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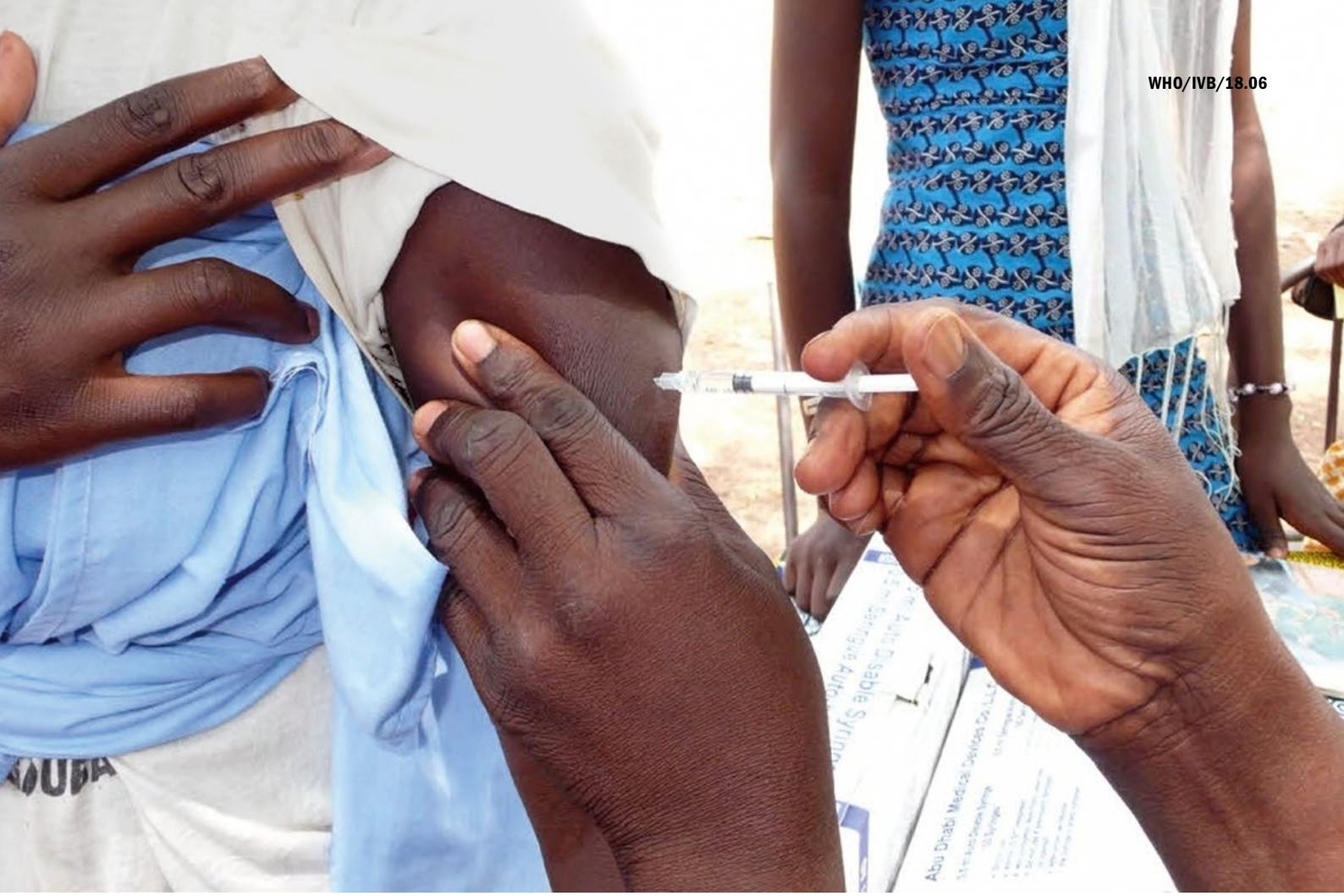

WHO Preferred Product Characteristics for New Tuberculosis Vaccines

DEPARTMENT OF IMMUNIZATION, VACCINES AND BIOLOGICALS

Family, Womens's and Children's Health (FWC)

World Health Organization

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This publication contains the collective views of an international group of experts of the WHO Tuberculosis Vaccine Working Group informed by a consensus building consultation process and does not necessarily represent the decisions or the policies of WHO.

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Process and acknowledgements

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WHO Secretariat

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ABBREVIATIONS & ACRONYMS

BCG	Bacille Calmette-Guérin
GVAP	WHO Global Vaccine Action Plan
GTB	Global Tuberculosis Programme
IGRA	Interferon-γ release assay
IVR	WHO Initiative for Vaccine Research
LMIC	Low and middle income country
MDR	Multi drug-resistant
XDR	Extensively drug-resistant
Mtb	*Mycobacterium tuberculosis*
PDVAC	Product Development for Vaccines Advisory Committee
PoD	Prevention of Disease
PoI	Prevention of Infection
PoR	Prevention of Recurrence
PPC	Preferred product characteristic
PQ	Prequalification
RCT	Randomized clinical trial
SDG	Sustainable Development Goals
TB	Tuberculosis
TST	Tuberculin skin test
UN	United Nations
VPPAG	Vaccine Presentation and Packaging Advisory Group
WHO	World Health Organization

SUMMARY

Spurring development of critically needed tuberculosis (TB) vaccines and ensuring that emerging TB vaccines are suitable for licensure and policy decisions to support optimal use where most needed represent high priority initiatives for the World Health Organisation (WHO) *(1, 2)*. The WHO Preferred Product Characteristics (PPCs) for TB vaccines described in this document provide guidance to scientists, funding agencies, and industry groups developing TB vaccine candidates intended for WHO prequalification (PQ) and policy recommendations. The PPCs do not replace existing requirements related to WHO programmatic suitability for PQ *(2)* but are intended to complement them. This document presents and discusses preferred characteristics, not minimally acceptable criteria. In addition to quality, safety, and efficacy aspects, it is important that developers and manufacturers consider parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delayed or unsuccessful introduction and deployment.

In this report, two sets of PPCs guiding TB vaccine development are provided.

The first set of PPCs (Section 2), focus upon efforts to develop TB vaccines for adolescents and adults. *Mycobacterium tuberculosis* (*Mtb*) is spread from persons with pulmonary TB. Adolescents and adults represent the key sources of *Mtb* stransmission and are the primary contributors to the overall disease burden *(4)*. Vaccines should provide protection in both subjects with and without evidence of latent *Mtb* infection *(5)*. Although mathematical modelling studies suggest TB vaccines may be cost-effective at relatively low vaccine efficacy (VE) *(4)* a preference for a VE above 50% is expressed, in order to better contribute to achieving the ambitious WHO End TB Strategy goals. The durability of protection will also be an important driver of impact *(4)*. At least 2 years

of follow-up post-vaccination should be planned for to produce the estimates of efficacy supportive of policy evaluation, with further follow-up beyond. The requirements for booster doses more than every 5–10 years would be an important logistic challenge.

The second set of PPCs (Section 3), addresses development of vaccines to improve upon Bacille Calmette-Guérin (BCG) vaccination in infants. The development of a safer, more effective, and more efficiently produced alternative to BCG vaccination in neonates and infants would represent an important public health advance, even if impact would be slower than a vaccine preventing pulmonary TB in adolescents and adults *(5)*. BCG boosting strategies also remain under consideration. The continued prioritization of efforts to develop early life vaccination strategies are also supported by observational and animal study data suggesting there may be a negative influence of past mycobacterial exposure on the ability to induce vaccine-derived protection against tuberculosis *(6)*.

Regarding clinical evaluation, proof of concept and pivotal trial design, three different endpoints are discussed in Section 2 that are relevant to TB vaccine development in adolescents and adults: prevention of pulmonary TB disease (PoD); prevention of recurrent TB disease in persons undergoing or completing treatment for active TB (PoR), which includes prevention of reactivation of existing infections and/or prevention of disease due to new infections; and prevention of sustained, *de novo* infection with *Mtb* (PoI) as documented on the basis of available infection diagnostic tools.

Unfortunately, tools available to developers of vaccines targeting some other infectious diseases, such as immune correlates or surrogates of protection, animal challenge models that are known to accurately predict the protective potential of vaccines in humans, and human challenge models, are not sufficiently established for TB vaccine developers to guide vaccine development with confidence. As the assessment of the PoD endpoint requires a large sample size and long duration of follow-up, PoR and PoI endpoints have been identified as alternative options to provide early evidence of biological activity in humans.

PoR may be valuable endpoint, but more evidence about the potential impact should be generated. Potential use and impact will likely differ according to the proposed timing of vaccination relative to initiation and completion of treatment.

A vaccine that would only provide protection against infection to subjects who don't have latent *Mtb* infection, will however take much longer to impact the population burden of disease, as compared to a vaccine capable of preventing TB disease both in subjects with and without latent

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