WHO Preferred Product Characteristics for New Tuberculosis Vaccines

World Health Organization
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WHO secretariat

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111 # Abbreviations & acronyms

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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

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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-Guerin (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 *Mtb* infection.[7] Further research is needed to establish the true relationship between vaccine-derived prevention of infection as we are presently able to diagnose it, and the subsequent risk of disease. Hence, the acceptability of PoI as a vaccine trial endpoint supportive of policy decisions implementing wide-scale application for this indication will require further discussions, intended to clarify the required evidence that would establish a sufficient relationship between PoI and PoD endpoints to merit a PoI indication.

It will be imperative for any new TB vaccine to be safe, affordable and accessible to persons in low and middle income countries (LMICs). New TB vaccines should be safe for use in HIV-infected individuals, given the extensive overlap between TB and HIV epidemics, and the devastating impact that TB has on HIV-infected persons. Advances in vaccine development efforts need to be brought to bear in controlling *Mtb*, now the globe's number one killer among infectious pathogens.

1. Background, purpose and target audiences

This document describes World Health Organisation (WHO) preferences for parameters of TB vaccines, in particular their priority indications, target groups, clinical data needed for assessment of safety and efficacy, implementation strategies and general determinants of the value proposition.[2] These preferences are shaped by the global unmet public health need in priority disease areas for which WHO encourages vaccine development for maximal impact and suitability for use in low- and middle-income countries (LMICs).

The primary audience for this document includes all entities intending to achieve widespread use of new tuberculosis vaccines. Preferred product characteristics (PPCs) are intended to inform research and development efforts, ensuring that they are prioritized to meet global public health needs. Characteristics specific for particular products are beyond the scope of these documents. PPCs do not quantify explicit minimal performance thresholds. Whether or not a vaccine meets the PPC criteria, it may be assessed by WHO for possible prequalification and policy recommendations by the WHO Strategic Advisory Group of Experts (SAGE) on immunization.[8] The WHO prequalification process assesses vaccine quality, safety, efficacy, and suitability for use in LMICs.[9] WHO prequalification is a prerequisite to procurement by United Nations (UN) agencies.[3, 10] Low programmatic suitability of new vaccines could constitute an important hurdle and delay introduction and deployment. These PPCs will be reviewed periodically and updated when necessary in light of changes in scientific knowledge and technology.

The PPCs are complementary to other WHO documents providing guidance on characteristics such as vaccine presentation, packaging, thermostability, or formulation and disposal. The WHO Vaccine Presentation and Packaging Advisory Group (VPPAG)[11] has developed a preferred product profile addressing these characteristics. Innovation aimed at improving programmatic suitability in the field of thermostability, ease of delivery and pain minimization are strongly encouraged.

2. New tuberculosis vaccines: a critical, unmet global public health need

Mycobacterium tuberculosis (*Mtb*) is the cause of a global epidemic of TB, with devastating public health and economic consequences. *Mtb* kills more persons than any other single infectious agent; an estimated 1.674 million persons died of TB in 2016.[12] Moreover, approximately 374,000 of these TB deaths occurred in HIV-infected individuals, making TB the number one cause of death among HIV-infected individuals worldwide.[12] Approximately 1.7 billion individuals, one-quarter of the world's population, are estimated to be infected with *Mtb*.[5] Ten per cent of these persons, approximately 170 million, are expected to develop active TB disease during their lifetime. In 2016 alone, an estimated 10.4 million cases of TB developed across the globe, with 6.76 million (65%) occurring among men, 2.64 million (25%) among women, and 1 million (10%) in children.[12]

To a great extent, TB represents a disease of the impoverished. While public hygiene and specific control measures have reduced the incidence of TB in many developed countries, *Mtb* infection and TB disease continue to occur at alarming rates globally.[13] *Mtb* infection results from inhalation of

Mtb aerosolized from the lungs of persons with active pulmonary TB. Living conditions in high density slums, in poorly ventilated rooms, packed mini-buses, stifling barracks for migratory workers, and overcrowded clinics where undiagnosed patients with active TB place many other patients at risk, are among the conditions that foster the spread of *Mtb* infection and the subsequent development of TB disease. Accordingly, control of TB ultimately has been considered a question of justice and human rights.[12]

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, with a risk of fatal outcome and devastating consequences for those who live or work in proximity. The development and global spread of drug-resistant *Mtb* strains now 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). In certain regions and countries, such as Eastern Europe, central Asia and Russia the proportion of cases caused by drug-resistant TB is much higher than the global average.[12] Although cases of drug-resistant tuberculosis (DR-TB) result from inadequate treatment of drug-sensitive TB resulting in the selection of drug-resistant *Mtb* strains, incident cases of MDR- and XDR-TB also may result from primary acquisition of drug-resistant strains.[14]

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, even the best attempts at cure may prove insufficient.[15] Estimates of the cost of treating MDR-TB range from 8-fold to 15-fold higher than for treating drug-sensitive TB; estimates for treating XDR-TB run from 25-fold to 32-fold higher. [7, 16] In low- and middle-income countries, these costs often make the treatment of MDR- and XDR-TB patients difficult if not impossible, subjecting the infected individual to a near certain death sentence while increasing the likelihood of the primary spread of these deadly and difficult-to-treat strains to others in the community.[14] While recent studies offer the potential for shorter and less expensive drug treatment regimens for drug-resistant TB [17, 18], the emergence of strains resistant to more drugs remain a risk with any drug treatment.

The WHO Global TB Programme (WHO-GTB) has developed the End TB Strategy, endorsed by the UN General Assembly, targeting a 95% reduction in TB deaths, and a 90% decline in new TB cases, between 2015 and 2035.[19] Reaching these targets will require an acceleration of the annual decline in global TB incidence rates from the 2% per year decline recorded in 2015 to a 10% per year by 2025. Beyond 2025, the rate of decline of TB cases will need to accelerate further, to an estimated 17% per year, to meet the 2035 goals. For this to occur, additional tools must be available by 2025. Reaching the End TB strategic goals will be dependent on the availability of vaccines to contribute to the global fight against tuberculosis. New vaccines are required to complement available and pipeline drugs and diagnostic technologies. As there is no evidence suggesting that molecular mechanisms of drug resistance in *Mtb* affect the susceptibility to immune control, it is likely that vaccine protection against drug-resistant TB will be equivalent to that against drug-sensitive TB. Development of new, safe and effective TB vaccines would represent a critical tool in halting the spread of both drug-sensitive and drug-resistant-TB.

3. BCG vaccination: current status

BCG is a relatively inexpensive, widely accessible vaccine, administered to more than 85% of infants in countries where it is part of the national childhood immunization programme. A number of BCG strains are recommended and used throughout the world. There is a lack of evidence as to whether efficacy and safety differ across strains. A recent meta-analysis of BCG clinical trials demonstrated substantial BCG protection of infants and young children against meningeal or miliary TB (RR, 0.10; 95% CI, .03-.77).[20] Protection against pulmonary TB was more variable across studies, ranging from substantial protection to an absence of clinically important benefit, and with the possibility of variation in protection according to geographical latitude and of a masking, or blocking effect on vaccine-induced protection resulting from past exposure to mycobacterial infection.[20, 21] Neonatal BCG may reduce the risk of de novo *Mtb* infection in infants and young children, but there is no consistent evidence of protection against active TB disease greater than 10 years after infant vaccination in tropical climates. Retrospective and observational studies in Northern climates showed some evidence of protection against active TB disease for 20 years or more following school-aged BCG vaccination, and as long as 50-60 years for following infant BCG vaccination.[20, 22, 23, 24]

WHO recommends that in countries with a high burden of TB, a single dose of BCG should be given to all infants as soon as possible after birth, including infants born to women of unknown HIV status in areas of high HIV endemnicity. BCG, however, can cause local and disseminated disease in immunosuppressed individuals. For infants with unknown HIV infection status and who demonstrate no signs or reported symptoms suggestive of HIV infection, but who are born to HIV-infected mothers, BCG vaccination should be given after consideration of local factors that would increase the risk of TB to the infant such as a high prevalence of HIV and TB in the population. Infants with known symptomatic or asymptomatic HIV infection, however, should not receive BCG. Additionally, infants whose HIV status is unknown but who have signs or reported symptoms suggestive of HIV infection, and who are born to HIV-infected mothers, should not receive BCG. BCG may be administered once virological testing has ruled out HIV infection.[25]

There is evidence that BCG provides partial protection against leprosy[26] and the effect on Buruli ulcer is being considered. There is also some suggestion from retrospective, observational studies that BCG may provide non-specific, beneficial immune-modulatory effects.[27] Research exploring the impact of BCG on leprosy, and the non-specific effects of BCG, is ongoing. Policy-oriented assessments of new vaccines being developed for BCG replacement, including the value proposition for their use, will need to be made when considering the full spectrum of protection provided by BCG, based on available evidence.

4. Strategic goals

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, the prevention of pulmonary TB disease in adolescents and adults is the priority strategic target in TB vaccine development. It may represent an effective means of preventing *Mtb* infection and TB disease in infants and young children, as well as in adolescent and

adult contacts.[28] 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, 7]

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

While infants and young children with TB do not represent an important source of *Mtb* transmission, they represent an important, vulnerable group, and there is a need to improve upon the BCG vaccines currently in use. The possibility that past mycobacterial exposure may impact the vaccine response in a negative way,[29] which would impact the technical feasibility of vaccine development success, also calls for continued efforts for early life TB vaccine research. 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. A global value proposition, taking into account the low price of the existing BCG vaccines, and their effect on leprosy and non-specific effects if such effects are established, will need to be considered.

5. Clinical development pathways

Translational science

The development pathway for TB vaccines remains a challenge due to a lack of guideposts that help chart the way for developers of vaccines against many other infectious diseases, including immune correlates of protection against disease or infection, animal challenge models that are known to reliably predict vaccine efficacy in humans, or an established controlled human infection model (CHIMs).

Despite extensive efforts, no correlates of immune protection have been reliably identified for TB vaccines. Identifying immune correlates of protection remains a high priority given the potential for such biomarkers to advance the development and selection of future vaccine candidate selection. Conservation of study samples for future use, as new knowledge and technology emerge, is strongly encouraged to support this effort.

Animal challenge models represent a mainstay of the TB vaccine development pathway. Initial, small animal assessments most commonly utilize mice, often with later advancement to larger animals

such as guinea pigs and/or rabbits. *Mtb* challenge experiments in non-human primate species, such as rhesus macaques and cynomolgus macaques, often represent the final determinant of sufficient vaccine potential to enter into a costly clinical trial process. Recently, advanced scanning techniques, such as utilization of combined positron electron tomography and computerized tomography (PET/CT) scanning, have been employed in the non-human primate (NHP) challenge model. These approaches offer the potential for more rapid assessment of vaccine protection while reducing reliance on necropsy and costly pathology assessments, but the link between early radiological changes and conventional disease and survival endpoints needs to be further established.[30] Additionally, reliance on NHP efficacy studies represents a potential bottleneck to clinical TB vaccine development, given the scarcity of NHP experimental facilities capable of carrying out *Mtb* challenge experiments, the cost of such experiments, and the ethical sensitivities around non-human primate research. Further work is needed to assess with confidence the degree of protection demonstrated in animal challenge models that predicts a meaningful degree of protection in humans.

Controlled human infection models have proven valuable in advancing vaccine development for influenza, malaria, enteric diseases and other infectious diseases. Efforts are ongoing to develop a CHIM to assess TB vaccines, and overcome a number of challenges. Sufficient test sensitivity and post-challenge observation time will be required to detect a vaccine effect on the course of experimental infection. Optimally, a CHIM of *Mtb* infection would permit a pulmonary administration of *Mtb* that is both safe and easily detectable. *Mtb* strains are being developed for potential aerosol administration in a CHIM on creating genetic modifications that allow sufficient occurrence of replication cycles to mimic the natural stages of early *Mtb* infection, but also permit rapid and highly efficient killing of all administered organisms at a predetermined time point to ensure the safety of participants in such studies. *Mtb* strains engineered for CHIM that have genetic controls which enable *in vivo* survival to be terminated to assure safety also are being modified in novel ways to allow investigators to assess the status of infection following aerosol administration. Additionally, efforts are ongoing using BCG as a model mycobacterial challenge agent, including administration via the aerosol route. [31, 32, 33] The successful development of a CHIM of *Mtb* infection would represent an important breakthrough in TB vaccine development efforts.

Vaccination research against zoonotic tuberculosis and animal models suggest that the quality of immune responses and protection are sensitive to the route of immunization.[34] Further knowledge should be generated from aerosol, oral and intravenous immunization translational research studies.

Proof of concept studies and late stage clinical development

Utilizing standardized clinical endpoints in assessing TB vaccine efficacy is critical to the production of robust data supporting comparisons between preventive intervention studies. Standardized clinical endpoints also are of central importance to efforts to identify correlates and biomarkers of protection. Accordingly, standardized clinical endpoints should be used in vaccine efficacy studies, in line with existing guidance.[35]

Prevention of pulmonary TB in adolescents and adults represents the most important target for global health impact. Optimally, the vaccine would provide protection against progression to TB disease following primary infection, as well as following re-infection(s) and re-activation in subjects with latent infection. Unfortunately, a definitive phase 3 trial designed to assess PoD efficacy will

necessarily be large, expensive and of long duration. Accordingly, efforts are being made to identify relevant endpoints that could be assessed at earlier stages in smaller trials, increasing confidence in the likelihood of phase 3 success. Given the absence of reliable correlates of immune protection, highly predictive animal challenge models or CHIMs of mycobacterial infection, efficacy endpoints other than PoD are being explored which could provide clinically relevant evidence of biological activity. These alternative efficacy endpoints may provide public health benefit and could represent legitimate TB vaccine indications.

Prevention of recurrent TB represents one alternative efficacy endpoint being explored for advanced TB vaccine clinical trials. Due to high rates of TB recurrence, up to about four times higher than the background rate of new TB [36], and the development of a majority of such recurrences within a year after discontinuation of treatment, a vaccine study to assess PoR is seen as readily feasible when considering sample size requirements. Such demonstrated PoR activity would provide evidence of biological activity supporting progression to a larger study not limited to subjects treated for TB, with a PoD endpoint. It should however be noted that there is no evidence that the outcome of a PoR study would predict the outcome of a PoD study, when considering the profound way tuberculosis disease impacts the immune system. Success in a PoR trial will not be sufficient to support a recommendation for using the vaccine in the general population. Likewise, PoR failure may not mean that a vaccine is not worth being considered as a vaccine to prevent infection or disease.

More evidence is required about the potential impact of vaccines intended for use in people previously diagnosed with TB, and various product profile details regarding this strategy need to be considered. An important attribute relates to the timing of use relative to drug treatment. The potential role of a 'therapeutic vaccine', intended for concomitant use with drug treatment, may differ from a vaccine administered after treatment completion. There could be some overlap in mode of action, because prevention of some relapse cases would require a 'therapeutic' effect, when the infection has not been totally controlled by treatment. The potential for vaccine-based adjunctive immunotherapy to shorten drug treatment duration should also be considered. Early decisions on the product profile will influence clinical development pathways and public health targets. In the absence of evidence-based estimates of the public health impact of a PoR vaccine, and more details about the key product profile attributes, the development of a PoR vaccine is not identified as a stand-alone strategic priority preference in this document. This may need to be revised upon availability of new evidence.

Preventing sustained *Mtb* infection represents an additional possible endpoint for early assessment of biological activity of TB vaccine candidates. PoI studies aim to enrol adolescent and young adult participants who are not *Mtb*-infected (a determination usually based upon testing negative on a validated TB antigen-stimulated interferon gamma release assay (IGRA-negative) or on a PPD skin test), living in high TB endemicity areas and therefore at risk of acquiring *Mtb* infection, and assess the efficacy of a vaccine candidate in preventing the acquisition of *Mtb* infection (conversion from IGRA-negative to IGRA-positive, conversion of a negative to positive PPD skin test) over a specified time period. As is the case for PoR studies, a PoI study can provide evidence of biological effect more readily than a PoD study, when conducted in communities with high annual rates of de novo *Mtb*

infection, sometimes running upwards of 10 percent per year. The possibility for a PoI endpoint to support policy decision making, remains unclear. Several aspects need to be considered:

- A PoI trial success would establish proof of concept in subjects without evidence of latent *Mtb* infection. Considering the potential influence of latent *Mtb* infection on vaccine immunogenicity, it cannot be assumed that the same vaccine would induce protective immunity against progression to disease from reactivation of latent TB or reinfection, in subjects already infected with *Mtb* at the time of vaccination. Due to the high prevalence of latent infection in high endemicity countries, public health impact would most rapidly result from prevention of disease in subjects with latent *Mtb* infection.
- Conceptually, preventing *Mtb* infection would be assumed to represent a valuable contribution to public health. This benefit would only accrue, however, if at least some of the averted *Mtb* infections would have progressed to TB disease in the absence of vaccination. While it seems intuitive that this should be the case, one must recall that among those infected with *Mtb*, only 10% develop active TB disease in their lifetimes. Accordingly, there is a theoretical concern that a TB vaccine demonstrated to be efficacious in preventing *de novo Mtb* infection may only be doing so in persons who otherwise would have controlled the infection and not progressed to active TB disease. Until a study is performed that correlates prevention of *Mtb* infection with prevention of TB disease, the concern over a PoI indication likely will persist.
- IGRA and PPD skin testing do not have 100% predictive value. Concerns with interpreting repeated IGRA assessments or PPD skin test to the precision required for accurate assessments of vaccine efficacy raise additional challenges to utilizing a PoI endpoint as a guide to decision making.
- Some vaccine platforms, such as BCG or *Mtb*-based vaccines induce PPD skin test and/ or IGRA reactivity, thereby potentially interfering with PoI assessment. Such vaccines may not be able to be evaluated according to this methodology unless alternative methodologies are developed, to overcome this complication. Note: While interference with TB diagnostic testing may constitute a source of complexity in the TB control strategy, this should not prevent the evaluation of promising candidates. On an individual basis, subjects participating in clinical trials of such vaccines should be informed that experimental vaccines may interfere with future TB diagnostic methods.

Altogether, the potential value of establishing proof-of-concept for some vaccine candidates in a PoI or PoR trial is acknowledged. It is however important to recognize that preventing an initial episode of TB disease, preventing the establishment of *Mtb* infection, and preventing recurrent disease may be mediated by different immunological mechanisms. Accordingly, a definitive PoD trial would be needed to generate conclusive evidence of protection against TB. Such a study would be expected to assess vaccine efficacy both in persons with latent TB infection at the time of vaccination, as well as in individuals uninfected with *Mtb* at the time of study enrolment.

While the PoD, PoR and PoI endpoints are intended for use in TB vaccine trials involving adolescents and adults, findings of efficacy in these trials should trigger further investigations to assess protection in infants and children.

6. PPC for new tuberculosis vaccines: use in adolescents and adults

6.1 Indication

Preferred characteristics: Immunization for prevention of active pulmonary TB disease

6.2 Target population

Adolescents and adults

Comments: Adolescents and adults with TB disease represent the most common sources of *Mtb* spread and are therefore the WHO priority target for TB vaccine development. Demographic changes in some high endemicity countries justify inclusion of older adults in the target population. The optimal timing for paediatric evaluation should be discussed with regulators and policy makers but a paediatric clinical development program should certainly be considered when proof of concept is established in adolescents and adults.

6.3 Outcome measure and efficacy

Preferred characteristic: 50% or greater efficacy in preventing confirmed pulmonary TB

Comments:

A vaccine with lesser vaccine efficacy against confirmed TB in adolescents and adults, if widely used in areas of high TB endemicity, may still prove valuable and contribute to reducing the spread of *Mtb* in a cost-effective way,[4] but this would fall short of the requirements necessary to meet the End TB goals by the 2035 target date.

A bacteriologically confirmed case of TB is the preferred endpoint for TB vaccine efficacy assessment. Preferred endpoint case definitions have been published.[35] A bacteriologically confirmed case is one from whom a biological specimen is confirmed positive by culture or WHO-approved rapid diagnostic method.[37] A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment.

The vaccine should be protective in both subjects with and without evidence of latent *Mtb* infection, in different geographical regions and latitudes, irrespective of environmental exposure to mycobacteria. In high endemicity countries, rapid population-level vaccine impact will be derived mostly from prevention of TB disease in subjects with latent *Mtb* infection.

Vaccine efficacy against recurrent TB (PoR) should be characterized. Preferences regarding efficacy outcome measures are similar to those used in PoD studies when considering prevention of recurrent TB disease.

It is anticipated that vaccines protecting against drug-sensitive TB would also protect against drug-resistant TB. Over the long term, the impact of vaccine use on the incidence of drug-resistant *Mtb* cases should be assessed to confirm this

effect, given the enormous public health benefit that would accrue from a reduction in cases of drug-resistant *Mtb*.

491 ## 6.4 Duration of protection

Preferred characteristic: Ten years or more of protection should be conferred after primary immunization.

Comments: Demonstrated efficacy over at least 2 years after completion of the primary immunization regimen to support initial policy decisions.

Longer-term follow-up studies, possibly after initial vaccine introduction, will be important in informing duration of protection and possible booster requirements.

492 ## 6.5 Safety

Preferred characteristics: Safety and reactogenicity profile should be favourable, similar to other current WHO-recommended routine vaccines for use in adolescents and adults.

Comments: Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination. Considering the severity and public health concern associated to the target disease, mitigations may need to be considered for mild reactions or very rare events.

Safety should be favourable in particular risk groups, such as individuals living with HIV/AIDS and other causes of immuno-deficiencies, the elderly, pregnant and lactating women. Careful investigations will be required for live platform vaccine candidates.

493 ## 6.6 Schedule

Preferred characteristic: A minimal number of doses and boosters required.

Comments: A requirement for more than three doses to achieve primary immunization would not be desirable due to logistical and cost concerns.

While complexity should be avoided if possible, heterologous prime boost regimes, are being considered.

Long term follow-up studies, possibly after receiving initial marketing approval, should determine the requirement for booster dose(s). If a booster is required, administration 10 years or more after completion of the primary immunization series would be preferred. A requirement for boosters to be administered more than every five years will likely be associated with delivery challenges.

494 ## 6.7 Co-administration

Preferred characteristic: Demonstration of favourable safety and absence of immunologic interference with other vaccines recommended for use in the same target population

Comment: In the absence of established correlates of protection, the impact of co-administration on markers of immune 'take' should be characterized and interpreted accordingly.

6.8 Immunogenicity

Preferred characteristic: Identification of a correlate/surrogate of protection, using a validated assay

Comment: No confirmed correlate/surrogate of clinical efficacy of a TB vaccine currently exists. The identification of immune correlates/surrogates of protection should be included as immunogenicity objectives in TB vaccine efficacy studies. In the absence of established correlates of protection, markers of immune 'take' should be characterized. The conservation of biological specimen for future use upon advances in technology and knowledge is encouraged.

6.9 Programmatic suitability and prequalification

Preferred characteristic: General guidance from WHO expectations about clinical evaluation of vaccines should be followed.[37] The WHO defined criteria for programmatic suitability of vaccines should be met, following guidance on vaccine presentation, packaging, thermostability, formulation and disposal.[11] The vaccine should be prequalified to support purchasing by United Nations agencies.[38]

Comment: Beyond the minimum requirements for WHO prequalification, innovation related to programmatic suitability, such as ease of administration and thermostability, would lead to major public health benefits and is strongly encouraged.

6.10 Value proposition

Preferred characteristic: Dosage, regimen, and cost of goods should be amenable to affordable supply. Favourable cost-effectiveness should be established and price should not be a barrier to access, including in low and middle income countries.

Comment: Modelling the impact of TB vaccines with various characteristics on the TB epidemic in general, and on drug-resistant TB specifically, as well as on TB-associated anti-mycobacterial drug use would be valuable. The vaccine impact on health systems (such as reduction of TB-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in both modelling and real vaccine use studies.

7. PPC for new tuberculosis vaccines: use in neonates and infants

7.1 Indication

Preferred characteristic: Prevention of TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children.

7.2 Target population

Preferred characteristic: Neonates and infants, in co-administration with other existing vaccines from the Expanded Program on Immunization.

7.3 Outcome measure and efficacy

Preferred characteristic: Equal to or greater than 80% vaccine efficacy as compared to baseline incidence, or superior efficacy as compared to BCG, in preventing TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children.

Comments: Considering existing recommendations and inclusion of neonatal BCG vaccination in standards of care based on the demonstrated efficacy profile of BCG, a new vaccine developed for BCG replacement should be compared to BCG in a randomized controlled study, powered to show superior vaccine efficacy as compared to BCG. Ethics committee(s) of record should confirm that the accrued evidence about the new candidate vaccines justify the absence or delay of BCG vaccination in at least one trial arm, if such a trial design is proposed.

BCG provides partial protection against leprosy. Policy decisions related to BCG replacement will also give due consideration, where relevant, to available evidence about the effects against leprosy and Buruli ulcer, as well as evidence established in carefully designed prospective BCG trials with pre-defined endpoints about the possible role of 'non-specific effects' of BCG.

Characterisation of vaccine efficacy against paediatric TB mortality and all-cause mortality is desirable, possibly in large-scale pilot introduction studies.

BCG boosting strategies are also being considered.

7.4 Duration of protection

Preferred characteristic: Ten or more years of protection should be conferred after primary immunization.

Comments: Demonstrated efficacy over 2 or more years after completion of the primary immunization regimen to support initial policy decision.

Longer-term follow-up studies will be important to inform the duration of protection and possible booster requirements.

501 **7.5 Safety**

Preferred characteristics: Improved safety as compared to current BCG.

Comments: Safety should be favourable in HIV-infected subjects. In countries with high HIV endemicity, many HIV-infected neonates and infants are vaccinated with BCG, which may result in severe local and/or regional BCG reactions or disseminated BCG infection, sometimes fatal. A new TB vaccine safe enough to be administered to neonates and infants with innate or acquired immunodeficiency, including HIV infected infants, would represent an important public health advance. Careful investigations will be required for live platform vaccine candidates.

Safety profile demonstrates no or only mild, transient reactogenicity and no serious adverse events related to vaccination. Injection site swelling, pain, drainage, and scarring, and local lymphadenopathy, are common adverse events associated with BCG infection. Reduction in the frequency and severity of these and related outcomes would represent welcomed improvement over BCG.

The absence of vaccine-related immune activation syndrome upon initiation of antiretroviral therapy in HIV-infected children should be demonstrated.

Efforts aimed at minimizing pain at the site of administration are strongly encouraged.

502 **7.6 Schedule**

Preferred characteristic: A minimal number of doses and boosters required.

Comments: A requirement for more than three doses to achieve primary immunization would not be desirable due to logistical and cost concerns.

While complexity should be avoided if possible, heterologous prime boost regimens, including those including neonatal BCG, are being considered.

Long term follow-up studies, possibly post initial introduction, should determine the requirement for booster dose(s). If a booster is required, administration 10 years or more after completion of the primary immunization series would be preferred. A requirement for boosters to be administered more frequently than every five years will likely be associated with delivery challenges.

503 **7.7 Co-administration**

Preferred characteristic: Demonstration of favourable safety and immunologic non-interference upon co-administration of other vaccines recommended for use in EPI

Comment: In the absence of established correlates of protection, the impact of co-administration on markers of immune 'take' should be characterized and interpreted accordingly.

504 ## 7.8 Immunogenicity

Preferred characteristic: Identification of a correlate/surrogate of protection, utilizing a validated assay.

Comment: No confirmed correlate/surrogate of clinical efficacy of a TB vaccine currently exists. The identification of immune correlates/surrogates of protection should be included as immunogenicity objectives in TB vaccine efficacy studies. In the absence of established correlates of protection, markers of immune 'take' should be characterized. The conservation of biological specimen for future use upon advances in technology and knowledge is encouraged.

505 ## 7.9 Programmatic suitability and prequalification

Preferred characteristic: General guidance from WHO on expectations about clinical evaluation of vaccines should be followed.[37] The WHO defined criteria for programmatic suitability of vaccines should be met, following guidance on vaccine presentation, packaging, thermostability, formulation and disposal.[11] The vaccine should be prequalified to support purchasing by United Nations agencies.[38] An improved production process relative to current BCG, contributing to ensuring affordable supply and avoid shortages, would be valuable.

Comment: Beyond the minimum requirements for WHO prequalification, innovation related to programmatic suitability, such as ease of administration and thermostability, would lead to major public health benefits and is strongly encouraged.

506 ## 7.10 Value proposition

Preferred characteristic: Dosage, regimen, and cost of goods should be amenable to affordable supply. The vaccine should be cost-effective and price should not be a barrier to access, including in low and middle income countries.

Comment: Modelling the impact of TB vaccines with various characteristics on the TB epidemics in general, and on drug-resistant TB specifically, as well as on TB-associated anti-mycobacterial drug use would be valuable. The vaccine impact on health systems (such as reduction of TB-related medical attendance and hospitalization) and other aspects of implementation science should be evaluated in both modelling and real vaccine use studies.

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