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

Concept note:

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

1. **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.

2. **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.

3. **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 will focus on two of the most advanced approaches, both of which focus on 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. 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.

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 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, with funding from The European Developing Countries Clinical Trials partnership (EDCTP,) and 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

Intended outcomes:

- 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
- Identification of high priority follow up work to the WHO-funded Full Value Assessment of TB Vaccines project
- Identification of how BMGF-funded M72/AS01 and BCG revaccination modelling project could be more useful to global and country stakeholders
- PDVAC recommendations on the draft TB vaccine roadmap, and a decision related to potential co-authorship

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06:00 Seattle; 8:00 Lima; 9:00 Washington DC; 14:00 London; 15:00 Johannesburg; 15:00 Geneva; 18:30 New Delhi, 21:00 Beijing; 22:00 Seoul

Time (Geneva CEST)	**Topic**	**Duration**	**Detail**	**Moderators, speakers**
15.00 – 15.05	Welcome and roll call			David Kaslow / Birgitte Giersing
15.05 – 15.10	The context for this PDVAC meeting	5’	• Rationale for the topic selection • Overview of pipeline • Objectives of the meeting	Birgitte Giersing
15.10 – 15.50	Update on Gates MRI TB Vaccine Development Activities	(25’ + 15’)	• Update on current status on phase IIb BCG revaccination study in South Africa; discussion related to additional studies and data required for policy change. • Review of M72/AS01 study plans, licensure and potential policy recommendation strategy; identification of critical areas for WHO/PDVAC input	Alex Schmidt (Gates MRI)
15.50 – 16.20	Review of the Global Roadmap for R&D for TB vaccines	(15 + 15)	• Purpose and process for developing the TB vaccine Roadmap • Review of the proposed 3 themes to advance TB vaccines, and how the activities relate to the 3 WHO development goals; are there gaps?	Frank Cobelens (AIGHD)
16.20 – 16.45	Modelling the potential value of TB vaccines	(15 + 10)	• Overview of the vaccine health and impact model framework and components, and the M72/AS01 and BCG revaccination specific modelling projects	Richard White (LSHTM)
16.45- 17.00	Discussion	15’	• Open session	All
17.00 – 17.30	**Discussion (closed session) – PDVAC only** o Are there 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? o Does PDVAC have recommendations on the draft TB vaccine roadmap? o Does PDVAC support WHO co-authorship of the roadmap? o Are there any recommendations for high priority follow up work to the WHO-funded Full Value Assessment of TB Vaccines project o Are there suggestions with respect to how the BMGF-funded M72/AS01 and BCG revaccination modelling project could be more useful to global and country stakeholders			