

Pipeline Report » 2019

Tuberculosis Vaccines

A large, abstract graphic composed of numerous overlapping, flowing red lines that create a sense of movement and complexity, resembling a stylized map or a network of paths. The lines are thin and vibrant red, set against a solid black background.

TAG

Treatment Action Group

The TB Vaccine Pipeline

M72/AS01E: Between Nature and Licensure

By Mike Frick

The white flowers bloom in summer, in clusters of three to five blossoms, each shaped like a five-pointed star. The leaves that surround these white flowers are green, glossy, and gently toothed at their edges. The bark covering the limbs that lift this dense foliage is gray, like ash at the end of a fire.¹ Known in Latin as *Quillaja saponaria*, the soapbark tree is native to Chile, accustomed to high altitudes, and tolerant of drought and poor soils.² This is not a spindly tree that hugs a narrow geographic range and only rarely grows outside of it. One can find the soapbark tree far from Chile, standing on the grounds of the national arboretum in Australia and shading the campuses of the University of California.^{3,4}

The soapbark tree is more than ornamental. Its inner bark is a rich source of saponins: bitter-tasting molecules with varied industrial and medicinal uses. When shaken in water, saponins foam like soap, giving *Quillaja saponaria* its name. In the language of the Mapuche—a people indigenous to the region of the Andes now divided between Chile and Argentina—*quillean* means “to wash.”⁵ This etymology signals that Andean peoples have recognized the soap-like properties of *Quillaja saponaria* since pre-Columbian times, in addition to using its bark to treat ailments such as chest pain and dysentery.⁶ Today, soapbark saponins lend their foaming properties to shampoos, laundry detergents, soft drinks, fire extinguishers, cosmetics, and pharmaceuticals.⁷ Concerning the last, a saponin molecule extracted from the soapbark tree called QS-21 is an important component of what may prove to be the world’s next tuberculosis (TB) vaccine—if only enough of it can be produced sustainably and affordably.

This dispatch from Treatment Action Group’s 2019 *Pipeline Report* takes a close look at this vaccine, known as M72/AS01E, in three sections. The first reviews positive results from the **primary analysis** of a phase IIb trial assessing the safety and efficacy of M72/AS01E compared to placebo in over 3,500 adults.⁸ Published in the *New England Journal of Medicine* (NEJM) on the eve of the first United Nations High-Level Meeting on TB, these results mark one of the most promising steps forward in the **century-long effort** to develop a new TB vaccine.

Turning this promise into public health benefit will depend on confirming the safety and efficacy of M72/AS01E in final analyses from the phase IIb trial, and then again in much larger phase III studies. The second section discusses possible paths forward for a phase III trial of M72/AS01E and some of the values at stake in debates about M72/AS01E’s future development.

The third section provides a primer on the AS01E component of M72/AS01E. AS01E is the **adjuvant system** used in the vaccine, and QS-21 is a key part of this adjuvant. Because some of the most difficult questions concerning future research on M72/AS01E hinge on access to AS01E—and to QS-21, in particular—activists, members of civil society, and funders of TB research must acquire a robust

Final results of this phase IIb study will be presented at the 50th Union World Conference on Lung Health in Hyderabad, India, in late October 2019.

The only licensed TB vaccine, bacillus Calmette-Guérin (BCG), was introduced in 1921. BCG protects infants and young children from severe forms of TB (e.g., TB meningitis and miliary TB) but offers little protection against pulmonary TB to adolescents and adults.

Adjuvants are used to boost the body’s immune response to a vaccine.

Adjuvant systems are combinations of different immunostimulatory molecules designed to provide broader and better protection than older, simpler adjuvants.

Antigens are substances—toxins, viruses, bacteria, or their parts—that provoke an immune response from the body.

Mycobacterium tuberculosis is the bacterium that causes TB infection and disease.

A week after publishing the phase IIb trial results, **Aeras** announced that it was ceasing operations and transferring its clinical assets and ongoing projects to another PDP, the International AIDS Vaccine Initiative (IAVI).

Interferon-gamma release assays (IGRAs) are blood-based tests that detect cell-mediated immune responses to MTB antigens (but do not measure MTB infection directly).

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

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

understanding of AS01E. This understanding should span technical questions of AS01E’s immunostimulatory effects, commercial considerations regarding its production and supply, and access concerns over its ownership. The TB vaccine field must also grapple with deeper moral questions about its origins in the natural world and roots in the traditional knowledge of Indigenous Andean Peoples, who long ago identified the medicinal value of *Quillaja saponaria*.

M72/AS01E is just one of 16 TB vaccine candidates under active clinical development. Ending the TB epidemic will, in all likelihood, require deploying more than one novel TB vaccine.⁹ Table 1 provides a comprehensive overview of candidate vaccines in the pipeline as well as recently completed, ongoing, and planned clinical trials (see p. 16).

I. Results from the Primary Analysis of a Phase IIb Clinical Trial of M72/AS01E

M72/AS01E is a subunit TB vaccine candidate owned by GlaxoSmithKline Biologicals (GSK). Subunit vaccines combine two distinct parts: proteins and adjuvants. The protein part is formed by **antigens**. When encountered by the immune system, these antigenic proteins induce an immune response. The adjuvant is a substance that boosts this immune response by, for example, making it stronger or longer-lasting. M72/AS01E consists of two ***Mycobacterium tuberculosis*** (MTB) proteins: Mtb32A and Mtb39A. Developed and owned by GSK, AS01E is the adjuvant used in the vaccine. AS01E is itself a combination of two immunostimulants—MPL (3-deacylated monophosphoryl lipid) and QS-21 (*Quillaja saponaria* Molina: fraction 21)—packaged together with liposomes.¹⁰

Study objectives and design

This phase IIb trial of M72/AS01E was sponsored by GSK and funded by GSK and **Aeras**, a not-for-profit product-development partnership (PDP).¹¹ Conducted in Kenya, South Africa, and Zambia, the trial enrolled 3,575 adults 18–50 years old, all HIV-negative and already infected with MTB (as indicated by a positive test for infection using the QuantiFERON-TB GOLD **interferon-gamma release assay**). Participants were randomly assigned to receive either two doses of M72/AS01E or two doses of placebo administered intramuscularly and spaced one month apart. Investigators followed all participants for three years after the second dose to see if they developed TB.¹² Because participants were already MTB-infected (IGRA-positive), this study is considered a prevention-of-disease (**POD**) trial, as opposed to a prevention-of-infection (**POI**) or prevention-of-recurrence (**POR**) trial.¹³

This phase IIb trial was carefully designed and well-conducted. The trial’s primary objective was to evaluate the efficacy of M72/AS01E in preventing progression from MTB infection to bacteriologically confirmed pulmonary TB disease.¹⁴ Since diagnosing TB can be challenging, the investigators devised a number of endpoints defined by varying levels of stringency. To meet the primary endpoint, a study participant had to 1) show clinical symptoms of TB (i.e., fever, weight loss, or cough lasting more than two

weeks), 2) test positive for TB on either culture or GeneXpert (or both), and 3) be HIV-negative at the time of TB diagnosis. Each participant with TB symptoms provided three sputum samples for testing; each sample was tested on both culture and GeneXpert (for a total of six tests). A positive culture or GeneXpert result on any one of the three samples was considered to be TB.¹⁵ Meeting the primary endpoint required that sputum be collected before the participant initiated TB treatment (since more time spent on treatment makes it more difficult to diagnose TB, as MTB bacterial counts drop as a result of effective chemotherapy).

Secondary study objectives assessed vaccine efficacy based on less stringent TB endpoint definitions (see Table 1 in the NEJM paper) as well as safety, **immunogenicity**, and vaccine **reactogenicity**.¹⁶

According to the study protocol, investigators could conduct the primary analysis after identifying 21 participants who developed TB, or after all participants completed 24 months of follow-up (whichever occurred first). The statistical analysis plan specified that the trial would meet its primary objective if the lower end of the two-sided 90% confidence interval (CI) for vaccine efficacy exceeded zero, which would indicate statistically significant levels of protection.¹⁷

Immunogenicity is the ability of a vaccine to elicit an immune response.

Reactogenicity refers to the ability of a vaccine to produce common, expected adverse reactions (e.g., mild injection-site swelling) that appear immediately and resolve quickly.

Main takeaway: *Incidence of TB disease among HIV-negative, MTB-infected adults was significantly lower among participants who received M72/AS01E compared with those who received placebo after two years of follow-up. M72/AS01E had an estimated efficacy of 54% (90% CI, 13.9–75.4). The vaccine appeared to be safe and demonstrated acceptable reactogenicity.*

Efficacy results

M72/AS01E met the statistical threshold for efficacy at the 90% confidence level. A preplanned analysis conducted after all participants completed two years of follow-up (mean 2.3 years) showed that participants who received two doses of M72/AS01E were half as likely to develop active TB disease as those who received placebo.¹⁸ Ten people who received M72/AS01E developed TB compared with 22 people in the placebo arm. This equated to a TB incidence of 0.3/100 person-years among M72/AS01E recipients versus 0.6/100 **person-years** in the placebo group, yielding an overall vaccine efficacy of 54% (90% CI, 13.9–75.4). This finding held after adjusting for potential confounding factors, including country of residence, sex, age, diabetes status, current smoking status, and previous vaccination with BCG. M72/AS01E also appeared to be efficacious at the stricter 95% confidence level (95% CI, 2.9–78.2).¹⁹

Investigators interrogated these results in a planned sensitivity analysis, which included only the 22 participants who tested positive for TB on at least two sputum samples via culture, GeneXpert, or both. Among these individuals, five received M72/AS01E and 17 placebo. The sensitivity analysis showed a vaccine efficacy of 70.3% (90% CI, 31.3–87.1; 95% CI, 19.4–89).²⁰

Person-years is a type of measurement that looks at both the number of people in a study and how much time each person spent in the study. It estimates how much “time at risk” participants contributed to a study.

Safety, reactogenicity, and immunogenicity results

There was no significant difference in the percentage of people reporting serious adverse events within six months of receiving the second dose of either M72/AS01E or placebo (1.6% for M72/AS01E versus 1.8% for placebo).²¹ Investigators did not observe any vaccine-related deaths; however, 24 participants died during the study, 14 from trauma-related injuries including gunshot, stabbing wounds, burns, and traffic accidents. Although unrelated to M72/AS01E, the high proportion of deaths due to trauma is worth calling out as a sobering reminder of the substantial interpersonal violence and public safety hazards so many young adults in these settings confront.²²

Participants who received M72/AS01E reported more adverse events within 30 days of vaccination than those in the placebo group (67.4% versus 45.4%). This difference stemmed from more injection-site reactions and flu-like symptoms among M72/AS01E recipients. Such common, mild, and transient adverse reactions can be taken as evidence of reactogenicity, as opposed to safety signals pointing to severe, long-term, or permanent adverse effects.²³ The proportion of people reporting such reactions appeared to be in line with previous M72/AS01E trials.²⁴

All participants (100%) in the M72/AS01E group mounted an immune response to the vaccine, indicating good immunogenicity.²⁵ Investigators measured immunogenicity by looking for **IgG** antibody responses to the M72 fusion protein in blood samples taken from a subset of participants.

Immunoglobulin G (IgG) is a type of antibody produced by B cells and plays a major role in humoral immunity.

Spotlight: Was M72/AS01E Safe in Pregnancy?

People who were pregnant were not eligible to enroll in this phase IIb trial. However, 33 participants became pregnant during the study.²⁶ Investigators followed these participants to determine pregnancy outcomes with respect to mother and fetus (with follow-up limited to six to eight weeks past the estimated date of delivery).²⁷ Twenty-eight participants delivered a healthy infant; no birth defects were noted. Investigators recorded three ectopic pregnancies and one spontaneous abortion; one pregnant participant was lost to follow-up. The trial's independent data-monitoring committee judged these events to be consistent with what one might expect to observe during pregnancy outside the study in the general population.²⁸ These results hint that the vaccine was not harmful in pregnancy, but more research is needed in this area to reach a firm conclusion.

Women of childbearing potential could enroll in the study if they agreed to use an adequate form of contraception, which was broadly defined. (However, the study did not provide participants with access to contraception.) Commendably, GSK did not require women with same-sex partners to use contraception as a condition of enrollment—a practice other TB clinical trials should adopt.²⁹

Subgroup analyses

Some of the most interesting findings from this phase IIb trial came from sub-group analyses. The results outlined below should be interpreted with abundant skepticism since the study was not statistically powered to detect differences between these subgroups.

- **Vaccine efficacy and age:** The efficacy of M72/AS01E appeared to be higher among participants 25 and younger (84.4%; 90% CI, 45.7–95.5) compared with those older than 25 (10.2%; 90% CI, -99.6–59.6).³⁰ Although this comparison was prespecified in the statistical analysis plan, the trial was not designed to detect differences in efficacy by age. (The decision to set 25 years as the cutoff for younger/older was selected arbitrarily before enrollment began and thus before investigators could know the median age of trial participants.³¹) There is some biological basis by which age might affect vaccine efficacy. Investigators pointed to time since primary MTB infection and recency of BCG vaccination as two factors associated with age that might mediate vaccine efficacy.³² If this finding holds in final analyses—based on all participants completing three years of follow-up—it could have major implications for the design of future M72/AS01E trials.
- **Vaccine efficacy and sex:** Investigators observed higher vaccine efficacy in men than in women. Among men, M72/AS01E had a vaccine efficacy of 75.2% (90% CI, 28.3–91.4) versus 27.4% among women (90% CI, -63.4–67.7). One should interpret this difference cautiously given a sex imbalance among younger participants in the trial: 66% of participants 25 and younger were men. In contrast, men and women were equally represented among older participants. The NEJM paper notes that this suggests “that the apparent difference observed according to sex was confounded by the effect of age and is probably an artifact.”³³
- **Vaccine efficacy and time since vaccination:** A **Kaplan-Meier** analysis charting the proportion of participants free of TB disease at different time points shows little difference between the M72/AS01E and placebo groups in the first nine months following the second dose of vaccine or placebo. TB incidence appears lower in the M72/AS01E group beginning in only the second year of follow-up. This result may be due to chance, though recent advances in TB basic science, particularly new notions about the interplay between MTB and the human immune system, may shed light on this observation.³⁴ Once seen as a state of dormant bacterial inactivity, MTB infection is now understood as a spectrum of host/pathogen biological activity encompassing categories termed “incipient TB” and “subclinical TB.”³⁵ These terms describe an infection that falls short of full-blown active disease but is progressing to such a point.

Kaplan-Meier curves are a type of time-to-event analysis and provide a way of looking not just at whether, but also when, an event (e.g., death, developing TB disease) occurs.

It is possible that some of the participants diagnosed with TB in the first year of follow-up may have had subclinical TB when they enrolled in the trial. M72/AS01E would have little expected effect against an infection already well on its way to becoming active disease.³⁶ The close clinical monitoring in the study may have increased the chance of detecting TB during such early stages of disease progression. In fact, one-third of the 32 TB diagnoses made during the study were confirmed by a single positive test (of the six performed on three sputum samples each for culture and GeneXpert). These “single-positive cases” were equally balanced across the study’s two arms and turned positive on culture “after an unusually long period or by PCR assay [GeneXpert] (3 cases) after an unusually high number of amplification cycles.”³⁷

This could happen if the samples contained few MTB bacteria, that is, the low bacterial load characteristic of incipient disease. If this was indeed the case, this phenomenon demonstrates the clinical importance of identifying people with incipient TB—a feat that will require developing better tests, ones able to predict progression from infection to disease (which current IGRA tests cannot do well) or more sensitive tests for TB disease that are able to pick up early disease states.

II. Building the Ship as We Sail It: Moving M72/AS01E into a Phase III Trial and toward Licensure

***... It's awkward
to have to do one's
planning in extremis
in the early years—
so hard to hide later.***

—Kay Ryan, *We're Building the Ship as We Sail It*³⁸

Evidence that a new vaccine may prevent TB disease among people with MTB infection should have made headlines around the world. After all, TB is responsible for over 1 billion deaths in the past 200 years and remains the leading cause of death from a single infectious agent globally.^{39,40} Yet, the publication of these promising phase IIb results generated ripples, not waves, in public attention.

To take just one indicator: the *New York Times* published two TB stories in September 2018, neither of which mentioned M72/AS01E. One carried the headline “Vaccines Against H.I.V., Malaria and Tuberculosis Unlikely, Study Says.”⁴¹ The second aired an internecine argument that referring to one-fourth of humanity as MTB-infected amounts to a “gross exaggeration” that has diverted resources away from addressing active, transmissible disease.^{42,43} Meanwhile, the bigger story went untold: The M72/AS01E phase IIb results provide the strongest evidence to date that developing a new TB vaccine is possible. They also hint that it might, in fact, be possible to preempt transmission by vaccinating people with MTB infection against developing disease—sidestepping tired debates pitting prevention against diagnosis and treatment.

GSK matched the lack of media coverage and public attention with a curious silence. The company issued a short press release and presented the study results at an annual TB conference, but it said little about next steps.^{44,45} The barely audible company reaction may have reflected caution while investigators waited to see if the positive findings from the primary analysis held in final analyses. But one got the distinct sense that GSK wanted to avoid having a conversation about the future.

The strongest response came not from the media, or GSK, or even the TB advocacy community, but instead from the World Health Organization (WHO). In a series of editorials published in prominent medical journals, WHO representatives made the case for quickly moving M72/AS01E into a phase III trial.^{46,47,48} Senior WHO leadership met with GSK in early spring 2019, and in April the WHO convened a “high-level

Mathematical modeling shows that a vaccine that prevents TB disease in adolescents and adults already infected with MTB would have the greatest impact on reducing TB incidence, projected out to 2050 (see Harris et al., 2016).

consultation on accelerating the development of the M72/AS01E tuberculosis vaccine candidate.”⁴⁹ The meeting sought “a way forward on the ideal pathway for the development of this vaccine, with a sense of collaboration and urgency.” The WHO followed this with a second meeting in July 2019 to build consensus on the “development pathway,” or how to design future clinical trials with the goal of licensing M72/AS01E as soon as possible.⁵⁰

Reports from both meetings reveal a valiant effort by the WHO to plan *in extremis*, or under difficult circumstances. To borrow the language of poet Kay Ryan, the WHO and its partners are “building the ship as they sail it,” pushing for further development in the face of scientific unknowns, financial uncertainty, and some corporate reticence to make clear, firm commitments. This is unfamiliar territory. With few phase III TB vaccine trials in history, there is little precedent to go by. Indeed, decisions taken on M72/AS01E could become precedential in shaping how other TB vaccines in the pipeline approach late-stage development.

Many parts must come together to make a whole. Before launching future trials of M72/AS01E, investigators must first confirm the primary results in final analyses of trial data. TB vaccine research and development (R&D) stakeholders must reach consensus on the design of future trials, including geographic scope, eligible populations, endpoint definitions, and subgroup analyses. Public- and private-sector interests must settle issues of access—which should include setting a target price for the final vaccine, drawing up plans for technology transfer, and establishing a clear understanding of patents, know-how, and trade secrets on the antigen and adjuvant components of M72/AS01E. Above all else, the field will need to raise massive amounts of **funding**.

Decisions taken in these early years will inevitably be second-guessed and scrutinized later when more is known. For now, two paths are emerging from the WHO consultations: one referred to as the “phase III **RCT** pathway” and the other as the “phase IIb **accelerated licensure** pathway.”⁵¹

- The phase III RCT pathway would seek to license M72/AS01E via a traditional regulatory process based on confirming the efficacy and safety of the vaccine in a phase III trial. Such a study would take place in high-TB-incidence settings and would enroll a similar population as that represented in the phase IIb trial in order to provide a more precise estimate of vaccine efficacy. This pathway would provide the most straightforward route to global licensure of M72/AS01E, though it would be long on time and money. The report from the July 2019 WHO consultation flags 2028 as the earliest date by which phase III trial data could be submitted to regulators for possible approval—and this assumes that funding is obtained quickly and that other preparations advance apace.⁵²

If the field follows this path, it is essential, in TAG’s view, that the phase III trial includes special populations to expand the vaccine’s indication beyond the HIV-negative adults represented in the phase IIb study. As a priority, the trial should enroll people living with HIV (PLHIV), and investigators should consider recruiting adolescents younger than age 18. Both of these groups face a much higher risk of TB and therefore should be at the forefront of efforts to develop new TB vaccines.

One estimate by GSK pegs the cost of a phase III trial of M72/AS01E at around \$1 billion in **funding**, inclusive of everything from upgrading manufacturing capacity to conducting the study to licensing the vaccine and preparing for rollout (see reference no. 49).

RCT stands for randomized controlled trial.

Accelerated licensure, or accelerated approval, occurs when regulators approve products that meet a serious unmet medical need based on surrogate endpoints, or before confirmatory phase III trial data are available. Accelerated approvals are often conditional on the sponsor conducting further studies.

Trials that include PLHIV will also need to offer participants TB preventive therapy (TPT), which is recommended by the WHO for all PLHIV, as well as young children and HIV-negative household contacts of people with TB.

The provision of TPT in TB vaccine trials conducted in at-risk populations is an ethical imperative and is analogous to the place of pre-exposure prophylaxis (PrEP) in HIV vaccine trials.

This report by TAG describes how the HIV vaccine field has incorporated preventive therapy into clinical trial design.

The **inclusion of PLHIV** could take several forms. For example, it may be sufficient to collect safety and immunogenicity data on M72/AS01E in PLHIV without including outcomes among HIV-positive participants in the primary efficacy analysis.

Many believe a phase III trial should include a subset of people *without* MTB infection to see whether M72/AS01E can prevent TB disease in people who are IGRA-negative.⁵³ The notion of screening people for MTB infection before administering M72/AS01E seems untenable for high-TB-incidence countries given the expense and shortcomings of current tests for TB infection.

Including a cohort of IGRA-negative people in a phase III trial would allow investigators to, at a minimum, demonstrate the safety and immunogenicity of the vaccine in people without MTB infection. Generating evidence in this population would facilitate the eventual introduction of M72/AS01E into public health systems by eliminating the requirement of pairing it with an expensive, imperfect diagnostic test.

- The second pathway would seek an accelerated approval of M72/AS01E based on the safety and efficacy data from the phase IIb trial. This approval would come with certain conditions, such as a requirement to demonstrate the effectiveness of the vaccine in large-scale implementation studies.⁵⁴ Such an approach may offer the fastest way to introduce M72/AS01E in the three countries that participated in the phase IIb trial (South Africa, Kenya, and Zambia). But regulatory authorities outside of these places—including the U.S. Food and Drug Administration and the European Medicines Agency—are unlikely to approve M72/AS01E based only on the existing phase IIb data. Even with regulatory approval, some country programs may hesitate to adopt a vaccine without confirmation of its safety and efficacy in phase III.

At best, this approach would quickly introduce a potentially effective vaccine in a handful of high-TB-burden countries that urgently need better ways to prevent TB. However, following this path would leave many scientific questions unanswered and would not bring the benefits of M72/AS01E to the world at large, at least not immediately. The use of M72/AS01E in special populations (such as PLHIV) would also remain uncertain. Regulators could decide to endorse the use of M72/AS01E in these groups—there is some safety and immunogenicity data on M72/AS01E in PLHIV from earlier phase II work—but the reassurance of data from additional phase II trials may be necessary before doing so.

In essence, this pathway provides a shortcut—a way to reach public health impact with less time and money than a traditional phase III trial would require. The value of preventing TB and saving lives in countries like South Africa, where the epidemic unfolds at terrifying scale, cannot be overstated. Ultimately, shortcuts are useful insofar as they lead one to the desired destination faster than otherwise possible. Before embarking in this direction, the TB vaccine field will need to gather the views of national regulatory authorities, normative bodies, public health programs, civil society, and the communities most affected by TB to ensure that all constituencies understand the trade-offs involved.

Regardless of the direction taken, several important activities should take place while the field decides on next steps:

- Nearly all (99%) of participants in the phase IIb study consented to storing blood samples taken pre- and post-vaccination for use in future research.⁵⁵ This biobank is a rich resource for basic and translational science to identify **biomarkers** that correlate with the protective immunity observed in the study. Rigorous biomarker discovery efforts should begin now and proceed in parallel with future trials. All future studies must include biobanking so that any possible correlates of protection identified from the phase IIb samples can be further interrogated—or validated, if efficacy is confirmed in a phase III trial. Specimen collection is an ethical imperative: Stored samples will help to ensure the social and scientific value of any future trial, regardless of study outcome, by informing future research endeavors that may guide the development of other TB vaccine candidates in the pipeline.⁵⁶
- One critical question concerns how to use the remaining doses of M72/AS01E manufactured for the phase IIb trial. GSK has indicated that 7,000 to 9,000 extra doses are available—not enough for a phase III study, but a resource that should not be wasted.⁵⁷ At the April 2019 WHO consultation, GSK proposed using this stock for studies to optimize the dose and dosing schedule of AS01E.⁵⁸ Considering that this adjuvant system is a thoroughly studied part of two licensed GSK products (see section III), there are probably better ways to use extant vaccine supply. Participants at the July 2019 WHO consultation concluded that “progress should proceed with licensure evaluations based on the dose and schedule used in the phase 2b trial.”⁵⁹ The meeting report suggested reserving 2,000 to 3,000 doses to support efforts to validate manufacturing process improvements or technology transfer in preparation for future trials. The remaining doses could then preferentially be devoted to a safety study of M72/AS01E in people living with HIV to generate more data in this key population.⁶⁰
- Manufacturing capacity for M72/AS01E—particularly the AS01E component—must be upgraded before a phase III trial begins. **Repeated shortages** of GSK’s herpes zoster (shingles) vaccine pose a major concern; this vaccine incorporates a higher dose of the same adjuvant used in M72/AS01E (read section III below).⁶¹ Ensuring a sufficient and stable supply of M72/AS01E may require GSK to share technology and know-how with developing-country vaccine manufacturers. GSK has indicated that it is open to licensing the M72 antigen to other manufacturers, but the company is not willing to include AS01E in any technology transfer. At the April 2019 WHO consultation, GSK presented its vision of maintaining proprietary control over AS01E while upgrading manufacturing capacity through external financing.⁶² It reiterated this position at the July WHO meeting.⁶³ For reasons described below, this unabashed ask for charity by one of the world’s largest pharmaceutical companies does not represent a good deal for the public and philanthropic funders that will be expected to pick up the tab for advancing M72/AS01E to licensure and then making it available through donor- and government-funded public health programs.

Biomarkers are measurable biological processes, clinical phenotypes, or gene activities that signify particular infection/disease states or the body’s response to vaccination/treatment.

The global rollout of the Shingrix vaccine has been stymied by **repeated shortages** since its introduction, with supply disruptions expected to last through 2019. GSK cites “high demand” to explain the shortages, which are believed to be related to manufacturing concerns tied to a limited supply of QS-21.

Marshaling the resources to bring M72/AS01E to licensure will require the global health community—governments, foundations, pharmaceutical companies, civil society, and TB-affected communities—to devise new models of working together. These collaborations will not be simple, straightforward, or without occasional rancor. All parties will need to lean on ethical and legal frameworks to resolve thorny questions of access and ownership. At present, some of the most difficult questions hinge on access to the AS01E adjuvant, and to QS-21, in particular.

III. Understanding the AS01E Adjuvant: A Primer for Activists, Members of Civil Society, and Funders

To a significant degree, the future clinical development of M72/AS01E, and advocacy to ensure its availability and accessibility, hinges on the AS01E adjuvant. This primer on AS01E aims to build critical understanding among activists, members of civil society, and funders of the clinical, commercial, and human rights issues surrounding this essential global health product.

What is AS01E?

Liposomes can be thought of as delivery vehicles for drugs or other molecules. They are spherical in shape and enclose water or other aqueous solutions.

Lytic refers to “lysis” (destruction), as in hemolytic anemia, in which red blood cells are damaged and destroyed.

AS01E is a proprietary adjuvant system owned and developed by GSK. It contains two immunostimulants—25 µg of 3-deacylated monophosphoryl lipid (MPL) and 25 µg of Quillaja saponaria Molina: fraction 21 (QS-21)—packaged together with **liposomes**. MPL is derived from the organism *Salmonella minnesota*.⁶⁴ As described above, QS-21 is a saponin molecule extracted from the Chilean soapbark tree. QS-21 is a **lytic** saponin. Pairing QS-21 with cholesterol defangs its hemolytic properties.⁶⁵ (In brief, the cholesterol absorbs any lytic effects of QS-21, thereby sparing human cells of damage.) The liposome in AS01E contains the cholesterol necessary to neutralize QS-21’s lytic properties, making it safe for use.⁶⁶

Who developed AS01E?

First used in the 1920s, **aluminum salt** (alum) remained the only adjuvant in human vaccines for the next 70 years.

Cytokines are small proteins that call and direct the behavior of other immune cells.

AS01E is just one member of a larger family of adjuvants developed by GSK.⁶⁷ GSK began developing the AS01 adjuvant system nearly 30 years ago with the goal of improving older adjuvant technologies, such as **aluminum salt**.⁶⁸ GSK scientists felt that developing vaccines against complex pathogens such as HIV, malaria, and TB would require devising so-called adjuvant systems built from a deliberate, considered combination of molecules that could speak to different parts of the immune system: not only humoral immunity driven by antibodies produced by B cells, but also the cell-mediated immunity of **cytokine**-producing T cells.⁶⁹ Through a decades-long process of design and iteration, GSK demonstrated that AS01 stimulates both humoral and cellular immunity. MPL activates antigen-presenting cells, including antigen-specific T cells producing **IFN γ** , **TNF α** , and other cytokines. QS-21 stimulates antigen-specific antibody responses as well as CD8+ T cells. Data from preclinical animal models suggest that QS-21 and MPL interact synergistically—that is, the two have a greater effect together than apart.⁷⁰

Interferon gamma (IFN γ) and **tumor necrosis-factor alpha (TNF α)** are cytokines thought to play an important role in immunity against TB.

By all measures, the adjuvant system development program at GSK has met with tremendous success. Today, AS01 is part of two licensed GSK vaccines: The RTS,S malaria vaccine contains the same AS01E adjuvant as M72/AS01E, and the Shingrix shingles vaccine uses AS01B, which is identical to AS01E except double its dose (50 µg of MPL and 50 µg of QS-21).⁷¹ The use of AS01 in two GSK vaccines on the market raises several important considerations:

- First, the ability of AS01 to contribute to vaccine-induced immunity against a remarkable range of pathogens—from a parasite (malaria) to a virus (herpes zoster) to now, potentially, a bacterium (MTB)—means that this adjuvant system should be recognized as an essential global health good.

- Second, the inclusion of AS01 in two licensed vaccines sends an encouraging signal about its safety. In a 2017 paper, Arnaud Didierlaurent and other GSK scientists wrote: “To date, more than 10,000 children and 30,000 adults have received AS01-containing vaccines.”⁷² These numbers are already much higher after large-scale pilot programs of RTS,S in Malawi, Ghana, and Kenya, and the recommendation in the United States that all healthy adults over age 50 receive a shingles vaccine.^{73,74}
- Third, it may be useful to think of adjuvant systems as a type of platform technology: a technology on which other applications can be built.⁷⁵ Essentially, AS01 is a platform for generating immunity in that antigens taken from different pathogens can be plugged into the same adjuvant system to generate various immunostimulatory effects. The most powerful platform technologies are open ones, available for use by different developers. In the case of AS01, its proprietary ownership by GSK makes this adjuvant system a scarce monopoly product, rather than an open resource available to the larger scientific community.

Who owns MPL and QS-21?

Understanding who owns the rights to use MPL and QS-21 in vaccine adjuvants requires tracing a labyrinthine history of financial relationships between GSK, small biotech companies, and private investment firms. The summary here introduces readers to some of the **major players** and sketches how they are connected. Understanding these connections is necessary to appreciate how multiple parties—private, public, philanthropic—contributed to the development of M72/AS01E.

MPL: The MPL used in AS01E originated at Corixa Corp., a small biotech company that manufactured MPL in Montana in the United States. In 2005, GSK acquired Corixa to gain control of MPL, an important component of several GSK vaccines under development, including ones for TB. Jean Stephenne, then-president of GSK Biologicals, said this “represents the next step in progressing GSK’s promising tuberculosis vaccine approach.”⁷⁶ Corixa Corp. not only made MPL, but it also played an instrumental role in developing the M72 fusion protein (which early in its development was called **Mtb72F**). The Stop TB Partnership Working Group on New TB Vaccines’ 2006–2015 strategic plan described Mtb72F as “a fusion protein developed by Corixa in Seattle, WA and delivered with an adjuvant formulation developed by GSK.”⁷⁷ Other papers from the time describe Mtb72F as being developed by scientists from Corixa Corp. and the Infectious Disease Research Institute in partnership with GSK.⁷⁸ The U.S. National Institutes of Health funded some of this early work.^{79,80}

QS-21: In presentations and reports, GSK describes QS-21 as belonging to Antigenics Inc., “a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation.”⁸¹ More precisely, Antigenics is Agenus: Antigenics changed its name to Agenus in 2011.⁸² In the press release announcing the name change, Agenus touted QS-21 (branded as Stimulon) as “Agenus’ versatile vaccine adjuvant ... currently being used in 14 clinical vaccine candidates through corporate partnerships with GlaxoSmithKline (GSK) and Janssen Alzheimer Immunotherapy.”⁸³ GSK licenses QS-21 from Agenus for use in the AS01 adjuvant system. In 2012, the two companies amended their licensing arrangement to give GSK additional rights to QS-21. The deal included a \$9 million payment to Agenus

Major players in AS01E development:

GSK: large, multinational pharmaceutical company headquartered in the United Kingdom. GSK developed the AS01 adjuvant system and is the lead developer of the M72/AS01E TB vaccine candidate.

Corixa Corp: based in Seattle, WA. Corixa manufactured the MPL in AS01 and helped develop the M72 antigen. Acquired by GSK in 2005.

Agenus Inc. (Antigenics): based in Lexington, MA. Agenus owns and manufactures QS-21, which it licensed to GSK for use in the AS01 adjuvant system.

An early patent on the **Mtb72F** fusion protein is ascribed to Yasir Skeiky, Steven Reed, and Mark Alderson of Corixa Corp.

US7186412B1
“Fusion proteins of Mycobacterium tuberculosis.” Filed: 2000; granted: 2007; expired: 2019.

“A composition comprising a MTB39 antigen ... and a MTB32A antigen ... from a Mycobacterium species of the tuberculosis complex.”

and royalty payments for “an undisclosed indication upon commercialization of a vaccine product.”⁸⁴ Agenus also gave GSK the “first right to negotiate for the purchase of Agenus or certain of its assets,” protecting GSK’s access to QS-21 against Agenus’ acquisition by other companies.⁸⁵

The corporate ownership of QS-21 grew more complex in January 2018, when Agenus announced a \$230 million royalty transaction with HealthCare Royalty Partners (HCR), giving HCR “the rights to royalties on sales of GlaxoSmithKline’s QS-21 containing vaccines.”⁸⁶ HCR describes itself as “a private investment firm that purchases royalties ... to invest in commercial or near-commercial stage life science assets.”⁸⁷ QS-21 is one of those valuable assets. Essentially, Agenus agreed to assign 100 percent of royalties paid by GSK on QS-21-containing vaccines to HCR in exchange for cash (\$190 million up front with \$40 million contingent on **milestones**).⁸⁸ Within the biotech industry, this kind of deal is sometimes called “**biobucks**,” a slang term for licensing arrangements in which only part of the payment is issued up front.⁸⁹

A complete understanding of QS-21’s corporate parentage would require mapping the landscape of patents on the QS-21 compound and related processes and applications. The box below provides a starting point for carrying forward this important work.

The QS-21 Patent Landscape: Starting Points

The most protected component of AS01 is the QS-21 molecule. Typing “QS-21” into Google’s patent search tool yields over 3,000 returns; a combined search for “QS-21” and “tuberculosis” turns up over 900 (search date: October 12, 2019).

The earliest patents for QS-21 (US5057540A; US5583112A) were filed by Cambridge Biotech Corp. in the early 1990s and are currently assigned to Antigenics. The patent on QS-21 composition of matter expired in 2008.

- US5057540A “Saponin adjuvant.” Filed 1990; granted 1991; expired 2008.
- US5583112A “Saponin-antigen conjugates and use thereof.” Filed 1992; granted 1996; expired 2013.

One of the first patents to mention QS-21 in relation to TB (US6350456B1) was filed by Corixa Corp.

- US6350456B1 “Compositions and methods for the prevention and treatment of M. tuberculosis infection.” Filed 1998; granted 2002; expired 2017.

Counting Google patent search hits is a crude way of assessing the patent landscape of a particular technology. A more sophisticated QS-21 patent analysis is urgently needed, and TAG calls on funders to support this work as a matter of priority.

According to U.S. Securities and Exchange Commission filings, these **milestones** include GSK vaccines meeting certain sales thresholds.

Biobucks deals hedge the risk that a product may fail in clinical development by making further payments conditional on milestones, e.g., completing a clinical trial, obtaining regulatory approval, etc.

Is QS-21 the product of bioprospecting or biopiracy?

Presumably, most of the commercial interest in QS-21 stems from its role in GSK's licensed shingles vaccine and its incorporation into candidate vaccines for cancers and Alzheimer's disease (the U.S. Army also licensed QS-21 for use in an experimental vaccine against the Ebola and Marburg viruses).^{90,91} Are the biobucks financing QS-21 development taking advantage of fair **bioprospecting**, or are they contributing to the monetization of a compound commercialized through **biopiracy**?

What separates bioprospecting from biopiracy? Respect for ethics and human rights. Janna Rose of the Grenoble School of Management writes that bioprospecting "involves ethical considerations such as prior informed consent, access and benefit sharing agreements, and material transfer agreements before research commences. Earnings from any commercial products should go towards local conservation efforts and the construction of infrastructure."⁹² Biopiracy lacks these ethical safeguards and takes resources from communities without prior informed consent.

Does this definition of biopiracy describe the use of QS-21 in the AS01 adjuvant system? The story of QS-21 does not start or end in Delaware, where Agenesis is incorporated, or in Lexington, Massachusetts, where Agenesis is headquartered, or in London, the location of GSK's head office, or even in Wavre, Belgium, where many of the scientists working on GSK's TB vaccine program are based. It begins in the Andes, where Indigenous Peoples including the Mapuche long ago recognized that soapbark tree bark held tremendous medicinal properties.^{93,94} The licensing deals described above show how GSK, Agenesis, and their investment partners have monetized QS-21, a compound that originates from a **natural resource** cultivated by Indigenous Peoples for centuries. What is less clear from the patent and licensing record is how Indigenous Andean Peoples are benefiting, if at all, from QS-21's immense pharmaceutical value.

Which groups, if any, can claim right-of-ownership over QS-21 is a question that will shape the availability and accessibility of M72/AS01E should the vaccine prove safe and effective in confirmatory studies. The answer to this question will resonate far beyond the TB field.

From exclusive ownership to equitable access and stewardship

A better framework for asking and answering this question would replace notions of "ownership" with the concepts of stewardship and conservation. Such a framework would privilege accessibility, benefit sharing, transparency, and sustainability over monopoly-protected profit generation. The legal basis for such a framework already exists in the **Convention on Biological Diversity (CBD)**, a legally binding international treaty. The CBD is an agreement by governments to pursue three major goals: 1) conserve biological diversity, 2) ensure the sustainable use of its components, and 3) promote the fair and equitable sharing of benefits arising from the use of genetic resources.⁹⁵ Broadly speaking, the CBD recognizes the right of states to govern access to genetic resources as part of their sovereignty over natural resources within their jurisdiction.⁹⁶

Bioprospecting describes the discovery and commercialization of new products from natural biological resources. This is a common practice across industries such as medicines and cosmetics.

Biopiracy is a form of bioprospecting in which traditional knowledge of biological resources held by Indigenous Peoples is commercialized for profit—often under patent-protected monopolies—without consent or agreed-upon benefit-sharing arrangements with Indigenous groups. Biopiracy is best understood as a form of scientific colonialism.

Currently, QS-21 can only be produced via **natural extraction** from the soapbark tree. In 2019, the Gates Foundation awarded \$1 million to Agenesis to develop a synthetic manufacturing process for QS-21 using a cell-culture-based technology.

Negotiated under the United Nations Environment Program, the **CBD** entered into force in 1993 and has 168 signatories.

Article 2 of the Nagoya Protocol defines **genetic resources** as not just material containing functional units of heredity (genes), but also derivatives of such material including “naturally occurring biochemical compounds resulting from the genetic expression or metabolism of biological or genetic resources.”

This includes aromas, small molecules, snake venom, and resins, to name just a few examples.

US6544518B1

“The present invention relates to novel adjuvant compositions for use in vaccines. In particular, the adjuvant compositions of the present invention comprise a combination of a saponin, and an immunostimulatory oligonucleotide, optionally with a lipopolysaccharide.”

Filed 2000; granted 2003; expired 2019.

US10039823B2

“Vaccine compositions comprising a saponin adjuvant.”

Filed 2011; granted 2018; adjusted expiration: 2027.

The Nagoya Protocol to the CBD, which entered into force in 2014, significantly expands the CBD’s framework on “access to **genetic resources** and the fair and equitable sharing of benefits arising from their utilization.”⁹⁷ Utilization under the Nagoya Protocol applies to the manufacture and sale of products generated from genetic resources, as well as to R&D on the genetic and biochemical composition of plants, animals, and microorganisms.^{98,99} This includes developing small molecules from plants—for example, extracting and purifying QS-21 from soapbark. Article 5.1 of the Nagoya Protocol takes an expansive view of benefit sharing, saying that it applies to the utilization of genetic resources as well as any subsequent applications.¹⁰⁰ In other words, the Nagoya Protocol covers the entire pipeline, from research to product development to commercialization.

Crucially, the Nagoya Protocol also governs the use of traditional knowledge in relation to genetic resources. Article 7 states: “Each Party [to the convention] shall take measures ... with the aim of ensuring that traditional knowledge associated with genetic resources that is held by indigenous and local communities is accessed with the prior and informed consent or approval and involvement of these indigenous and local communities, and that mutually agreed terms have been established.”¹⁰¹ This article articulates a number of important human rights principles. Foremost, the requirement of obtaining prior and informed consent from traditional knowledge holders before using genetic resources. Such consent must be given free of coercion; communities have the right to say “no.”¹⁰² Second, the importance of ensuring the participation of local communities in crafting access and benefit-sharing agreements.

TAG has found no evidence in the public domain to indicate that GSK or Agenus or the commercial suppliers of soapbark extract have obtained informed consent or established any kind of benefit-sharing framework with Indigenous Peoples in Chile for the utilization of QS-21. The absence of these safeguards established by international law calls for a much closer look from the TB scientific community before funders enter into any kind of agreement with GSK or Agenus on the future development of M72/AS01E.

The notion that QS-21 falls under the jurisdiction of the Nagoya Protocol is not a mere thought exercise. In 2013, to help assess how the Nagoya Protocol might affect UK businesses, the UK government commissioned a report on patents filed from 1976 to 2010 that involve genetic resources and associated traditional knowledge. The report’s chapter on plant species and pharmaceuticals highlighted a patent on “the use of saponins from *Quillaja saponaria* in a vaccine adjuvant composition by GlaxoSmithKline” (**US6544518B1**).¹⁰³ In fact, patents held by GSK on soapbark saponins were the 10th largest patent family involving genetic resources or traditional knowledge identified in the UK patent data (**US10039823B2**). This reveals the economic importance of QS-21 (the size of a patent family is a proxy for commercial interest). The report notes: “The use of this bark as part of an adjuvant for use in a vaccine combination is of significant economic importance and patents were filed in the mid-2000s. However, it appears that the original research on the species and its saponins was conducted in the 1970s.”¹⁰⁴

It is difficult to trace knowledge back to its source. Knowledge is set apart from other goods by how it grows, rather than diminishes, when shared.¹⁰⁵ And it can germinate from more than one seed at the same time. The many medicinal uses of saponin molecules such as QS-21 illustrate this special quality. Indigenous Peoples around the world have used saponin-producing plants for hygiene and health for thousands of years—from the soapbark tree in Chile to soapnut in Nepal and India to lather leaf in China.¹⁰⁶ Even by the standards of the international patent system, the monopolistic ownership structures limiting access to QS-21 and AS01 deserve scrutiny. Agenus was not the first to recognize QS-21's potential—one review of QS-21 adjuvant applications cites a 1925 article on saponins and antibody responses to diphtheria and tetanus and a 1964 article on the potential use of saponins from *Quillaja saponaria* as adjuvants.^{107,108,109}

In summary: *QS-21 is manufactured by Agenus, licensed to GSK, protected by a labyrinthine maze of intellectual property holdings, and in short supply. Agenus entered into a series of licensing deals to monetize the benefits of QS-21. GSK acted to secure access to QS-21 as an essential component of its AS01 adjuvant system, a platform technology that would be more powerful if treated as an open resource rather than a proprietary product. Neither company discovered QS-21 or can even claim to be the first to study QS-21's potential as an adjuvant. By the standards of the Nagoya Protocol, the benefits of QS-21 utilization should accrue to the Indigenous Peoples who held knowledge of the soapbark tree's medicinal properties. There is a strong case that QS-21 and the AS01 adjuvant system that contains it should be considered global public goods, offshoots of a natural inheritance that should be shared, managed, and conserved for the benefit of all of humanity.*

Where does this leave M72/AS01E?

The long line of traditional knowledge of and scientific inquiry into QS-21 makes GSK's stated resistance to sharing its AS01E technology indefensible. When offered a range of bad options by Big Pharma, the TB community needs to get into the habit of saying "none of the above." Knowing what we know about M72/AS01E, the field should not be quick to settle for any arrangement that would marshal unprecedented levels of public and philanthropic financing to develop a product that remains controlled by a pharmaceutical company that has openly confessed its lack of interest in investing its own money. The provision of public funding creates public goods, and public goods must be made equitably available to the publics that underwrite their development. Indigenous pharmaceuticals should only be commercialized with free and informed consent in the context of agreed-upon frameworks for ensuring that traditional knowledge holders can enjoy the benefits of scientific progress. These are the higher standards established by international human rights law to which the TB vaccine field should hold itself—and any industry partners—accountable as the field moves M72/AS01E into late-stage development and toward licensure.

Table 1. TB Vaccines in Clinical Development

Agent	Type	Sponsor(s) and major partners	Status*
Notable recently completed, ongoing, or planned clinical trials			
M. vaccae	Whole-cell <i>M. vaccae</i>	Anhui Zhifei Longcom	Phase III
Recently completed a phase III POD trial in 10,000 MTB-infected, HIV-negative adults (age 15–65 years) in China (NCT01979900); results not yet published			
MIP	Whole-cell <i>M. indicus pranii</i>	Indian Council of Medical Research (ICMR), Cadila Pharmaceuticals	Phase III
Undergoing a phase III POD trial among 12,000 household contacts (≥6 years old) of people with TB in India (CTRI/2019/01/017026). Expected completion: 2022**			
VPM1002	Live rBCG	Serum Institute of India, Vakzine Projekt Management, Max Planck Institute for Infection Biology, ICMR	Phase III
<ol style="list-style-type: none"> 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) Undergoing a phase II/III POR study in 2000 HIV-negative adults successfully treated for DS-TB in India (NCT03152903). Expected completion: December 2021 Recently completed a phase II study in 416 BCG-naïve, HIV-exposed and HIV-unexposed newborn infants in South Africa (NCT02391415) and planning a phase III POI trial in the same population (N = 10,000) in South Africa, Uganda, Kenya, Tanzania, and Gabon 			
M72/AS01E	Protein/adjuvant subunit vaccine	GlaxoSmithKline	Phase IIb
Recently completed a phase IIb POD study in 3,575 HIV-negative, MTB-infected adults (age 18–50 years) in Kenya, South Africa, and Zambia (NCT01755598); primary results published in the New England Journal of Medicine in September 2018 with final results expected late October 2019 at the 50th Union World Conference on Lung Health			
DAR-901	Inactivated whole-cell non-tuberculosis Mycobacterium	Geisel School of Medicine at Dartmouth	Phase IIb
Completing a phase IIb POI study in 650 BCG-vaccinated, HIV-negative, MTB-uninfected 13- to 15-year-old adolescents in Tanzania (NCT02712424); results expected 2020			
H56:IC31	Protein/adjuvant subunit vaccine	Statens Serum Institut (SSI), IAVI, Valneva—IC31 adjuvant	Phase IIb
<ol style="list-style-type: none"> Undergoing a phase IIb POR study in 900 HIV-negative adults successfully treated for DS-TB in South Africa and Tanzania (NCT03512249). Expected completion: December 2022 Undergoing a phase I study as a therapeutic vaccine given with and without COX-2 inhibitors in 39 adult patients with TB in Norway (NCT02503839). Data analysis ongoing 			

BCG revaccination	Whole-cell <i>M. bovis</i>	Aeras, Sanofi Pasteur (entry 1 below), Gates Medical Research Institute (entry 2 below)	Phase II
<ol style="list-style-type: none"> 1. Published results of a phase II POI study in 990 HIV-negative, MTB uninfected adolescents in South Africa in the New England Journal of Medicine in July 2018 (NCT02075203) 2. Planning for a second phase II study to replicate findings from the phase II POI study described above 			
ID93/GLA-SE	Protein/adjuvant subunit vaccine	Infectious Disease Research Institute, Quratis, Gennova Biopharmaceuticals	Phase II
<ol style="list-style-type: none"> 1. Published results of a phase IIa safety/immunogenicity study in 60 HIV-negative adults successfully treated for DS-TB in South Africa (NCT02465216) 2. Undergoing a phase IIa POI trial in 107 BCG-vaccinated, MTB-uninfected healthcare workers in South Korea (NCT03806686). Expected completion: March 2020 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. 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 2019¹ 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: 2020¹ 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 Network¹ 7. Under consideration for a possible POI or POR trial in children with the U.S. NIH International Maternal Pediatric Adolescent AIDS Clinical Trials Network¹ 			
MTBVAC	Live genetically attenuated MTB	University of Zaragoza, Biofabri, TBVI, IAVI	Phase IIa
<ol style="list-style-type: none"> 1. Published results of a phase Ib/IIa dose escalation safety/immunogenicity study comparing MTBVAC to BCG in 36 infants with a safety arm in 18 adults (NCT02729571) in the Lancet Respiratory Medicine. 2. Undergoing a phase IIa dose-defining safety/immunogenicity study in 99 South African infants (NCT03536117). Expected completion: December 2020 3. Undergoing a phase Ib/IIa study in 144 adults with and without MTB infection in South Africa (NCT02933281). Expected completion: March 2021 			
RUTI	Fragmented MTB	Archivel Farma	Phase IIa
Undergoing a phase IIa safety/immunogenicity therapeutic vaccination study in 27 adults being treated for MDR-TB (NCT02711735). Expected completion: July 2020			
TB/FLU-01L	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase IIa
<ol style="list-style-type: none"> 1. Completed a phase I safety/immunogenicity study in BCG-vaccinated adults (NCT03017378; results presented at 5th Global Forum on TB Vaccines) 2. Reportedly planning a phase IIa study in MTB-infected adults (no clinical trials record available) 			

ChAdOx1 85A + MVA85A	Viral vector	Oxford University	Phase I/IIa
<p>1. Undergoing a phase I/II dose escalation and age de-escalation study of ChAdOx1 85A in adults and adolescents in Uganda. Planning to follow with a phase IIa study comparing the immunogenicity of an intervention of ChAdOx1 85A prime and followed by MVA85A boost with BCG revaccination in adolescents (NCT03681860).</p> <p>2. Undergoing a phase I study comparing ChAdOx1 85A aerosol vs. intramuscular vaccination in 39 BCG-vaccinated adult volunteers in Switzerland (NCT04121494). Expected completion: December 2020</p>			
GamTBvac	Protein/adjuvant subunit vaccine	Ministry of Health of the Russian Federation	Phase IIa
<p>1. Published results of a phase I safety/immunogenicity study in 60 BCG-vaccinated, MTB-uninfected adult volunteers (NCT03255278) in the Bulletin of the Russian State Medical University</p> <p>2. Undergoing a phase IIa safety/immunogenicity study in 180 BCG-vaccinated, MTB-uninfected adult volunteers (NCT03878004) in Russia. Expected completion: March 2020</p>			
Ad5Ag85A (aerosol)	Viral vector	McMaster University, CanSino	Phase I
<p>Undergoing a phase I safety/immunogenicity study in 28 BCG-vaccinated healthy volunteers in Canada (NCT02337270). Expected completion: April 2021</p>			
AEC/BCO2	Protein/adjuvant subunit vaccine	Anhui Zhifei Longcom	Phase I
<p>Undergoing a phase I safety/immunogenicity study in 135 adult volunteers in China (NCT03026972). Expected completion: January 2020</p>			
<p>NCT: ClinicalTrials.gov entry of ongoing or recently completed clinical trials.</p> <p>* Status indicates the most advanced phase of either ongoing or recently completed trials.</p> <p>** Expected completion date is the anticipated date of the last study participant's last visit, per the ClinicalTrials.gov definition. This is not the date by which results will be available.</p>			
<p>ChAd: chimpanzee adenovirus vector BCG: bacillus Calmette-Guérin COX-2: cyclooxygenase-2 DAR-901: <i>M. obuense</i> DS-TB: drug-susceptible TB DR-TB: drug-resistant TB EPI: Expanded Programme on Immunization <i>M. bovis</i>: <i>Mycobacterium bovis</i> MDR-TB: multidrug-resistant tuberculosis MIP: <i>Mycobacterium indicus pranii</i></p>		<p><i>M. obuense</i>: <i>Mycobacterium obuense</i> MTB: <i>Mycobacterium tuberculosis</i> <i>M. vaccae</i>: <i>Mycobacterium vaccae</i> MVA: modified vaccinia virus Ankara POD: prevention of disease POI: prevention of infection POR: prevention of recurrence rBCG: recombinant bacillus Calmette-Guérin</p>	
<p>Information compiled from ClinicalTrials.gov, the India Clinical Trials Registry, and the World Health Organization International Clinical Trials Registry Platform. Information checked against pipeline summaries published by Aeras and the TuBerculosis Vaccine Initiative and augmented by additional information provided by sponsors.</p> <p>1 Corey C. ID93 + GLA-SE as adjunctive immunotherapy to reduce the global burden of tuberculosis. Presentation to: IMPAACT TB Scientific Committee. 2019 September 25.</p>			

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