

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

**Participants:**

**PDVAC:** Barney Graham, Isabelle Bekeredjian-Ding (for Klaus Cichutek), Sinead Delany-Moretlwe, Bernard Fritzell, Gagandeep (Cherry) Kang, Ruth Karron, David Kaslow (PDVAC Chair), Jerome Kim, Claudio Lanata, Shabir Mahdi,; Mark Papania, Alejandro Cravioto (SAGE chair, ex-officio member) Peter Smith, Marian Wentworth

*Apologies:* Yiming Shao, Beno Nyam Yakubu

**WHO:** Birgitte Giersing, Mateusz Hasso-Agopsowicz, Erin Sparrow, Martin Friede, Isabel Frost.

**Observers and non-member participants:** Please see [list of participants](#)

**Executive Summary**

*Rationale for the meeting:*

WHO and collaborators have articulated global strategic public health goals for TB vaccines, and have developed Preferred Product Characteristics guidance for vaccines intended to prevent pulmonary disease in adolescents and adults. There is one candidate, M72/AS01<sub>E</sub> that has demonstrated efficacy in this target population to date in a Phase 2b study. In addition, BCG revaccination of adolescents suggests that BCG revaccination of adolescents may prevent sustained Mtb infection in high transmission settings. This PDVAC session focused on these two approaches specifically, since there are impending questions related to pivotal study design and data/evidence that if collected, could help to inform future policy recommendations. PDVAC also noted that the TB vaccine pipeline is diverse with respect to platforms, and several candidates are in the clinical pipeline.

In addition to the clinical pipeline, there are other enabling activities underway that will help to accelerate and shape TB vaccine product development and delivery strategies. These include the R&D Roadmap for tuberculosis vaccines developed by the Amsterdam Institute for Global Health and Development, and vaccine impact modelling studies for both the approaches, led by the London School of Hygiene and Tropical Medicine. PDVAC input on both the draft roadmap and modelling approaches was requested, to ensure they were optimally positioned to support advocacy, inform strategic priority setting and decision-making, as well as to prepare future candidates for licensure, policy consideration, implementation and impact.

The intended outcomes of the PDVAC session were:

- Identification of critical activities that would benefit from PDR/PDVAC leadership and engagement, either related to M72/AS01 and BCG revaccination specifically, or enabling TB vaccine development more generally;
- PDVAC recommendations on the draft TB vaccine roadmap, and a decision related to potential co-authorship with WHO;
- Identification of high priority follow up work to the WHO-funded Full Value Assessment of TB Vaccines project

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

- Identification of how BMGF-funded M72/AS01 and BCG revaccination modelling project could be more useful to global and country stakeholders

*PDVAC Conclusions and Recommendations:*

*BCG ReVax and M72/AS01<sub>E</sub> – preparing the pathway:*

- The M72/AS01<sub>E</sub> Phase 3 clinical trial design and endpoint discussion will benefit from SAGE input, before the clinical protocol is finalized. The PDVAC secretariat within WHO can co-ordinate internal workstreams/stakeholders, including requesting SAGE input on Phase III and early policy considerations, establishing a working group and preparing for a session in Q4 2021.
- PDVAC members are able to participate in Gates MRI's Scientific Advisory Board (SAB) on Phase 3 design and endpoint definition and are encouraged to do so, to foster a link with WHO through PDVAC and SAGE. The SAB will convene in Q1 2021.
- In order to mitigate against failure and the long timelines associated with M72, PDVAC strongly supports the continued product development of the remaining pipeline vaccines and development of new vaccine antigens/adjuvants for clinical evaluation.
- WHO should contemplate development of a 'preferred policy profile' for the most advanced TB vaccine types, in particular vaccines targeted to adolescents and adults that will not be deployed within the infant/childhood EPI programme.

*TB Vaccine R&D Roadmap:*

- The draft TB vaccine roadmap developed by AIGHD provides an excellent assessment of the challenges, gaps and needs in TB vaccine R&D, particularly with respect to addressing diversification of the pipeline and clinical development considerations. However, to maximize public health impact, an integrated strategy that involves supporting and co-ordinating policy decision-making, developing implementation approaches, building public demand and acceptance and preparing the pathway for financing and procurement is needed. There is insufficient consideration of these elements in the current draft, and these are core elements of what a roadmap developed or endorsed by WHO would be expected to include.. In particular, areas where the current roadmap would need to be expanded include:
  - Discussion of what is needed to ensure manufacturing capacity is in place for commercialisation and to meet global demand;
  - Considerations for programmatic delivery and implementation research needs to occur in parallel to clinical studies – this deserves a more prominent focus
  - Specific section on strategy to license TB vaccines for and delivery of vaccines to key target populations, most notably PLHIV, since these will be outside of the childhood EPI schedule;
  - Plans for continued community engagement, building the case for the emerging candidates and creating demand;

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

- Focus of the impact that a TB vaccine could have on AMR, and how this could contribute to the full value assessment for TB vaccines should be strengthened;
  - The need to develop clarity on data/evidence needed for a WHO policy recommendation and PQ (pre-requisite for Gavi financing and Unicef procurement)
  - Should include establishing novel mechanisms/incentives for investment in TB vaccines
  - The issue of long term sustainability for TB vaccines, particularly as countries transition from Gavi support, needs to be highlighted
  - For next generation candidates, consider whether the lead candidate of M72/AS01 (for PoD in adolescents and adults) be used as a comparator for preclinical studies;
  - As a general comment, there is deviation from structure and standardised terminology in other WHO roadmaps.
- Given that the vaccine R&D challenges are well-described within AIGHD roadmap, and that additional components and time will need to be developed to expand the roadmap for WHO co-publication, AIGHD should proceed with publication of its R&D Roadmap for tuberculosis vaccines. However, some of the downstream issues identified in this document need to be addressed upstream during the R&D phases (e.g. mfg process design and economic-related endpoints in PIII trials). This point should be noted in the final R&D Roadmap publication.
  - To complement the AIGHD TB vaccine R&D Roadmap, and leveraging the efforts of AIGHD to date, WHO should engage in the development of guidance for 'downstream' aspects, specifically related to commercialization, policy development, financing and implementation. WHO and AIGHD should continue to work together on this.

Post meeting note:

- AIGHD/EDCTP have agreed to proceed with finalisation and publication of the current form of the TB vaccine R&D Roadmap.
- WHO has initiated discussions on the need to develop 'preferred policy profiles' for adolescent TB vaccines, with partners, including WHO's SAGE. There is interest and support in the concept, and this work will initiate in early 2021.

*TB vaccine mathematical and economic modelling efforts:*

- As presented, the TB vaccine modelling is critical to informing acceptable ranges for the vaccine target product profiles and potential vaccine implementation strategies and could help policy deliberations. If not already included in the models it could be useful to:
  - include sensitivity analyses in the outputs by modelling a range of assumptions/scenarios, to take account of uncertainties and determine thresholds for the various product attributes that are modelled. Age and pre vs post infection status are likely to have the most significant impact on outcomes.
  - apply modelling to evaluate the relative effectiveness of national vs sub-national implementation, to target high burden areas – if epidemiology data are available. (This may be possible in Brazil).

***2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)  
Virtual Consultation 6: An update on Tuberculosis vaccine development activities  
3 September 2020***

- include an assessment of delivery costs to achieve vaccination of an adolescent/adult population, and clarity of the platform that will be used in various countries.
- consider the cost benefit beyond that of the vaccine, to assess the use of therapeutics, antibiotics over the life course and the overall economic benefits of protecting of key populations susceptible to TB (e.g. employees and children).

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

**Meeting summary**

**1. Context of the meeting (Birgitte Giersing, Product & Delivery Research, WHO)**

Through consultation with global experts, WHO has identified three development goals for TB vaccines:

*I. A safe, effective and affordable TB vaccine for adolescents and adults*

Given the substantial disease burden in adolescents and adults, and the critical role that those with active pulmonary TB disease play in transmission of Mtb infection, the *prevention of pulmonary TB disease in adolescents and adults* is the priority strategic target in TB vaccine development.

*II. Affordable TB vaccine for neonates and infants with improved safety and efficacy as compared to BCG*

There is a need to *improve upon the BCG vaccines currently in use* by i) providing improved and longer duration of protection, ii) easing the safe administration to infants with HIV infection or other causes of immune suppression and/or iii) improving the manufacturing process to secure sustainable supply.

*III. A therapeutic vaccine to improve tuberculosis treatment outcomes*

Such a vaccine should *improve outcomes of drug therapy* by increasing the cure rate at the end of drug treatment and/or decreasing the frequency of recurrences following initial cure.

While there are several experimental [TB candidates in the vaccine pipeline](#), this PDVAC meeting focused on two of the most advanced approaches, both of which are related to development goal 1:

- **M72/AS01** was found to be significantly protective against TB disease in a Phase IIb trial conducted in Kenya, South Africa and Zambia, in individuals with evidence of latent tuberculosis infection (LTBI). The point estimate of vaccine efficacy was 50% (95% CI, 2.1 – 74.2), over three years of follow-up ([Tait et al, 2019](#)). These results present an unprecedented opportunity for potential licensure of a new TB vaccine within the next decade. There are critical questions that must be addressed now, for consideration in the design of the global Phase III study design and licensure strategy, and to mitigate against a delay to global implementation.
- In the **H4/BCG revaccination** Phase IIb trial, conducted in South Africa, enrolled adolescents who tested negative for TB and HIV infection and had undergone neonatal BCG vaccination were randomized to receive H4:IC31, BCG revaccination, or placebo. The BCG vaccine reduced the rate of sustained QFT conversion (a secondary outcome) over 2 years, with an efficacy of 45.4% (P=0.03), as compared to the efficacy of 30.5% (P=0.16) for the H4:IC31 vaccine. BCG revaccination could potentially present an interim strategy to prevent disease in adolescents and adults, but there are still many hurdles and gaps in evidence (specifically establishing that prevention of sustained infection leads to prevention of disease and that the observed effect is not limited to a single geography) that need to be addressed to support revision of the existing BCG policy recommendation. In the event of a recommendation for BCG revaccination, for BCG supply that will scaled up to meet increased demand and avoid vaccine shortages.

The pathway to availability, implementation and impact for vaccines is long, costly and risky. To mitigate this, many initiatives are underway to create an enabling environment; these are intended to provide

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

clarity to stakeholders engaged in vaccine development, policy consideration and implementation as to the preferences for vaccine use in low- and middle-income countries, and to expedite the licensure, policy recommendation and implementation strategy. WHO Preferred Product Characteristics (PPCs) for [New Tuberculosis Vaccines](#) and [Therapeutic Vaccines to Improve Tuberculosis Treatment Outcomes](#) were published in 2018 and 2019, respectively. A TB vaccine roadmap has been drafted by the Amsterdam Institute of Global Health and Development (AIGHD), with funding from The European Developing Countries Clinical Trials partnership (EDCTP). Extensive TB vaccine epidemiological and economic modelling is being carried out by the LSHTM and global partners, including a WHO-funded 'Full Value Assessment of TB Vaccines' project, and a BMGF-funded M72/AS01 and BCG-revaccination specific modelling project. These efforts are intended to further support the development of data that will be needed for decision making, through a coordinated and collaborative approach that engages all stakeholders along the vaccine value chain. Looking ahead to the evidence that will be needed for funding and introduction decisions will be crucial to ensure the candidates are well positioned to deliver impact.

**Meeting objectives:**

Within this context, the objectives of this PDVAC meeting on TB are to:

- Understand the current status, future plans and critical issues related to the M72/AS01 product development plan and the potential BCG revaccinations strategy;
- Review the proposed workstreams of the TB vaccine roadmap development and assess how they align with progressing the 3 WHO TB vaccine development goals;
- Introduce the ongoing WHO-funded Full Value Assessment of TB Vaccines project and assess how this progresses the WHO's Full Value of Vaccines Assessment approach, and what if any, high priority follow-up work is advised
- Introduce the ongoing BMGF-funded M72/AS01 and BCG revaccination specific modelling project, and advise if and how it could be more useful to global and country stakeholders
- Assess the immediate TB vaccine development related needs and priorities, from PDR/PDVAC

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

**2. Update on TB vaccine development activities: spotlight on BCG revaccination approach and GSK's M72/AS01. (Alexander Schmidt, Gates Medical Research Initiative, USA)**

**2.1 BCG Revaccination strategy.**

The [Phase 2 BCG revaccination study](#) (Aeras C-040-404) was performed in 990 Quantiferon (QTF) negative adolescents (12-17 years, who had been immunised as neonates with BCG), randomly assigned to receive either the H4:IC31 candidate, BCG revaccination, or placebo. The primary endpoint was *M. tuberculosis* (*Mtb*) infection, as defined by initial conversion on QFT after study Day 84, performed every 6 months during a 2-year period. The secondary endpoint was sustained QFT-conversion, i.e., 3 consecutive positive QFTs over 6 months. BCG reduced the rate of sustained QFT conversion, with an efficacy of 45.4% (95%CI 6.4-68.1%, P=0.03), suggesting BCG revaccination of adolescents may prevent sustained *Mtb* infection in high transmission settings.

The Gates MRI is seeking to confirm the efficacy signal in its BCG ReVax study ([NCT04152161](#)), a randomized, placebo controlled, observer-blind, Phase 2b study in South Africa. The trial is being performed in 1,800 QFT-negative participants, 10-18 years of age, randomized 1:1 to receive a single intradermal injection of BCG or placebo. The primary endpoint is sustained QFT conversion (initial conversion and IGRA positivity 3 & 6 months thereafter). The aim is to demonstrate prevention of sustained QFT conversion, i.e., to generate statistically robust data that may inform a BCG revaccination policy consideration, and to identify potential correlates of protection by collecting biomarkers every 6 months and 4 and 12 weeks after IGRA conversion. Conversion is considered a surrogate of infection and reversion is hypothesized to be a surrogate of a protective response. This work is driven by a large consortium looking at both cellular and humoral immunity, as well as systems biology approaches.

With respect to current status, 5 sites in South Africa (SATVI, CAPRISA, Wits RHI, Desmond Tutu HRF, Be Part) are enrolling. The study started in late 2019, experienced a pause due to Covid19 and restarted in July 2020. Approx. 800 (November 2020) of 1,800 participants are enrolled with enrolment completion anticipated in late 2021. Primary endpoint analysis will occur when a total of 118 sustained *Mtb* infection events have occurred in the mITT efficacy population (anticipated in late 2023, or early 2024).

In terms of data availability, candidate Correlate of Protection (CoP) data for prevention of sustained infection (PoSI) (based on Aeras revaccination study biospecimens) is expected in 2023. If a candidate CoP were identified, it would be confirmed with biospecimens from Gates MRI BCG ReVax study. Correlate analysis will also be performed with specimens from the M72 prevention of disease (PoD) M72 Phase 2b trial, with data expected in 2023. Likewise, this will be confirmed with biospecimens from the M72/AS01 Phase 3 study. One hope is that it will be possible to find a correlate that links PoSI with PoD. This will be needed to advance the BCG revaccination strategy since it is very unlikely that there will be resources available to fund a large Phase III prevention of disease study.

The BCG ReVax primary endpoint data, based on sustained IGRA-conversion (PoSI) is expected in 2024. The hope is that other stakeholders will sponsor BCG ReVax PoSI studies, with other BCG strains, in other

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

geographies to generate data that could support a policy recommendation to broaden the target population.

*Discussion (open session):*

*What is Gates MRI considering as a step beyond the current BCG ReVax study to support/prepare the pathway for expanding the use case for BCG and revising the policy recommendation for revaccination of adolescents and adults? Do we know what evidence is needed to drive policy consideration?*

The BCG ReVax programme is not considered product development, since BCG is commercially available (AJ Vaccines, Danish strain) and licensed in South Africa for children and adults. A label or indication is not needed; the intent was to collect evidence that may inform policy for an expansion of use.

As it stands, the current BCG ReVax data policy package may be considered weak since the studies do not have a disease endpoint; the endpoint is PoSI and there is currently no evidence to relate the two, i.e. that prevention of sustained infection will prevent disease. Relating the two will rely on identifying a common correlate between the BCG ReVax and M72 studies that would demonstrate PoSI leads to PoD. Also, it is unknown if the effect of BCG ReVax will differ with geographies or strains; the hope is that there will be interest and funding to run a replicate study in another region but there is no commitment to this, currently. Without further studies, correlates are the only route to a broader policy recommendation for BCG.

*Will the BCG ReVax study evaluate the interaction between BCG and Covid19? And if there is an effect, how could this impact BCG availability and the risk of supply shortages?*

BMGF and others are aware of the potential supply issue, in the event that BCG is shown to have a protective effect on Covid19. The BCG ReVax study was paused because of the South Africa lockdown in March, and when it restarted, exploratory endpoints were added to test participants suspected of Covid19 infection. SARS-CoV-2 serology will be performed every 6 months for a duration of 2 years. However, BCG ReVax is not powered to detect a protective effect for Covid19; there is no active or enhanced passive surveillance for respiratory illness in the amended protocol.

*What kind of modelling has been done in terms BCG uptake in adolescent/adults is needed to have impact? (especially if it cannot be administered to people living with HIV (PLHIV?))*

GMRI has not done any modelling. The only data is on PoSI and there'd need to be assumptions about how this relates for PoD. Without intervention, 95% of those infected will not progress to disease. Even if sustained IGRA conversion were reduced in the study, it would not be possible to assess how many of these individuals would have progressed to TB disease.

*Regarding the BCG ReVax programme, and other novel live BCG approaches, what safety data/evidence would be necessary to include PLHIV into the target population for these vaccines?*

There are safety concerns with respect to BCG and PLHIV, especially those who are not on ART; it's a risk benefit discussion. The hope is that developers working on improved BCG approaches will address this.



**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

*For IGRA positive individuals, does this indicate functional T-cells and a reduction of risk, and is this a potential PLHIV population for which it may be safe to administer BCG (and M72)? (and if it's negative, could it be a correlate of risk)*

Possibly. With respect to AS01-adjuvanted vaccines such as M72/AS01, it is noteworthy that AS01-adjuvanted HPV vaccine induced reasonable immune responses in immunocompromised individuals and conferred protection from disease, so this could be interpreted as suggesting that there is an opportunity for M72/AS01 in PLHIV.

## 2.2 M72/AS01<sub>E</sub> product development

The [M72/AS01<sub>E</sub> Phase 2b prevention of disease study](#) in a QFT-positive population was conducted in HIV-negative adults, 18 to 50 years of age, with latent M. tuberculosis infection living in Kenya, South Africa, and Zambia. Participants were randomly assigned (in a 1:1 ratio) to receive two doses of either M72/AS01<sub>E</sub> or placebo and demonstrated 49.7% (95% CI 2.1 to 74.2%) vaccine efficacy for prevention of disease (PoD).. The efficacy lasted through [final analysis](#), 3 years later.

Following these encouraging data, GSK licensed M72/AS01<sub>E</sub> to the Gates MRI, enabling continued vaccine development and potential use in LMICs. Under the commercial license terms, GSK will support tech transfer to Gates MRI, Gates MRI will lead product development and sponsor future clinical trials and GSK will provide AS01 adjuvant for the development program and beyond. The goal is to accelerate development, access and public health impact of the M72 candidate.

Gates MRI have developed a Target Product Profile for this candidate. The profile for first registration includes the target population of 16-35 years (no restriction in terms of QFT status and PLHIV), at least 50% efficacy over 3 years duration initially, single dose vial for each of antigen and adjuvant for mixing at the point of administration, 2 dose regimen given 4 weeks apart.

Several key questions related to the Phase 3 study design, will need to be addressed to reach that goal:

- Phase 2b study provided evidence that M72/AS01<sub>E</sub> prevents disease in IGRA-positive individuals, but there is no data on the duration of protection beyond 3 years, or whether the vaccine is able to prevent infection and/or disease in IGRA-negative individuals in whom risk of disease is expected to be later..
- With respect to the Phase III clinical trial design, consensus is needed on appropriate primary endpoint definition for PoD, which age range to be included, , which countries to include and how to enrich for high risk to adequately power the study.
- Strategy is to target first registration in South Africa, because there is data that could support a regulatory filing and burden is high. However, the Phase III will need to include additional countries in as Africa, Asia, and Latin America where IGRA-positive individuals is expected to be lower. A large epidemiology study is planned to identify potential sites and to build Phase 3 capacity.
- The delivery considerations depends on target age group and whether vaccine has efficacy in IGRA -ve individuals, as well as IGRA +ves. If it works in both, school delivery strategies become a

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

possibility. If it does not, this will be challenging because screening for QFT status in national programs is currently not feasible.

- GMRI are eager to understand what needs to be included in the Phase 3 study design, and what implementation research is needed to support WHO policy recommendation, PQ and financing.

**Critical path and assumptions**

- Generate safety and immunogenicity data in a Phase 2 study (NCT04556981) to support inclusion of PLHIV in Phase 3 VE trial.
- Develop Phase 3 protocol jointly with stakeholders, subject matter experts; select countries for the study and engage with national regulatory authorities to agree protocol design.
- Need to identify and prepare sites for Phase 3 vaccine efficacy (VE) trial based on epidemiology studies to identify high incidence sites, and to build capacity at those sites.
- Conduct Phase 3 vaccine efficacy study
- In parallel, the M72 antigen and adjuvant manufacturing process must be scaled up for Phase 3 and to support commercialization
- The new drug product must be produced to supply Phase 3 clinical trial material, and this involves identifying a commercial manufacturer / marketing authorization holder, and technology transfer drug product manufacturing

**Current Status:**

- Manufacturing development to support Phase III is underway for both the drug substance and drug product
- The Phase 2 in PLHIV (NCT04556981) will start in late 2020 in South Africa, with read-out expected in early 2022 so that this data can be included in the submission for the Phase III submission (intended for mid-2022); aim is to generate sufficient safety data to support licensure in this population,
- The epidemiology study will begin in late 2021, expanding to new countries and sites that are intended for inclusion in Phase 3. Major objectives are to assess baseline IGRA status by age and site, and to describe the incidence of TB disease to inform selection of high burden sites. Intent is to establish operational feasibility for each site (QFT-positivity by age, quality of TB surveillance & study procedures) so that for epi sites can seamlessly transition to Phase 3.
- Discussion on design of Phase 3 studies is underway, trial is intended to start in early 2023. The aim is to unequivocally demonstrate safety and VE for PoD in QFT-positive participants to support licensure for use, irrespective of QFT status and including in PLHIV, so that QFT screening is not a pre-requisite. Trial simulations suggest that at least 14,000 subjects in very high incidence settings are needed to demonstrate VE in a randomized controlled trial (1:1 vs placebo) but could be as high as 20,000 depending on incidence. An interim analysis for VE could be explored once the

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

lower bound is at 0, to potentially accelerate submission of a first dossier while collection of efficacy data is continued until the lower bound is reached that is stipulated by regulators.

Key knowledge gaps, challenges and mitigation strategies in planning for Phase 3:

There is significant uncertainty with regards to incidence of *Mtb* infection and TB disease and a need to aim to emulate the attack rate that is seen in poor communities in South Africa and other LMICs to avoid the study becoming unfeasibly large or long. The highest possible TB incidence rate is needed to increase probability of unequivocally demonstrating efficacy. There is significant uncertainty with regards to true vaccine efficacy (VE); in the Phase 2b trial the primary endpoint demonstrated 50% VE but sensitivity analyses suggest that the primary endpoint definition will impact VE and incidence rate in IGRA-positives. As mentioned, we have no data on VE in IGRA-negative populations or PLHIV.

These gaps and challenges can be addressed by determining site-level QFT prevalence to select sites with highest incidence and to build capacity at those sites, by designing an adaptive trial with event-triggered primary analysis and interim analysis and ensuring IDMC oversight of unblinded data.

Trial simulations suggest key determinants of trial size relate to assumed vaccine efficacy and the lower bound of the 95% CI required by regulators; VE will drive the number of events needed to definitively conclude on VE. Study size to accrue the number of cases (events) depends on TB incidence. For QFT -ves, the study is unlikely to be powered to detect VE for PoD in QFT -ves. The impact TB preventative therapy (TPT) implementation will need to be considered in the trial design (is it feasible to include household contacts in the context of evolving TPT recommendations, how will IGRA-conversion while on study be managed?)

The Phase 3 study start is anticipated in Q2 2023, with interim VE data anticipated in 2028. There's an urgent need to define trial design and endpoints, trial population, participating countries and sites, and understand what data will be needed for recommendation should Phase 3 data be supportive.

Country selection has been initiated; site epidemiology study to start late 2021. Gates MRI is establishing a scientific advisory board to discuss primary endpoints, case definition and Phase 3 trial design and to gather input from stakeholders, subject matter experts and LMIC national regulatory agencies. WHO participation in defining trial design is critical to the success of the program.

*Discussion (open session):*

*Is there a way to accelerate the timeline to licensure, projected to be 2030 –to reduce the dependency on the epi study to identify and build capacity at sites, and rather to maximise wherever possible, data and capacity from Phase 2 studies?*

The epi study is not on the critical path to initiating the Phase 3 study; the development of manufacturing processes and the manufacturing of clinical trial material is. Site selection, readiness assessment and capacity building will happen in parallel to manufacturing process development.

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

*Given the timeline to efficacy data, is there any appetite from Gates MRI to explore antigen optimisation in parallel? Or optimisation of the presentation (currently separate vials for antigen and adjuvant with bedside mixing)? How much of the response is dependent on the adjuvant alone?*

The Phase 2b programme, and the positive efficacy signal was obtained with this antigen and adjuvant presentation; the developers and funders will incur significant risk and cost if there is deviation at this stage. With respect to the adjuvant supply, GSK has offered to supply adjuvant for clinical development and to enable market introduction. That said, the potential demand size for this vaccine is uncertain since it will depend on efficacy in IGRA -ve individuals; if there is no efficacy, the market, and demand for adjuvant will be significantly smaller than if the vaccine is broadly effective and can be administered to PLHIV.

While BMGF is supporting the GMRI's M72 strategy, it is in parallel interested in exploring next generation candidates, both with respect to antigens and adjuvants.

*Have you considered a futility analysis as part of the interim analysis for M72? (if there was futility, and this was associated with a potential correlate in the BCG analysis, this may change the prioritisation of and investment in a BCG revaccination strategy)*

Gates MRI is planning an adaptive trial design, but the clinical trial simulations suggest that all participants would already be enrolled at the time of interim analysis, so a futility analysis wouldn't impact trial size. There's not been any discussion as to how negative Phase 3 M72 data would impact interest or focus on the BCG ReVax strategy.

To conclude, PDVAC members can participate in Gates MRI's Scientific Advisory Board (SAB) in Phase 3 design & endpoint definition and are encouraged to do so, to provide a link to WHO. The SAB will convene in Q1 2021. The PDVAC secretariat within WHO can co-ordinate workstreams/stakeholders within WHO, including requesting SAG input on Phase III and early policy considerations, and preparing for a session in Q4 2021.

**3. R&D Roadmap for tuberculosis vaccines (Frank Cobelens Amsterdam Institute for Global Health and Development, AIGHD)**

In 2019, EDCTP commissioned AIGHD to develop a Global Roadmap for Research and Development for TB vaccines that:

- provides global stakeholders such as researchers, funders, industry, regulatory and policy decision makers with key actionable priorities that could help guide their actions.
- lists the short-term and the long-term strategic objectives for global TB vaccine development.

The roadmap lays out the path for developing and delivering affordable safe and effective vaccines for use in low- and middle-income countries and is framed with the 3 strategic vaccine development goals in mind, as defined by the WHO vaccine PPC guidance.

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

The roadmap lists activities under three themes: diversifying the pipeline, accelerating clinical development and ensuring public health benefit, and also categorises what enablers needed to maintain momentum in terms of funding, open science and stakeholder engagement. Activities are categorised by short term, medium term (2-5years), long term (beyond 5 years) and the inter-dependencies between them are mapped.

In terms of the process, the roadmap was developed in collaboration with WHO, and broadly replicated WHO's guidance development process:

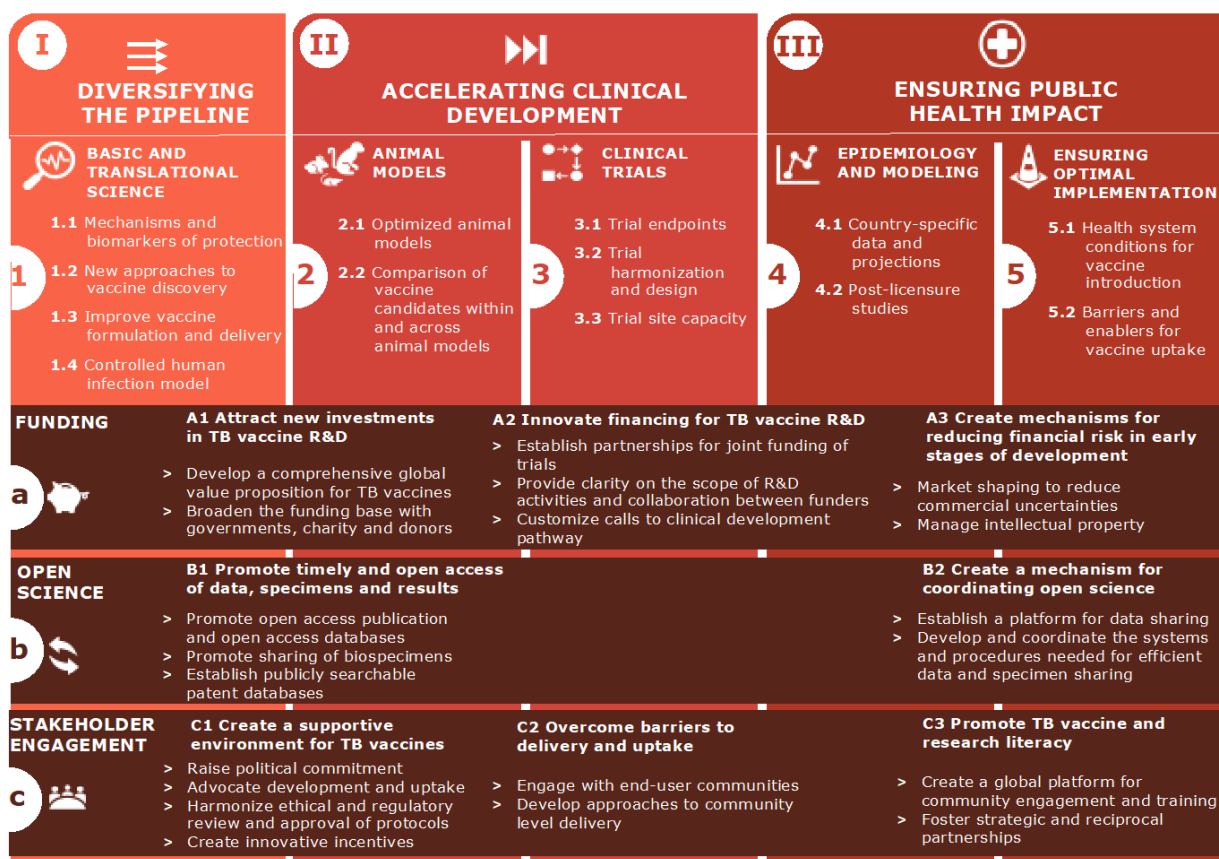
Between October and December 2019, 22 global expert stakeholders were interviewed to review the status of the clinical development pipeline and to assess how the candidates and their trajectory aligns with the 3 strategic TB vaccine development goals. The intent of this was to identify barriers to achieve the goals and to define solutions to overcome these barriers, considering the needs across preclinical development, clinical testing and post-licensure assessment.

The outcomes from these interviews were presented at a consensus building workshop in March 2020, co-organized with WHO and co-convened with a broader set of global stakeholders, including academics, vaccine manufacturers, regulators, funders, advocacy & community representatives, national TB program managers/policy makers, national EPI managers/policy makers and modellers. The objectives of this consensus workshop were to clarify and specify the overall goals and key challenges of TB vaccine development, define knowledge gaps and actions addressing the key challenges across the development pathway, reach consensus about prioritization, interdependencies and timing of the actions and lastly to define supportive conditions and next steps in the design of the TB vaccines R&D roadmap. A draft roadmap was developed based on these discussions.

The stakeholders from both the interviews and the consensus meeting provided input into the initial draft through several iterations, and the final draft was sent to PDVAC for review in early August. The specific request to PDVAC is to provide recommendations on the final draft and to endorse co-WHO authorship prior to publication. Regardless of PDVAC's endorsement, the next step of this process will be public consultation of the final draft to consider additional input.

The key barriers, activities and enablers proposed in the roadmap are described in the TB meeting presentation on the PDVAC website, [here](#), and summarized in the figure below.

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)  
Virtual Consultation 6: An update on Tuberculosis vaccine development activities  
3 September 2020**



*Discussion (open session):*

The current draft is an excellent assessment of the challenges and gaps that that need to be overcome in TB vaccine R&D.

*Who is the intended audience for the roadmap?*

The intended audience for this roadmap is broad, including researchers, funders, vaccine developers, regulators, EPI managers, community-based organizations, policy makers, procurement agencies.

*General comments from the PDVAC:*

The expectation of a WHO-authored roadmap is that the 'downstream elements' related to commercialization, policy and implementation will feature prominently, since the intended audience includes stakeholders across the product development to uptake continuum.

Some specific aspects of the roadmap could be expanded to strengthen the assessment of what will be needed to drive the downstream components and mitigate against late stage market access, delay or failure. These include

- manufacturing scale up and delivery (device) strategy – consideration of the vaccine presentation in relation to delivery considerations;

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

- strategy for sustainable manufacturing through commercialization and ensuring supply;
- plans for continued community engagement, building the case for the emerging candidates and creating demand;
- specific section on strategy to license TB vaccines for and delivery of vaccines to key target populations, most notably PLHIV;
- in general, the need to identify/propose programmatic delivery for vaccines intended for adolescent/adults/PLHIV needs to be strongly highlighted, since these will be outside of the childhood EPI schedule;
- the need to understand the drivers for policy making at the global level;
- preparation for the financing and procurement of TB vaccines in different settings

These elements could be further elaborated and incorporated into the current draft, drawing on material generated from the extensive consultation process so far.

**4. Current and future evidence on TB vaccines from mathematical and economic modelling (*Richard White, London School of Hygiene and Tropical Medicine*)**

Mathematical modelling is used to help determine full vaccine value assessments for new TB vaccines, to inform strategic prioritization and product development of the most promising candidates. Models can be used to project impact of potential vaccine characteristics and implementation strategies to guide or refine TPP/PPCs, and as clinical trial data becomes available, they help to estimate potential future epidemiological effectiveness to guide decision making. LSHTM has published systematic reviews of studies that contribute to TB vaccine impact modelling and periodically update them; the last one was in 2016 and summarised 23 studies ([Harris et al, 2016](#)). Since then, an additional 4 studies have been published.

The vaccines that are modelled are categorised by mechanism of action (PoD or PoSI, or both), whether it is effective in uninfected or infected individuals, or both, the target population, duration of protection and level of efficacy. To summarise what has already been gleaned from vaccine impact modelling, assuming vaccine introduction in 2025 with impact over 25 years to 2050:

Prevention of infection (PoSI) versus prevention of disease (PoD):

- Globally, prevention of disease vaccines would provide faster and greater impact than prevention of infection, but
- Impact of prevention of sustained infection vaccine increases in higher transmission settings, eg India & SA ([Harris et al, 2020](#))

Pre- versus post-infection:

- In China, South Africa and India, a vaccine efficacious for prevention of disease in post-infection populations would have greatest impact, but

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

- Vaccines efficacious for prevention of infection or disease in pre-infection populations, had increasing impact in higher transmission settings eg India & SA

Duration of protection:

- In LMICs, as little as 5 years protection may be cost effective if targeted at adolescents and adults
- With 10-yearly mass campaigns, and 50% VE, duration of protection around 5 years in China, 4 years in S Africa and 3 years in India could lead to ~25% reduction in TB incidence in 2050

Vaccine efficacy:

- In LMICs, as low as 20% VE could be cost effective (we could measure vaccine efficacy that low) if delivered to adolescents/adults

Age:

- In LMICs, adolescent and adult vaccination may deliver greater and faster impact than infant vaccination because the sources of infection are removed from the population
- To reduce TB in 0-4 year olds, vaccination of adolescents/adults may be more effective than vaccinating neonates directly
- Vaccines suitable for latently infected older adults (>60 years) may provide greater impact than adolescent vaccination in ageing, reactivation driven epidemics, such as China

HIV

- Population-level impact in S Africa would be higher with a vaccine safe and effective in HIV positive populations.

In terms of implications of these insights on vaccine development, development of vaccines for adolescents/adults should be prioritized for maximum population-level impact by 2050. In populations with high LTBI levels, such as China, inclusion of older adults in clinical trials (at least 60-64 years) would be beneficial. Vaccine impact in post-infected individuals is important in all settings, but pre-infection populations should also, or instead, be recruited in higher transmission settings such as India & SA. Ideally, if feasible, trials should be powered to assess efficacy in both pre- and post-infected populations. It will be important to demonstrate safety and efficacy in PLHIV.

*With respect to endpoints*, in all settings, disease endpoints would be useful for demonstrating future impact, however, in higher transmission settings infection endpoints could be used, especially as proof of concept, as would be the case in India and South Africa. If feasible, it would be useful to power studies to detect low levels of efficacy since these could still have significant public health impact in high transmission settings. Studies would benefit from extended follow up to 5+ years (e.g. immuno subgroup), but shorter duration vaccines may be impactful and cost-effective.



**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

The vaccine impact of both M72 and BCG ReVax are being modelled by LSHTM. If efficacy signals are confirmed in the planned or current efficacy, respectively, both vaccines could deliver substantial population-level impact. For BCG ReVax, it will be important to explore efficacy on prevention of disease.

For M72, models need to explore duration of protection, pre-infection efficacy and prevention of infection as well as feasibility of mass campaigns. Preliminary work on vaccine cost effectiveness, assuming an indication of PoD, 50% VE and 15 years duration of protection, equally safe and protective in PLHIV, deployed in South Africa and India between 2025-2050. The vaccine delivery was through routine immunization in 10 or 15 year olds, no mass campaigns, with 80% coverage. The vaccine was a 2 dose regimen, at \$5/course and 3% discounting. Two scenarios were assessed: vaccination post infection, and pre and post infection.

The incremental cost per DALY averted: (discounted 2025-50, incl vaccine and TB treatment costs) in South Africa, ranged from \$24 (2- 66) for a pre- and post-infection vaccine delivered to 10 year olds, to \$316 (182 - 636) for a post infection vaccine delivered to 15 year olds. All scenarios explored were cost effective when compared to the latest (conservative) 'revealed' willingness to pay threshold of \$547/life year saved [Meyer-Rath PLoS ONE 2017]. In India, the incremental cost per DALY averted ranged from \$143 (43-337) for a pre- and post-infection vaccine delivered to 10 year olds, to \$1,660 (718-4,246) for a post infection vaccine delivered to 15 year olds. Using the GDP per capita threshold of 1,939 (2017) in India, all scenarios are cost effective. However, a local preliminary analysis of opportunity costs gave a lower bound for a WTP threshold of \$223 (Ochalek, CHE working paper 2019) => a post infection only vaccine delivered to 15 year olds may not be cost effective. In summary, a M72-like vaccine could be cost effective in both settings, depending on willingness to pay.

WHO is funding an assessment of full value of vaccine assessment (FVVA) for TB vaccines. The scope includes all LMICs, as well as individually in the 5 BRICS countries. It involves data collection, transmission modelling with health systems and societal economic assessment, based on the attributes of vaccines described in WHO PPCs (includes M72-like and BCG ReVax-like candidates). Several outcomes are planned including impact on TB incidence, morbidity and mortality, CE and budget impact outputs, RoI impact on equity impact on GDP and impact on AMR. It is aimed at country and global decision makers and funders. The project will proceed until Sept 2021

Work is also underway to evaluate introduction strategies, in both Gavi and non-Gavi eligible countries, assessing the impact of both supply side (supplier prioritization, financing and procurement criteria) and country driven factors (demand, political will, health systems readiness, regulatory assumptions).

BMGF is funding a M72/AS01 and BCG revaccination specific modelling project, looking at the epidemiological and economic impact of M72 and BCG ReVax in South Africa & India. It assesses uncertainty and implications of variability in product characteristics, introduction policy and implementation strategy (what are the product attributes, will it be deployed by routine/special immunization campaigns, PLHIV on ART, which vaccine will we have first, and what will the indication of that vaccine be?) in the context of future health systems projections. The audience is BMGF to inform investment decision making, but likely to be other stakeholders who would consider the analysis informative for strategic planning. The project will run until end 2022.

**2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)**  
**Virtual Consultation 6: An update on Tuberculosis vaccine development activities**  
**3 September 2020**

Related to this is work ongoing with decision makers in each of South Africa, India and China to get input into potential implementation scenarios for M72 and BCG ReVax, the associated, acceptable costs, within the different contexts of each country, and the feasibility of deploying a vaccine for the adolescent/adult TB population. This project will complete in early 2021.

Discussion (open session):

*Do we know if the mask wearing to control Covid19 had any impact on TB transmission in the countries where these vaccines are being modelled?*

There is work ongoing to look at this, and it may have an effect on reducing transmission, but this is not expected to outweigh the disruption in treatment for TB – so long term, Covid19 is likely to cause an increase in TB. There is some perspective that physical distancing in combination with a moderately efficacious TB vaccine could increase effectiveness.

*How do you factor in the potential impact of transmission in the modelling?*

This is built into assumptions of the vaccine and the scenarios that are run in the dynamic model, that looks at transmission; it remains to be seen if effects will be observed in clinical studies or post implementation.

*Are pregnant women included?*

They could be included in the BRICS analysis if these countries elect use in pregnancy as a risk strata to the model.

*How is the cost effectiveness data being generated for AMR? Are other diseases being used as proxies?*

Model doesn't use proxies, but it does assume a proportion of TB that is multi-drug resistant, and that can be impacted by a vaccine (and reduces the use of antibiotics).