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## Product Characteristics for New Tuberculosis Vaccines : WHO preferences

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Just a few months away from the United Nations General Assembly first ever meeting on tuberculosis (TB), it is useful to insist on a central assumption of the World Health Organization (WHO) 'End TB' strategy: a new tuberculosis vaccine halting the spread of both drug-sensitive and drug-resistant *Mtb* strains is required to reach the expressed goals (1).

*Mycobacterium tuberculosis* (*Mtb*), the cause of the devastating global TB epidemic, kills more persons than any other single infectious agent; an estimated 1.674 million persons died of TB in 2016. Approximately one-quarter of the world's population – 1.7 billion individuals –are estimated to be infected with *Mtb*; of which five to fifteen percent likely will develop TB disease during their lifetime. While months-long, multi-drug regimens offer hope for cure from active TB disease, many cases of TB in low- and middle-income countries go undiagnosed and untreated. Additionally, the global spread of drug-resistant *Mtb* strains represents an ominous threat. Approximately 10% of TB cases globally are caused by multi-drug resistant (MDR-TB) or extensively drug-resistant TB (XDR-TB). Treating patients with MDR- and XDR-TB currently demand therapeutic regimens with multiple, often toxic drug combinations, given for long durations of time. For XDR-TB, the costs associated to treating drug-resistant strains are exorbitant, and even the best attempts at cure may prove insufficient (1).

The accelerated development of new tuberculosis (TB) vaccines suitable for licensure, policy decision and optimal use and impact where needed represents a major priority for the

World Health Organization (WHO) (2). On 3-4 October 2017, WHO convened a meeting of experts in Geneva to review and comment upon proposed WHO preferred product characteristics (PPCs) intended to provide guidance to scientists, regulators, funding agencies and industry groups developing TB vaccine candidates intended for WHO prequalification.

### **PREFERRED PRODUCT CHARACTERISTICS FOR TB VACCINES**

WHO presented two sets of TB vaccine PPCs, one guiding the development of TB vaccines for adolescents and adults, the other addressing TB vaccine development for infants (Annex). The full document, with contextual background information is presented elsewhere (3). The need for two related but distinct PPCs for these different indications mainly stemmed from the additional implications that need to be considered when developing TB vaccines for infants intended either as replacements for the currently recommended bacille Calmette-Guérin vaccine (BCG), or as adjuncts to BCG vaccination, considerations different from those relevant to vaccinating adolescents and/or adults with new TB vaccines.

#### ***Developing a safe, effective and affordable TB vaccine for adolescents and adults***

Given the central role that adolescents and adults with active pulmonary TB disease play in spreading *Mtb* infection, including to infants and young children (4), the prevention of pulmonary TB disease in adolescents and adults is a priority strategic target in TB vaccine development. The vaccine should be protective in people with or without evidence of *Mtb* infection, and prevent progression to TB disease following primary infection, as well as following re-infection(s) and re-activation in subjects with latent infection. Mathematical modelling studies suggest that the ability for vaccines to prevent pulmonary disease in subjects already *Mtb* infected will be a most important driver of impact on incidence in the short term,

given the prevalence of latent infection in high endemicity countries and their contribution to the maintenance of transmission (4, 5).

***Developing an affordable TB vaccine for neonates and infants with improved safety and efficacy as compared to BCG***

A new TB vaccine intended for administration in early life, providing both a superior degree and longer duration of protection as compared to the current BCG vaccines, that could be safely administered to infants with HIV infection or other causes of immune suppression, would represent an important public health advance. Improved manufacturing securing sustainable supply would represent an additional improvement. Clear evidence of superiority would likely drive policy change, but demonstrating only marginally improved characteristics may not support global implementation as a BCG replacement. BCG boosting strategies are also being considered. The possibility that past mycobacterial exposure may impact the vaccine response in a negative way also calls for continued efforts for early life TB vaccine research (6).

**CONCLUSION**

Developing new, effective TB vaccines represents a critical global health imperative. The WHO calls for a strengthening of this effort. The PPCs for TB vaccine development targeting adolescents and adults, and infants, respectively, presented here are offered to help guide this important and challenging initiative.

**ACKNOWLEDGEMENTS:**

The expression of WHO preferred product profile for new TB vaccines build on a consensus-generating wide expert, stakeholder and public consultation process (3). The document represent the collective views of a WHO Tuberculosis Vaccine Working Group.

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