africa (<a href="#">NCT02378207</a>).</li> <li>2. Completed a phase I the safety/immunogenicity study of H6:IC31 given with and without COX-2 inhibitors as a therapeutic adjunct in 39 adults being treated for TB disease in Norway (<a href="#">NCT02503839</a>). Indication: therapeutic adjunct. Results not yet published.</li> <li>3. 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 successfully treated for DS-TB in South Africa and Tanzania (<a href="#">NCT03512249</a>). Indication: POR. Expected completion: April 2022.</li> </ol>			
<b>BCG revaccination</b>	Whole-cell <i>M. bovis</i>	Gates Medical Research Institute	Phase IIb
<ol style="list-style-type: none"> <li>1. Undergoing a phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in 1,800 BCG-vaccinated, MTB-uninfected adolescents in South Africa (<a href="#">NCT04152161</a>). Indication: POI (sustained QFT conversion). Estimated completion: April 2023.</li> <li>2. Planning for a phase IIa safety/immunogenicity study of VPM1002, BCG revaccination, and ID93/GLA-SE in HIV-unexposed and HIV-exposed children aged 8–14 years. Protocol number: CAP555.<sup>1</sup></li> </ol>			
<b>MTBVAC</b>	Live, genetically attenuated MTB	Biofabri, University of Zaragoza, TBVI, IAVI, U.S. Department of Defense	Phase IIa
<ol style="list-style-type: none"> <li>1. <b>Published results</b> of a phase Ib/IIa safety/immunogenicity study comparing MTBVAC to BCG in 36 infants with a safety arm in 18 BCG-vaccinated adults in South Africa (<a href="#">NCT02729571</a>).</li> <li>2. Undergoing a phase IIa dose-defining safety/immunogenicity study in 99 South African infants (<a href="#">NCT03536117</a>). Indication: in preparation for future POD trial in infants. Expected completion: December 2020.</li> <li>3. Undergoing a phase Ib/IIa study in 120 adults with and without MTB infection in South Africa (<a href="#">NCT02933281</a>). Indication: in preparation for future POD trial in adults. Expected completion: March 2021.</li> </ol>			
<b>ID93/GLA-SE</b>	Protein/adjuvant subunit vaccine	Quratis, IDRI, NIH (ACTG and IMPAACT)	Phase IIa
<ol style="list-style-type: none"> <li>1. Undergoing a phase IIa safety, immunogenicity, and efficacy study of ID93/GLA-SE (vs. placebo) in 107 BCG-vaccinated, MTB-uninfected healthcare workers in South Korea (<a href="#">NCT03806686</a>). Indication: POI (QFT conversion). Estimated completion: March 2020.</li> <li>2. Undergoing a phase Ib safety/immunogenicity study in 36 BCG-vaccinated, MTB-negative adolescents in South Korea (<a href="#">NCT03806699</a>). Expected completion: September 2020. Following this, Quratis is reportedly planning a phase IIb trial in 1,000 adolescents and adults in South Korea, Indonesia, the Philippines, Thailand, and China. Indication: POD (unconfirmed).</li> <li>3. Planning for a phase IIa safety/immunogenicity study of ID93/GLA-SE given as a therapeutic adjunct in people being treated for DS-TB. Protocol number: A5397.<sup>2</sup></li> <li>4. Planning for a phase IIa safety/immunogenicity study of VPM1002, BCG revaccination, and ID93/GLA-SE in HIV-unexposed and HIV-exposed children aged 8–14 years. Protocol number: CAP 555.<sup>1</sup></li> </ol>			
<b>RUTI</b>	Fragmented MTB	Archivel Farma	Phase IIa
<ol style="list-style-type: none"> <li>1. 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 (<a href="#">NCT02711735</a>). Indication: therapeutic vaccination. Expected completion: July 2020.</li> </ol>			
<b>TB/FLU-01L &amp; TB/FLU-04L</b>	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase IIa
<ol style="list-style-type: none"> <li>1. Reportedly planning for a phase IIa study in MTB-infected adults (no clinical trials record available).</li> </ol>			



Agent	Type	Sponsor(s) and Major Partners	Status*
<i>Notable recently completed, ongoing, and planned clinical trials.</i>			
<b>GamTBvac</b>	Protein/adjuvant subunit vaccine	Ministry of Health of the Russian Federation	Phase IIa
1. Completed a phase IIa safety/immunogenicity study in 180 BCG-vaccinated, MTB-uninfected adult volunteers ( <a href="#">NCT03878004</a> ) in Russia. Results not yet published.			
<b>ChAdOx1 85A + MVA85A</b>	Viral vector	Oxford University	Phase I/IIa
1. <b>Published results</b> of a phase I safety/immunogenicity study of ChAdOx1 85A (prime) followed by MVA85A (boost) in 42 adult volunteers in the United Kingdom ( <a href="#">NCT01829490</a> ).			
2. Undergoing a phase I/II dose and age de-escalation 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 with BCG revaccination in 60 adolescents ( <a href="#">NCT03681860</a> ). Estimated completion: January 2020.			
2. Undergoing a phase I safety/immunogenicity study of ChAdOx1 85A (aerosol versus intramuscular vaccination) in 30 adult volunteers in Switzerland ( <a href="#">NCT04121494</a> ). Estimated completion: June 2020.			
<b>BCG (aerosol)</b>	Whole-cell <i>M. bovis</i>	University of Oxford	Phase I
1. Completed a phase I human challenge trial to evaluate safety/immunogenicity of BCG (aerosol versus intradermal vaccination) in 46 BCG-naïve adult volunteers in the United Kingdom ( <a href="#">NCT02709278</a> ). Results not yet published.			
2. Undergoing a phase I human challenge trial to evaluate safety of aerosol BCG in 65 BCG-vaccinated, MTB-uninfected adult volunteers ( <a href="#">NCT03912207</a> ). Results expected: December 2020.			
<b>Ad5Ag85A (aerosol)</b>	Viral vector	McMaster University, CanSino	Phase I
1. Undergoing a phase I safety/immunogenicity study of Ad5Ag85A (aerosol vs. intramuscular vaccination) in 28 BCG-vaccinated healthy volunteers in Canada ( <a href="#">NCT02337270</a> ). Expected completion: June 2021.			
<b>AEC/BCO2</b>	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase I
1. Completed a phase I safety/immunogenicity study in 25 adult volunteers in China ( <a href="#">NCT03026972</a> ). Results not yet published.			
2. Undergoing a phase Ib safety/immunogenicity study in 30 adult volunteers in China ( <a href="#">NCT04239313</a> ). Estimated completion: December 2020.			
* Status indicates the most advanced phase of either ongoing or recently completed trials.			
** Expected completion date is the "estimated primary completion date" in <a href="#">ClinicalTrials.gov</a> , or the date of final data collection for the primary outcome measure. This is not the date by which results will be available.			
ACTG: AIDS Clinical Trials Group	M. bovis: Mycobacterium bovis	PLHIV: people living with HIV	
ChAd: chimpanzee adenovirus vector	MDR-TB: multidrug-resistant tuberculosis	POD: prevention of disease	
BCG: bacillus Calmette-Guérin	MIP: Mycobacterium indicus pranii	POI: prevention of infection	
COX-2: cyclooxygenase-2	M. obuense: Mycobacterium obuense	POR: prevention of recurrence	
DS-TB: drug-susceptible tuberculosis	MTB: Mycobacterium tuberculosis	QFT: QuantiFERON	
EDCTP: European and Developing Countries Clinical Trials Partnership	M. vaccae: Mycobacterium vaccae	rBCG: recombinant bacillus Calmette-Guérin	
ICMR: Indian Council of Medical Research	MVA: modified vaccinia virus Ankara	SII: Serum Institute of India	
IDRI: Infectious Disease Research Institute	NIH: U.S. National Institutes of Health	SSI: Statens Serum Institut	
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network		TB: tuberculosis	
		TBVI: TuBerculosis Vaccine Initiative	
Sources: Information compiled from <a href="#">ClinicalTrials.gov</a> 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.			
Unlinked references:			
1. Cranmer, Lisa, and Day, Cheryl (Emory University, Georgia, USA). Personal communication with: Mike Frick (Treatment Action Group, New York, USA). 2020 July 31..			
2. Churchyard Gavin Cross-network TB vaccines working group update. Presentation to: ACTG Tuberculosis Transformative Science Group semi-annual meeting. 2020 June 15			

**M72/AS01E: preparing for phase III, pursuing licensure**

M72/AS01E is a subunit TB vaccine composed of an antigen (M72) and an adjuvant (AS01E). The M72 antigen is a fusion of Mtb32A and Mtb39A, two MTB proteins. AS01E is an adjuvant system developed by GlaxoSmithKline (GSK) that contains two active compounds designed to stimulate the immune system: MPL (3-deacylated monophosphoryl lipid) and QS-21 (*Quillaja saponaria* Molina: fraction 21).

In more than coincidence, many of the IDRI scientists who developed ID93/GLA-SE contributed to early work on another subunit TB vaccine candidate: M72/AS01E. Last year's *Pipeline Report* reviewed positive results from the primary analysis of a **phase IIb trial** assessing the safety and efficacy of M72/AS01E compared with placebo in over 3,500 HIV-negative, QFT-positive adults in Kenya, South Africa, and Zambia.<sup>24</sup> In the primary analysis, M72/AS01E conferred 54% (90% CI: 13.9–75.4) protection against developing bacteriologically confirmed pulmonary TB disease.<sup>25</sup>

The primary analysis occurred when all participants had completed at least two years of follow-up after receiving two doses of either M72/AS01E or placebo. Investigators from GSK have since presented and published final results based on data from three years of follow-up. In the final analysis, 13 participants in the group receiving M72/AS01E developed TB compared with 26 participants in the placebo arm for an estimated vaccine efficacy of 49.7% (90% CI: 12.1–71.2).<sup>26</sup> Initial subgroup analyses based on the primary findings had pointed toward higher vaccine efficacy among younger participants and among men; these results did not hold in the final analysis. In both the primary and final analyses, M72/AS01E appeared safe, was well tolerated by participants, and elicited an immune response. Encouragingly, vaccine efficacy was similar at the end of years 2 and 3, and investigators observed sustained vaccine-specific antibody and T-cell responses through the duration of the study.<sup>27</sup>

Two aspects of the M72/AS01E story deserve attention here. First, the handoff of M72/AS01E from GSK to the **GMRI** and the implications this has for access and benefit sharing. Second, the GMRI's clinical development plans for the vaccine.

M72/AS01E access and benefit sharing: GSK developed M72/AS01E and conducted the phase IIb trial with Aeras and through the support of **many public funders**, but the future of the vaccine rests with the GMRI. In January 2020, GSK announced that it had licensed M72/AS01E to the GMRI for "continued development and use in low-income countries with high TB burdens."<sup>28</sup> The license settled a simmering anxiety in the TB field that despite the positive efficacy signal in the phase IIb trial, GSK would not advance M72/AS01E into the larger phase III study required for regulatory approval.<sup>29</sup> Under the license, that responsibility now falls to the GMRI, which will lead vaccine development and sponsor future clinical trials. In a February 2020 communication with TAG and RESULTS UK,

The M72/AS01E **phase IIb trial** was sponsored by GSK and funded by GSK and Aeras (which has now merged with IAVI).

The Gates Medical Research Institute (**GMRI**) is a nonprofit biotech organization and a wholly owned subsidiary of the Gates Foundation. Based on Boston, the GMRI's mission is to translate preclinical discovery into clinical development for technologies addressing TB, malaria, enteric/diarrheal disease in children, and maternal mortality.

The **many public funders** that contributed to the M72/AS01E development program include the U.K. Department for International Development, the Dutch Directorate-General for International Cooperation, the Australian Department for Foreign Affairs and Trade, and the European Commission. The US National Institutes of Health funded earlier work on the M72 antigen.

spokespersons for GSK clarified that the M72/AS01E license covers “low-income countries with a high TB burden, as well as some middle-income countries with a high TB burden. GSK will retain rights outside the territory licensed to Gates MRI.”<sup>30</sup> GSK has not provided a list of which countries qualify as low and middle income under the arrangement.

The agreement sounds simple enough, but there is a risk that the GMRI-GSK license splits the kitchen to cook meals separately, so to speak, by taking a single product (M72/AS01E) and assigning its constituent parts (M72 and AS01E) to different owners. The GMRI will manufacture the M72 antigen following a technology transfer from the company, and GSK will provide the AS01E adjuvant. As detailed in the 2019 *Pipeline Report*, AS01E belongs to a highly successful (and lucrative) adjuvant system family that undergirds two licensed GSK vaccines (**Shingrix™** and **Mosquirix™**) and is a part of experimental vaccines against illnesses ranging from various cancers to Marburg virus to Alzheimer’s disease.<sup>31</sup>

The company’s reticence to part with AS01E is unsurprising. This decision to retain control over AS01E merits full public disclosure of the terms under which GSK will supply the adjuvant for both the M72/AS01E clinical development program and eventual commercialization if the vaccine proves successful in phase III. According to GSK, “the agreement includes provisions to ensure there is sufficient supply of adjuvant for the clinical development and first adoption in developing countries with a high TB burden. For broader implementation, GSK is committed to work with our partners to ensure there is **sufficient supply**.” Public disclosure of the license—or at a minimum its provisions governing supply, pricing, and access—is further justified by the fact that the **QS-21 molecule** in AS01E originates in traditional knowledge held by the Mapuche people of the Andes. The development and commercialization of Indigenous knowledge of genetic resources such as QS-21 is subject to **international legal standards** on access and benefit sharing (ABS); free, prior, and informed consent (FPIC) of the knowledge holders; and fair use under mutually agreed terms (MAT).

Regulatory approval of M72/AS01E is years away. That makes the present the right time to address access and benefit sharing. For its part, GSK has defined its role narrowly as supplying the adjuvant and retaining marketing rights in high-income/low-TB-burden countries. A press release announcing the license quotes GSK president of global affairs Philip Thomson: “For us, this type of alliance means we can take a more sustainable approach to global health, focusing our efforts and expertise on science and research, while partnering with others to ensure their development and delivery.”<sup>32</sup> This represents an inversion of the prevalent ‘big pharma’ business model, in which companies spend more on development and delivery than on scientific research. It also begs the question of why the world’s largest vaccines company by revenue needs “a more sustainable approach to global health.”<sup>33</sup> The need actually points in the other direction: in order to sustain itself through pandemics new (COVID-19) and old (TB), global health needs a fairer contract with big pharma. At a minimum, the TB community needs to see

In 2019, GSK reported that its **Shingrix™** vaccine against shingles (herpes zoster) generated £1.81 billion in turnover, driving growth of 21% (AER) in the company’s vaccine division.

**Sufficient supply** is a legitimate concern since the QS-21 molecule in AS01E can only be derived from its natural source, the soapbark tree. Past shortages of the Shingrix™ vaccine have been partly attributed to QS-21 sourcing issues.

For a detailed review of the provenance of **QS-21** in traditional knowledge held by indigenous peoples, see TAG’s 2019 TB vaccines *Pipeline Report*.

**International legal standards** establishing rules of ABS, FPIC, and MAT are set forth in the *Nagoya Protocol* and the *Bonn Guidelines*, both instruments of the Convention on Biological Diversity.

the terms of the GSK-GMRI license so that all stakeholders—potential funders of the M72/AS01E phase III trial, the TB-affected communities that will host the study, and the individuals at risk of TB who will be expected to participate in it—can understand how their contributions will translate into the advent of an affordable, accessible public health good.

M72/AS01E clinical development: The GMRI is drawing up plans for a phase III placebo-controlled efficacy trial of M72/AS01E and a smaller phase II safety/immunogenicity study in PLHIV.<sup>34</sup> The study in PLHIV will enroll 400 people in South Africa. Participants will be 16–35 years old, on ART for at least three months, and virally suppressed with CD4 cell counts  $\geq 200$ . The study will randomize participants to receive either two doses of M72/AS01E or placebo and follow them for safety. Secondary objectives will explore immunogenicity, that is, M72/AS01E-specific antibody and cellular immune responses. The GMRI hopes to open the study for enrollment in November 2020.<sup>35</sup>

The phase II study in PLHIV will use vaccine from the same clinical trials material used in the phase IIb study. This study will add safety and immunogenicity data to the **earlier studies of M72/AS01E in PLHIV** sponsored by GSK and is intended to support the inclusion of PLHIV in the phase III trial.<sup>36</sup> The GMRI deserves commendation for enabling the inclusion of PLHIV in phase III. Too often, PLHIV are either excluded from vaccine efficacy trials where safe inclusion is possible.<sup>37</sup> The effect is to exclude PLHIV from the potential direct benefit of receiving new vaccines.

As currently envisaged, the phase III trial will aim to demonstrate the efficacy of the vaccine in preventing TB disease in a population of **QFT**-positive and **QFT**-negative adults. The GMRI will power the study to demonstrate efficacy for the prevention of disease (**POD**) in the overall population and among **QFT**-positive participants, and to detect efficacy for the prevention of infection (**POI**) in **QFT**-negative people.<sup>38</sup> The intent is to ensure the vaccine can be given to someone irrespective of **QFT** status in order to avoid making **IGRA** testing a requirement for M72/AS01E administration.<sup>39</sup> Pairing a vaccine with an accompanying diagnostic test could limit scale-up by adding expense and logistical complexity to implementation efforts. There is also a chance that currently available **IGRA** tests such as **QFT** may be replaced by more sensitive, or altogether different, tests for TB infection by the time the phase III trial concludes.

By including **QFT**-negative individuals, the phase III trial will differ from the phase IIb study, which only enrolled people with a positive **QFT**. Other aspects of the trial's design require careful deliberation. To inform these discussions, the GMRI is running simulations to understand how assumptions made about the prevalence of **MTB** infection, TB incidence, and other factors that may influence vaccine efficacy (e.g., **BCG** vaccination history, HIV status, age) will affect the trial's size, design, and statistical analysis plan.<sup>40</sup> Regardless of the assumptions made, the trial will be much larger than the phase IIb study, enrolling up to 10,000 participants per arm.

**Earlier studies of M72/AS01E in PLHIV** evaluated safety and immunogenicity in both people on ART and ART-naïve individuals in India (NCT01262976) and in people on ART in Switzerland (NCT00707967).

QuantiferON (**QFT**) is a type of test made by Qiagen and known as an interferon-gamma release assay (**IGRA**). **IGRA**s are used to infer infection with TB but do not measure infection directly.

TB vaccine trials can be classified according to three overarching objectives:

1. **POI** trials assess whether a vaccine prevents infection with **MTB**.
2. **POD** trials assess whether a vaccine prevents active TB disease.
3. **POR** trials assess the ability of a vaccine to prevent either relapse or reinfection in people who have completed TB treatment.

Any assumptions will carry some uncertainty. These uncertainties can be tempered, but not eliminated, by thorough preparation. To prepare for the phase III study, the GMRI will conduct a large epidemiological study to assess the prevalence of MTB infection and TB incidence at potential trial sites. The study will enroll up to 8,000 participants at dozens of sites and follow them over one to two years for QFT conversion and TB diagnosis.<sup>41</sup> This epidemiological study also affords the opportunity to train sites to conduct the efficacy trial and to start engaging local communities before enrollment opens. The goal is for the epidemiological study to open in late 2021 and the phase III trial in 2023. If it takes the phase III trial four or five years to accumulate the number of TB disease events required to assess efficacy, then 2028 is the earliest results could be available. This timeframe is daunting but necessary to unequivocally demonstrate the efficacy and safety of M72/AS01E in a general population in high-TB-burden countries.

Before finalizing the phase III study design, the GMRI will need to make decisions on two other important points:

- **Adolescent inclusion:** Will the phase III trial open enrollment to adolescents (the phase IIb study of M72/AS01E did not)? Currently, the GMRI's proposal is to enroll people aged 16–35 years. This age range reflects the need to recruit participants at high risk of developing active TB disease in order to observe enough endpoints for the efficacy analysis. As a group, adolescent participants (especially younger adolescents) may be less likely than adults to enter the trial with TB infection and may therefore contribute fewer TB disease endpoints.<sup>42</sup> Recent TB drug trials have demonstrated that it is possible to include a modest cohort of adolescents even if the trial is primarily powered on outcomes among adult participants.<sup>43</sup> Like the inclusion of PLHIV, the involvement of adolescents in phase III trials broadens the equity proposition of studies by making their benefits accrue to a larger age group. If the trial showed efficacy against the POI endpoint among QFT-negative participants, then it would be possible to deliver the vaccine through school-based campaigns.
- **TPT and standard of care:** Should the phase III trial offer participants TPT? The question was always ethically resonant but is unavoidable now that revised WHO guidelines recommend TPT for a much broader group of people than just PLHIV and young children. This broader recommendation includes HIV-negative people with known TB exposure or close contact with someone with TB disease.<sup>44</sup> For the first time, the recommendation to consider TPT for HIV-negative household contacts applies to all countries, regardless of income or TB incidence level, including those countries likely to host the M72/AS01E phase III trial (previous recommendations on this point were directed toward high-income, low-TB-incidence settings). TPT is a highly effective intervention for preventing TB; giving TPT to participants in a vaccine study will have huge implications for the feasibility of demonstrating vaccine efficacy over and above the high level of protection afforded by TPT.

Certainly, any PLHIV who enroll into the phase III trial must be offered TPT. The WHO has recommended TPT for all PLHIV since 2011.<sup>45</sup> The current guidelines state: "Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a

comprehensive package of HIV care” (emphasis added).<sup>46</sup> The question is less clear cut for HIV-negative adult trial participants. Here, the language of the WHO guidelines shifts from “should” to “may”: “Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment” (emphasis added).<sup>47</sup> The word “may” suggests that there are circumstances in which not giving TPT to such persons might be acceptable. Is a phase III TB vaccine trial one such circumstance?

This is a freshly urgent conversation for TB vaccine developers that taps into a long history of debate about the ethics of standard of care in biomedical research. **The Declaration of Helsinki** states that new interventions must be tested against “the best proven intervention(s)” except in select circumstances where no proven intervention exists or “where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one... is necessary to determine the efficacy or safety of an intervention.”<sup>48</sup> This may give TB vaccine developers an opening to test M72/AS01E without accompanying TPT. If TPT is not offered to HIV-negative adults in the phase III trial, then investigators must, at a minimum, fully inform all participants about the efficacy of TPT and offer them the choice to take it instead of enrolling (at this point in the TB epidemic, all countries in the world have access to at least one WHO-recommended TPT option). It is incumbent on the trial team to make its case based on “compelling and scientifically sound methodological reasons;” the Declaration of Helsinki cautions that “extreme care must be taken to avoid abuse of [the] option” not to compare an experimental treatment/vaccine to the **best proven and available intervention**.<sup>49</sup>

How should the GMRI and other developers make decisions on the role of TPT in TB vaccine trials? Framing matters: one can view TPT as an obstacle to vaccine development or as an opportunity to ethically develop effective TB vaccines in concert with other preventive interventions. Here, TB vaccine developers can draw inspiration from how the HIV vaccine field has defined the role of PrEP in HIV vaccine trials. For example, in discussing the role of PrEP in HIV vaccine trials at AIDS2020, Susan Buchbinder from the University of California–San Francisco outlined three study design structures: (1) *compare* an experimental product to existing prevention (PrEP), (2) *layer* by comparing an experimental vaccine to placebo on top of using existing prevention, or (3) *combine* by comparing existing prevention options **combined** with experimental vaccines.<sup>50</sup> Scientists should articulate similar possibilities for TPT and TB vaccine trials.

From the beginning, conversations about PrEP and HIV vaccine trials made room for a plurality of voices and centered on the perspectives of people with and at risk of HIV.<sup>51</sup> Decisions on the “standard of prevention” for TB vaccine trials can only claim consensus if arrived at after close consultation with TB-affected communities and representatives from civil society. These consultations should be convened by neutral arbiters and not by the GMRI or other developers with a financial or scientific interest in the outcome. And they must occur before future TB vaccine efficacy trials—of M72/AS01E or other candidates—are initiated.

Published by the World Medical Association, the **Declaration of Helsinki** is a landmark global document on the ethics of research involving humans.

Access to the **best proven and available interventions** is a requirement of the *human right to science*, which obligates governments to provide “the best available applications of scientific progress necessary to enjoy the highest attainable standard of health.”

An example of the **combined** approach is the PrEPVacc trial, which will compare two PrEP options (F/TAF and F/TDF) plus vaccine and then remove the PrEP regimens after six months to follow the effects of the vaccine.

**BCG revaccination: confirming what we thought we saw in phase IIa**

BCG is a live attenuated form of *Mycobacterium bovis*, the organism that causes TB in cattle. Given to infants soon after birth, BCG protects children against TB meningitis and other severe forms of childhood TB. It is often touted as the most widely administered vaccine in the world.

In 2018, Aeras presented results from a phase IIa trial of BCG revaccination in 990 adolescents 12–17 years old in Worcester, South Africa.<sup>52</sup> (The trial also involved the experimental H4:IC31 vaccine, which has since been discontinued.) All adolescents entered the trial uninfected with TB, as indicated by a negative QuantiFERON-TB Gold test (i.e., participants began the study QFT negative). The trial looked at whether revaccination with BCG prevented adolescents from acquiring MTB infection (as indicated by a positive QFT), and whether those who acquired infection maintained a positive QFT (sustained conversion) on repeat readings over a certain period of time, or whether subsequent QFT tests changed back to negative (reversion). The trial's primary endpoint was QFT conversion (negative to positive) three months post-randomization. The secondary endpoint—sustained QFT conversion—is where things got really interesting.<sup>53</sup>

Sustained QFT conversion is not an intuitive endpoint. But unpacking it is essential for understanding why this phase IIa trial inspired the larger phase IIb study that followed. In the phase IIa study, an outcome of sustained QFT conversion required a positive reading on three consecutive QFT tests over six months. IGRA tests such as QFT detect immune sensitization to MTB antigens, but they do not measure MTB infection directly. QFT turns positive when infection with MTB occurs, but sometimes a person will have a positive QFT turn negative upon subsequent re-testing. This positive-to-negative reversion is not well understood—does it signal the body clearing infection, reflect an artifact of the test itself, or mean something else?<sup>54</sup> Imagine inferring the presence of something by looking for its shadow. At first glance, a cast shadow makes one think something is present, but when one looks again, at the same time of day and under similar conditions, the shadow might be gone or appear to be something else. Pinpointing sustained MTB infection within the limits of QFT is similarly vexing and interpretive.

BCG revaccination did not prevent initial QFT conversion (the primary endpoint). But it did reduce the rate of sustained conversion (the secondary endpoint): 6.7% of people in the BCG group converted from negative to positive and kept a positive QFT reading versus 11.6% in the placebo group. Based on this difference, revaccination with BCG had an estimated vaccine efficacy of 45.4% (95% CI: 6.4–68.1) against sustained QFT conversion.<sup>55</sup> Rigorous discovery work on stored specimens from the study will hopefully shine additional light on this signal and what it means.<sup>56</sup> In parallel to this biomarker discovery, the study's investigators called for further clinical trial evaluations of BCG revaccination: “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” (emphasis added).<sup>57</sup>

H4:IC31 was a subunit vaccine developed by the Statens Serum Institute and Sanofi Pasteur. Based on the outcome of the phase IIa trial discussed here, Sanofi Pasteur decided not to continue developing H4:IC31. The discussion in this section therefore focuses on the BCG revaccination results.

The italicized emphasis in the above quotation conveys the investigators' proposal that the phase IIa POI study be followed by a POD trial. The GMRI has taken a different tack by supporting another POI trial of BCG revaccination. In 2019, the GMRI began a phase IIb POI study comparing the efficacy, safety, and immunogenicity of BCG revaccination versus placebo in 1,800 QFT-negative South African adolescents aged 10–18 years. The primary endpoint of the BCG ReVax study is sustained QFT conversion, defined similarly to the secondary endpoint in the earlier phase IIa study.<sup>58</sup> BCG ReVax participants must enter the study as QFT negative, HIV negative, and previously vaccinated with BCG (demonstrated either by medical record or healed BCG scar). The study will randomize participants to receive either BCG or placebo and then follow them for a minimum of four years; participants will complete a QFT test every six months. Essentially, the trial seeks to verify the positive signal seen in the phase IIa study in an adolescent population that is nearly twice as large and with sustained conversion as the primary, not a secondary, endpoint. (The protocol contains some other important technical differences from the earlier study, e.g., using the QuantiFERON-TB Gold Plus assay rather than the older-generation QuantiFERON-TB Gold in-tube assay.)<sup>59</sup> The trial will also seek to identify and validate immune correlates of BCG-mediated protection, part of a larger biomarker discovery initiative using stored samples from the phase IIa BCG revaccination study.

Will the BCG ReVax trial be enough, if successful, to change BCG vaccination policy? Some scientists have argued that “in order to inform policy recommendations for BCG revaccination, the significance of efficacy against the POI endpoint... should be confirmed in trials that test efficacy of vaccination of IGRA-negative populations against prevention of TB disease.”<sup>60</sup> By this thinking, POI studies should be followed by POD trials. Partly this is about uncertainty concerning whether a vaccine that prevents (sustained) infection will also prevent TB disease. If regulators agree with this approach, that would mean studying the efficacy of BCG revaccination against a POD endpoint before making a recommendation to revaccinate adolescents with BCG.

### ***TB vaccine R&D and COVID-19: it's not entirely bad news***

By the time the BCG ReVax trial finishes, the BCG vaccine will be over a century old. The timescale of TB vaccine R&D offers an important reminder that good science does not always progress in a straight line at warp speed. More often, vaccine development entails careful, iterative work, a mix of rational design and empirical development shaped by twists and turns. Some turns respond to scientific advances, while others result from external forces beyond the scientist's direct control—a global pandemic caused by a novel coronavirus, for instance.

There is a real risk that the COVID-19 pandemic will upset even the most perfect of plans drawn up by TB vaccine developers. The global acceleration of COVID-19 in February and March had the immediate effect of temporarily halting most



TB clinical research. Trial sites had to suspend study enrollment and rethink everything from participant visit schedules to adverse event monitoring to sample transport to community engagement.<sup>61</sup> Research is resuming in some locations, but a resurgence in COVID-19 would impose further delays. Countries such as India and South Africa that host a majority of the world's TB vaccine clinical trials are also grappling with the largest COVID-19 epidemics in their regions. In the long run, advocates worry that massive investments in COVID-19 research will divert funding away from TB and other global health challenges.<sup>62</sup> The governments that provide the most funding for TB vaccine R&D (e.g., the United States, the United Kingdom, India) are weathering unprecedented public health emergencies exacerbated by deep-set political dysfunction and attendant crises of record unemployment, reduced tax revenues, and depleted state budgets.<sup>63</sup> The 'vaccine nationalism' transforming the race for a COVID-19 vaccine into a zero-sum contest between national governments may amplify public mistrust in science—already a fragile resource in vaccine development.<sup>64</sup>

The forecast is grim and difficult to predict. What is clear is that past investments in TB research have put the world in a better place to respond to COVID-19. Developers have leveraged scientific concepts, tools, infrastructures, and even some candidate vaccines and diagnostic technologies originally developed for TB to advance COVID-19 research.<sup>65</sup> The cross-pollination is particularly evident for TB immunology and vaccinology. These **broad benefits** of TB research make a powerful case for increasing funding for TB R&D so that research activities—including those with potential cross-disease applications—continue to progress in the face of COVID-19.

In terms of cross-disease benefits, the most obvious area of overlap is research to test whether BCG protects vulnerable populations against COVID-19. As reviewed by TAG in April 2020, the notion that BCG may help protect against COVID-19 arises from evidence of its so-called **nonspecific effects** i.e., that BCG confers protection against illnesses other than TB.<sup>66</sup> The WHO has compiled a “compendium of research projects at the interface of tuberculosis and COVID-19” that, as of August 18, 2020, listed 30 studies of BCG or **rBCG** vaccines against COVID-19.<sup>67</sup> Most are comparing BCG or rBCG (e.g., **VPM1002**) to placebo in healthcare workers or other high-risk populations such as the elderly. One of the first studies of BCG and COVID-19 is the BRACE trial in Australia, the Netherlands, and Spain. The BRACE trial is evaluating whether BCG vaccination (versus placebo) reduces the incidence of COVID-19 disease or severe COVID-19 disease in more than 10,000 healthcare workers over 12 months.<sup>68</sup>

Even if it works, BCG will not obviate the need to develop novel vaccines against COVID-19. Writing in *The Lancet*, WHO director-general Tedros Ghebreyesus and investigators from the BRACE trial and other BCG/COVID-19 studies described BCG as a potentially useful tool for blunting the impact of the pandemic among vulnerable populations and essential workers while the world waits for an efficacious COVID-19 vaccine: “If the BCG vaccine or another inducer of trained

The **broad benefits** of TB R&D—i.e., the ways that investing in TB research advances infectious disease research writ large and strengthen global epidemic preparedness—are reviewed in a [TAG policy brief](#).

Immunologically, these “**nonspecific effects**” may represent heterologous immunity (protection against one pathogen provides cross-protection against others) and/or trained immunity (BCG alters gene expression related to pathogen recognition and immune response).

Recombinant BCG (**rBCG**) is BCG that has been genetically modified for improved safety or efficacy. **VPM1002** is one example of an rBCG TB vaccine candidate.

immunity provides non-specific protection to bridge the gap before a disease-specific vaccine is developed, this would be an important tool in the response to COVID-19 and future pandemics.”<sup>69</sup>

Developers are pursuing similar studies involving other TB vaccine candidates. The WHO compendium lists several studies of VPM1002 and COVID-19 in Australia, Canada, Germany, and India.<sup>70</sup> Originally developed by the Max Planck Institute for Infection Biology, VPM1002 is licensed to Vakzine Projekt Management and sublicensed to the Serum Institute of India. Similar COVID-19 studies are underway for TB vaccine candidates **MIP** and **RUTI**. In addition, researchers in Australia have taken their prior work on rBCG to create a new, BCG-based COVID-19 vaccine candidate: BCG:CoVac.<sup>71</sup> The novel BCG:CoVac candidate has completed an initial preclinical study in mice and will enter further animal model work to select the best formulation while preparing for a phase I trial.<sup>72</sup> Relatedly, the TB vaccine candidate **MTBVAC** may be evaluated against COVID-19 based on evidence from mice challenged with *Streptococcus pneumoniae* (a kind of lethal pneumonia) that MTBVAC may induce similar nonspecific effects as BCG.<sup>73</sup>

Other potential vaccines against COVID-19 are making use of vaccine constructs and platforms developed, at least in part, through TB research. For example, the University of Oxford/AstraZeneca’s **ChAdOx1 nCoV-19** vaccine uses the ChAdOx1 viral vector, which has been studied in several TB vaccine clinical trials (including one that tested a novel aerosol delivery mechanism).<sup>74,75,76</sup> In China, CanSino is developing a COVID-19 vaccine based on the **Ad5** viral vector, which is also a part of the Ad5Ag85A TB vaccine (developed in partnership with Canada’s McMaster University and being tested under aerosol administration). Even COVID-19 human-challenge studies—though their utility remains much debated and ethically fraught—have benefitted from years of work to develop a safe human challenge model to aid TB vaccine development. Techniques and facilities used to develop a TB challenge model using aerosol BCG, led by researchers at the University of Oxford, have demonstrated the feasibility of aerosol pathogen challenge and built experience with monitoring immune responses in the lungs and peripheral blood.<sup>77</sup>

In short, today’s TB vaccine pipeline is an invaluable scientific resource with potential benefits that stretch far beyond the TB field. It took two decades of patient investment and careful scientific work to build this resource from the ground up, with only minimal resources at hand. Funding for TB vaccine R&D has never come close to matching the resources required to develop a new vaccine against the world’s deadliest infectious disease (as of September 2020, deaths from TB still outstripped those reported for COVID-19). In any given year, TB vaccine research receives one-seventh the money spent on HIV vaccine R&D—a pittance measured against the TB epidemic’s human toll.<sup>78</sup> Researchers had to fight for every dollar spent on TB research in the last 20 years. Over time, this struggle for funding conditioned the field to accept a fiscal austerity that the

**MIP**, a TB vaccine candidate consisting of whole-cell *M. indicus pranii* (sometimes called *Mycobacterium W*), is being studied in critically ill COVID-19 patients in India (NCT04347174).

**RUTI**, a TB vaccine candidate made of fragmented *M. tuberculosis*, is registered for a clinical trial of protection from COVID-19 in healthcare workers (NCT04453488).

**MTBVAC** is a live, attenuated form of *M. tuberculosis* weakened through the deletion of two virulence genes. The vaccine was developed by scientists at the University of Zaragoza in Spain.

**ChAdOx1 nCoV-19** has been renamed AZD1222. ChAdOx1 is a chimpanzee adenovirus vector.

**Ad5** is a common viral vector in vaccine development for a number of diseases. An HIV vaccine based on the Ad5 vector was discontinued after two efficacy trials (STEP and Phambili) showed that participants receiving the vaccine had a higher risk of HIV acquisition than those getting placebo; see TAG’s [information note](#) on Ad5 and HIV risk for more information.

COVID-19 pandemic has revealed to be the total sham many advocates knew it to be all along. The speed at which governments have awarded tens of billions of dollars in contracts for COVID-19 vaccine research—including committing money toward candidates with almost no clinical trial data attesting to their safety or efficacy beyond small studies trumpeted by press release alone—should shatter the timidity with which TB vaccine developers ask for modest funding and accept far less. The many plans for advancing TB vaccine research being written this year will mean nothing if not paired with commitments to fully fund their execution. It is past time to start expecting more.

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