

WHO Evidence Considerations for Vaccine Policy Development for Tuberculosis Vaccines Intended for Adults and Adolescents

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Cover photo credit: Muna Garage camp is located 10kms from the outskirts of Maiduguri area and is home to some 16 000 people, living in mainly makeshift shelters. Although there has been humanitarian assistance of shelter, water and sanitation, food and health services, the camp remains at high risk for disease outbreaks during the ongoing rainy season. © WHO

Contents

Acknowledgements iv

Declaration of interests iv

Abbreviations v

Executive summary vii

1. Concept and strategic intent 1

1.1 Purpose and intended audience 1

1.2 The relationship of the WHO ECVP and SAGE 2

1.3 The process of developing WHO ECVP guidance for TB vaccines for adults and adolescents 2

2. TB burden and public health need 3

2.1 Current drug treatment options and opportunities for new TB vaccines 3

2.2 Adolescents and adults as a priority target population for new TB vaccines 4

3. Vaccine development status and product development considerations 5

3.1 Status of vaccine candidates targeting adolescents and adults 5

3.2 Clinical development considerations for TB vaccine candidates targeting prevention of disease 5

4. Regulatory considerations to facilitate policy decisions 6

5. Stakeholder roles and engagement across the product development-to-uptake continuum for new TB vaccines 8

6. Tables 10

Table 1. Vaccine product-related parameters 10

Table 2. Delivery-related parameters 15

Table 3. Vaccination of other target populations 16

Table 4. Regulatory strategy considerations for initial licensure to help facilitate policy review 19

Table 5. Implementation considerations 21

7. References 26

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The draft document was posted on the WHO website for one month, from 26 September to 28 October 2022, to enable public consultation. The call for review was broadly disseminated, including to WHO's Strategic Advisory Group of Experts on Immunization (SAGE), the regional advisors on immunization in each of the WHO regional offices, the chairs of each Regional Immunization Technical Advisory Group (RITAG), the GTB Programme and WHO's Product Development for Vaccines Advisory Committee (PDVAC). Members of the Developing Countries Vaccine Manufacturers Network (DCVMN) and the International Federation of Pharmaceutical Manufacturers (IFPMA) were also invited to comment.

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Declaration of interests

Declarations of competing interests were received from all expert applicants and evaluated as part of the working group recruitment process. None of the working group members was considred to have any relevent conflicts.

Abbreviations

ADIPs	antimicrobial resistance
AMA	African Medicines Agency
AMRH	Africa Medicines Regulatory Harmonization
AVAREF	African Vaccine Regulatory Forum
ART	antiretroviral therapy
BCG	Bacille Calmette-Guérin
CI	confidence interval
CMA	conditional marketing authorization
COVID	coronavirus disease
ECVP	Evidence Considerations for Vaccine Policy
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
EUL	emergency use listing
EU-M4All	EU Medicines for All
FDA	Food and Drug Administration
Gavi	Global Alliance for Vaccines and Immunization
GACVS	Global Advisory Committee on Vaccine Safety
HCWs	health and care workers
HBC	high-burden countries
HIV	human immunodeficiency virus
HPV	human papillomavirus
ICMRA	International Coalition of Medicines Regulatory Authorities
IM	intramuscular
IND	investigational new drug
IVIRAC	Immunization and Vaccines Related Implementation Research Advisory Committee
LMICs	low- and middle-income countries
LTBI	latent TB infection
MDR-TB	multidrug-resistant tuberculosis
mRNA	messenger ribonucleic acid
MSF	Médecins San Frontières

Mtb	*Mycobacterium tuberculosis*
NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
PCR	polymerase chain reaction
PDVAC	Product Development for Vaccines Advisory Committee
PHC	primary health care
PHEIC	public health emergency of international concern
PLHIV	people living with HIV
POD	prevention of TB disease
POI	prevention of Mtb infection
POR	prevention of recurrent TB
PPC	Preferred Product Characteristics
PQ	prequalification
QALY	quality-adjusted life year
R&D	research and development
RITAG	Regional Immunization Technical Advisory Group
RR-TB	rifampicin-resistant TB
SAGE	Strategic Advisory Group of Experts on Immunization
SAHPRA	South African Health Products Regulatory Authority
SC	subcutaneous
SEARN	South-East Asian Regulatory Network
TB	tuberculosis, the disease resulting from *Mycobacterium tuberculosis* (Mtb) infection
TPP	target product profile
TPT	TB preventive treatment
UNICEF	United Nations Children's Fund
UNHLM	United Nations High Level Meeting
VIS	Gavi Vaccine Investment Strategy
WHO	World Health Organization
WLA	WHO listed authority

Executive summary

Access to new vaccines in low- and middle-income countries (LMICs) is sometimes delayed because critical evidence must be generated post-licensure to support World Health Organization (WHO) global vaccine policy and country introduction decisions. In line with the vision of Immunization Agenda 2030, WHO is developing tools and enablers to ensure that everyone, everywhere, at every age, fully benefits from vaccines to improve health and well-being, and has developed the Evidence Considerations for Vaccine Policy (ECVP) framework to reduce the likelihood of such delays. The ECVP facilitates **early engagement and alignment across the stakeholders involved in vaccine development and those responsible for vaccine regulatory, policy, funding and country introduction decisions.** This framework aims to anticipate and collectively delineate the clinical trial, observational and other data likely to be required by global and national policy-makers, and to do so when most valuable – during development of the late-stage clinical plan, including the design of the pivotal licensure trial. **Proactively generating this evidence as part of or in parallel to clinical development – where feasible – rather than reactively post-licensure, creates an opportunity to accelerate vaccine policy formulation, adoption and impact, particularly in LMICs.** Development of the generic ECVP framework and this ECVP for tuberculosis (TB) vaccines intended for adults and adolescents is an outcome of a broad stakeholder consultation that was convened in 2021, where TB vaccine development stakeholders, including policy-makers at the global, regional and national levels, unanimously agreed that this type of earlier guidance on evidence considerations is needed to inform vaccine development strategies and investment decisions.

The ECVP is a new type of guidance developed by WHO, and this ECVP for TB vaccines intended for adults and adolescents is the first ECVP to be developed. The primary audience for this ECVP includes all stakeholders intending to support the product development, regulatory approval, introduction, access and widespread use in LMICs of new TB vaccines intended for use in adults and adolescents. The ECVP does not pre-empt policy or implementation decision-making, but aims to reduce the risk of evidence gaps and consequent delays between vaccine regulatory approval and vaccine impact. While global policy recommendations from WHO may facilitate introduction at the country level, the decision to implement any new vaccine is highly context specific and the relative importance of considerations described in this ECVP will differ depending on setting. For this reason, WHO has also developed a *Global framework to prepare for country introduction of new TB vaccines for adults and adolescents* that is broadly aligned with the generic principles described in the WHO guidance on developing a National Immunization Strategy.

> "The ECVP facilitates early engagement and alignment across the stakeholders involved in vaccine development and those responsible for vaccine regulatory, policy, funding and country introduction decisions."

The only currently available vaccines for TB are the Bacille Calmette-Guérin (BCG) vaccines. BCG vaccination at birth is effective against tuberculous meningitis and military tuberculosis in young children, but has limited efficacy against infection and disease in adults and adolescents, in whom 90% of TB cases occur. Modelling indicates that **a vaccine that prevents disease in adolescents and adults will be the most effective way to reduce both the incidence of TB cases and transmission of new *Mycobacterium tuberculosis* (Mtb) infections,** across all age groups.

Several candidates have entered, or are poised to enter, phase III clinical trials. It is therefore timely to outline the likely evidence needs for policy-making for this category of vaccine. This ECVP guidance for TB vaccines builds upon, and will ultimately replace, WHO's *Preferred Product Characteristics for new TB vaccines to be used in adults and adolescents*, published by WHO is 2018, and leverages the *WHO guidance on programmatic suitability for prequalified vaccines*, updated in 2015. WHO Preferred Product Characteristics (PPCs) describe WHO's preferential product attributes for vaccines to facilitate their use in LMICs, and they are usually provided early in clinical product development.

This TB vaccine ECVP includes five tables summarizing the following.

1. **Vaccine product-related considerations** – which build upon and expand existing WHO PPCs for TB vaccines intended for adults and adolescents, and include priority population(s), i.e., the populations who will be the primary recipients of the vaccine after approval.

2. **Vaccine delivery-related considerations** – which cover aspects such as the delivery setting, thermostability and presentation.
3. **Other target populations** – beyond the priority population/s for which the vaccine may receive an initial policy recommendation following regulatory approval. This section identifies additional target populations for introduction, once there is sufficient safety and vaccine effectiveness data.
4. **Regulatory strategy considerations** – the potential approval pathways available for this category of TB vaccines and the potential stakeholders that need to be engaged.
5. **Implementation considerations** – the data and evidence beyond that required for regulatory approval that will likely be important for global policy, financing and vaccine-introduction decisions. This table represents an initial view based on discussions with stakeholders and is intended to support dialogue with decision-makers, in order to refine data needs and expectations, depending on specific contexts and policy scenarios. Vaccine developers, international funders and international and local agencies supporting immunization and country-level decision-makers are not expected to generate all the data described, but these stakeholders, including regulators, are encouraged to engage in understanding the evidence needs for policy decisions and to collaborate to find ways to address them. Generating this data will likely require additional resources from several stakeholders and collaboration across organizations.

The parameters described within Tables 1–4 are categorized as **high priority** (listed in red) or **medium priority** (listed in blue) for policy recommendation. Data/evidence are identified as being required for either **initial** (at time of vaccine introduction) or **expanded** (post-introduction) policy considerations. Each table includes the rationale underpinning the recommended requirements.

Summary of initial policy considerations – please refer to Tables 1–3 for all considerations and full explanation/rationale.

The following data from pivotal licensure studies and pre-introduction studies should be provided to inform timely WHO policy recommendations and country-introduction decisions:

- data demonstrating prevention of pulmonary TB disease as the primary endpoint, predicted to ensure the most rapid impact on the TB epidemic by reducing transmission;
- a safety and reactogenicity profile supportive of widespread use of a preventive vaccine;
- data demonstrating safety and 50% or greater efficacy in preventing confirmed pulmonary TB disease; the 50% efficacy target is based on health and economic modelling of vaccine impact;
- data from adults and adolescents with evidence of prior multidrug-resistant tuberculosis infection, since this population accounts for 90% of TB disease, and adults represent the most common source of Mtb spread;



Group of colorfully dressed, happy children running in central Kenya, East Africa.
Photograph courtesy of © Hadynyah

- safety and immunogenicity data from adults and adolescents without evidence of prior Mtb infection to support immunobridging to potential surrogates or correlates of protection, and to avoid the need for screening prior to vaccination;
- safety and immunogenicity data from people living with HIV (PLHIV) to enable rapid recommendation for use in this priority population;
- efficacy data from sufficiently diverse representative geographies to support global policy-making; and
- data demonstrating duration of protection for the disease indication of at least 2 years.
- dosing regimens, schedules, and delivery strategies designed for optimal cost-effectiveness and, to achieve equitable impact, where possible, to be integrated within delivery systems for other vaccines or non-immunization programmes.
- data relating to end-user acceptability, based on community engagement to ensure vaccine acceptance.

Summary of expanded policy considerations – please refer to Tables 1–3 and 5 for all considerations and full explanation/ rationale.

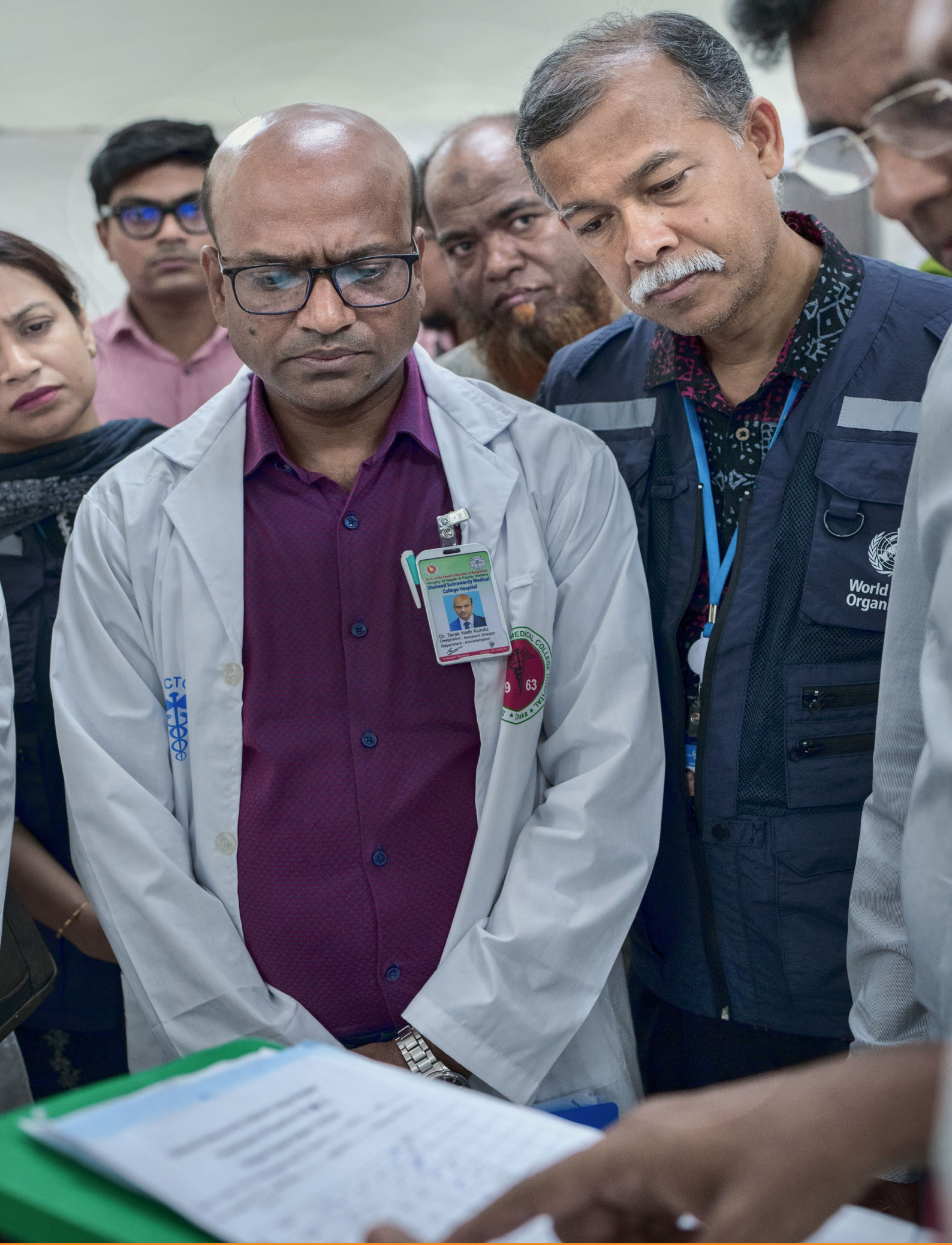
Data and evidence to support expanded policy will be obtained from **longer-term follow-up of participants in licensure studies and from additional studies**, including post-introduction effectiveness and safety studies. Such data and evidence would include:

- assessment of a broad range of immunological responses during the phase III efficacy study will be essential to identify potential surrogate markers or correlates of protection to enable immunobridging to additional key populations, where it may not be feasible to measure efficacy;
- safety, immunogenicity and effectiveness data from younger adolescents and from other target populations such as older adults and pregnant women;
- data on duration of protection, to clarify any requirement for booster doses and their timing;
- data from countries/regions not adequately represented with key characteristics, such as heterogeneity in burden, or 'hot spots', i.e., areas of high latent TB infection and/or disease, which could impact vaccine performance or programmatic delivery;
- data from populations that may not have been adequately represented in licensure studies, but are important in certain contexts (e.g., populous countries where the disease burden is predominantly in older adults);
- effectiveness and impact data on mortality rates and drug-resistant TB;
- safety and immunogenicity data when the vaccine is administered with other vaccines in the intended delivery setting;
- additional safety data from pharmacovigilance activities for potential rare events not identified through the large clinical trials, or additional populations not included in clinical trials;
- evidence on the ease of (1) supply chain logistics, (2) practicality of the vaccine presentation, (3) programmatic integration into existing primary health care services (e.g., TB, non-TB, or immunization programmes), and (4) administration, i.e., ease of immunization relative to alternative TB control strategies;
- values and preferences of priority and other key populations;
- health impact, i.e., the benefit of vaccination to vaccinated individuals and to the wider population, including indirect effects;
- economic impact, i.e., contribution of vaccine introduction to micro- and macro-economic benefits per country; and
- access and affordability, i.e., ensuring that a vaccine is made broadly and equitably available at an affordable price.

This ECVP represents the current understanding of what evidence will likely be important to inform global and national policy recommendations for new TB vaccines for adults and adolescents, but **it is not a formal WHO guideline.** It does not aim to be prescriptive, but provides WHO guidance to vaccine-development stakeholders, to inform their scientific-advice discussions with regulators on specific candidates. The document may undergo updates as scientific knowledge evolves.

Policy recommendations at the country level rest with National Immunization Technical Advisory Groups (NITAGs) and TB programme advisory groups, informed, as relevant, by recommendations from WHO's Strategic Advisory Group of Experts on Immunization (SAGE) at the global level and advice from the respective Regional Immunization Technical Advisory Group (RITAG).

"This ECVP represents the current understanding of what evidence will likely be important to inform global and national policy recommendations for new TB vaccines for adults and adolescents"



WHO's Rajib Chowdhury on a duty visit with other doctors in a ward of Suhrawardy Hospital in Sher-E-Bangla-Nagar, Dhaka, on 3 October 2023.
Photograph courtesy of © WHO / Fabeha Monir

1. Concept and strategic intent

1.1 Purpose and intended audience

Introduction of new vaccines in low-and middle-income countries (LMICs) is sometimes delayed because evidence needed for definitive policy and/or introduction decisions goes *beyond* that needed for regulatory approval *(1, 2)*, and often, though not always, can be generated post-licensure *(3)*. The WHO Evidence Considerations for Vaccine Policy (ECVP) framework is designed to **facilitate early engagement and alignment across stakeholders involved in vaccine development and those responsible for regulatory, policy and programmatic use, funding and introduction decisions.** It aims to support the collective delineation of the clinical trial and observational data or other evidence, anticipated to be needed for policy decisions relating to new vaccines. These are indications of where no vaccine currently exists or of new vaccine classes, for example, vaccines for new target populations. Delays between vaccine licensure and policy formulation, adoption and introduction, particularly in LMICs, can thereby be minimized.

As outlined in the Immunization Agenda 2030 (IA2030) *(4)*, the accelerated development of vaccines with optimal suitability and effectiveness for use in LMICs is a major global objective. Under the auspices of its Product Development for Vaccines Advisory Committee (PDVAC) *(5)*, WHO develops Preferred Product Characteristics (PPCs) for new vaccines in WHO priority disease areas, early in clinical development. Typically developed when products are in phase I or pre-phase II clinical development, WHO PPCs aim to provide guidance on preferential attributes that position vaccines for use in high-burden, low-resource settings, including those that affect programmatic suitability. However, PPCs do not include guidance regarding potential vaccine delivery strategies, implementation parameters, or potential regulatory strategy.

The ECVP builds on PPCs, providing additional information and clarity on what is required for establishing global and national policy recommendations, so that data needs can be anticipated and evidence generated during development programmes, thereby shortening time to introduction and use.

> "...the accelerated development of vaccines with optimal suitability and effectiveness for use in LMICs is a major global objective."

The ECVP is intended to engage and align the multiple stakeholders who have an interest in the vaccine policy and introduction pathway (see section 5). Key stakeholders include the following.

- **Regulators**, who review the safety, quality and efficacy of vaccines, and the benefit–risk profile on the disease outcomes on an individual level, but not population-level performance.
- **National, regional and global policy-makers** (including immunization and disease programme advisory groups at national and regional levels), who need to consider additional population-based disease outcomes and aspects, such as cost-effectiveness, budget impact and affordability. Other aspects important to them (see section 5), relative to other interventions for the same disease or other diseases, also need to be considered. These groups consider issues such as programmatic suitability, dosing regimens and vaccine performance outcomes that may not have been quantified during clinical trials for regulatory approval, such as vaccine-preventable disease transmission at the population level. For some vaccines, population-based impact is a critical policy-making attribute, especially as it relates to evidence regarding vaccine impact on pathogen transmission.
- **Vaccine developers/manufacturers/global and regional funders**, who seek clarity on what data are needed to support vaccine introduction and uptake decisions.
- **Immunization partners and civil society organizations**, who seek to ensure a vaccine is acceptable and responsive to the needs of people who deliver and receive it, and who help to generate demand and counter misinformation.

An ECVP also seeks to catalyse timely discussion and promote alignment across the various **WHO advisory committees** concerned with vaccine development and introduction, including the PDVAC, the Immunization and Vaccines Related Implementation Research Advisory Committee (IVIRAC), the Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Strategic Advisory Group of Experts on Immunization (SAGE) *(6)*. As such, ECVPs could inform WHO's **Coordinated Scientific Advice procedure**, whereby product developers can approach WHO and obtain advice on the most appropriate approach to generate robust evidence to obtain a WHO policy recommendation and prequalification *(7)*. An ECVP could also inform candidate-specific consultations with national regulatory authorities (NRAs), providing a foundation for discussions on the specific data requirements for an expedited policy decision.

WHO ECVP guidance is applicable to general vaccine indications, for example TB vaccines for adults and adolescents, rather than to specific vaccine candidates, for example M72/AS01E. The depth and specificity of the guidance within ECVPs will likely differ depending on the stage of vaccine candidates in development and on the level of

certainty in the data relating to each parameter for the vaccine indication and/or class; ECVPs for indications where candidates are at an earlier developmental stage may be more general. For this reason, ECVP guidance will be updated throughout the development and lifecycle of relevant vaccines.

An ECVP represents the current understanding of what will likely be important for global and national policy recommendations, but **it is not a formal WHO guideline**.

1.2 The relationship of the WHO ECVP and SAGE

ECVP discussions and the ECVP document itself do not constitute formal advice from SAGE; nor are they a formal part of the independent SAGE evidence-to-recommendation process *(9)*, which is required for all vaccines seeking a WHO policy recommendation. However, the process of developing an ECVP will likely catalyse earlier formal discussions with SAGE on the anticipated evidence needs for future policy deliberations on priority vaccines, as they approach pivotal licensure studies.

At least two SAGE members are anticipated to participate in the development of an ECVP. However, there will be no overlap between ECVP working group members and those who participate in a SAGE working group assessing a vaccine relevant to that ECVP. This mutual exclusivity is necessary to preserve the independence of SAGE. SAGE working groups are usually established when a vaccine approaches licensure, approximately 3 years after ECVP development (assuming an ECVP is developed prior to phase III clinical study design).

1.3 The process of developing WHO ECVP guidance for TB vaccines for adults and adolescents

Following a global stakeholder consultation to discuss the concept and need for ECVP-type guidance, for new TB vaccines in particular *(8)*, WHO established an expert working group composed of national, regional and global-level stakeholders to draft both a generic ECVP framework (to be used as the basis for topic-specific ECVP development), broadly based on SAGE's Evidence to Recommendation Framework *(9)*, and a TB vaccine ECVP as the first application of the generic framework. The expert group included TB and vaccine development subject matter experts as well as individuals from national regulatory agencies (serving and retired), global, regional and national policymaking bodies for both immunization and TB programmes, global financing and procurement agencies and civil society. The existing WHO PPC for new TB vaccines intended for adults and adolescents served as a starting point for ECVP development *(10)*. The initial draft was posted on the WHO website for one month to collect comments as part of a public consultation. The call for review was broadly disseminated, including to SAGE, the regional advisors on immunization in each of the WHO regional offices, the chairs of each Regional Immunization Technical Advisory Group (RITAG), the Global TB Programme and WHO's PDVAC. Members of the Developing Countries Vaccine Manufacturers Network (DCVMN) and the International Federation of Pharmaceutical Manufacturers (IFPMA) were also invited to comment. The WHO prequalification team reviewed the draft prior to finalization of the ECVP document.

The process of ECVP development for TB vaccines for adults and adolescents uncovered gaps in knowledge, such as specific pre-implementation studies that are needed to inform policy. Given the anticipated evolution of policy-related discussions for this indication ("prevention of pulmonary TB disease in adults and adolescents), the ECVP is expected to be reviewed and potentially revised within 18–36 months of publication so that it remains current and to ensure continued stakeholder alignment.

Triggers for further ECVP revision could include publication of scientific advice from national regulatory authorities on efficacy study designs, new information on anticipated delivery or programme integration strategies, or clarity on what specific data gaps need to be filled pre-implementation.

"...WHO established an expert working group composed of national, regional and global-level stakeholders to draft both a generic ECVP framework..."

2. TB burden and public health need

> "About a quarter of the world's population, approximately 2 billion people, have been infected with Mtb."

TB, the disease resulting from *Mycobacterium tuberculosis* (Mtb) infection, is a global epidemic with major public health and socioeconomic consequences. In 2021 alone, TB caused an estimated 1.4 million deaths among HIV-negative people and a further 187 000 deaths among persons living with HIV (PLHIV). Due to the impact of the COVID-19 pandemic on health systems, this is an increase from 2019 and 2020 estimates, and is at the level last seen in 2017 *(11)*. There were an estimated 10.6 million cases of TB in 2021, 90% of which were in adults and adolescents over 15 years of age. An estimated 40% of TB cases were undiagnosed or unreported. Untreated TB has devastating health and social consequences for those with TB, and these individuals are the main source of Mtb transmission *(11)*.

About a quarter of the world's population, approximately 2 billion people, have been infected with Mtb. Although only 5–10% of such people will progress to TB disease during their lifetime, this represents 200 million people. The likelihood of progression to active TB is higher among those recently infected or with predisposing attributes such as HIV infection, diabetes, cigarette smoking, excessive alcohol use or undernutrition, and higher among adolescents than at any other time of life outside early childhood.

While TB is a global disease, the epidemic occurs predominantly in eight high-burden countries – Bangladesh, the People's Republic of China, the Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan and the Philippines – which account for two thirds of the total number of incident cases. Thirty high-burden countries account for 87% of incident TB disease worldwide *(11)*.

In 1993, TB was the first infectious disease to be declared a global health emergency by WHO *(12)*. TB is a WHO priority disease, and the WHO End TB strategy, endorsed by the World Health Assembly in 2014, envisions "a world free of TB, with zero deaths, disease and suffering due to the disease". Specifically, the End TB strategy targets a 90% reduction in patients with active TB, and a 95% reduction in deaths from TB by 2035 compared to 2015 levels, while also protecting families from catastrophic costs associated with TB *(12)*. A United Nations High Level Meeting was convened in 2018 and key targets and commitments to accelerate efforts to ending the TB epidemic were endorsed by all Member States *(13, 14)*. Ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals (SDGs). By 2022, US$13 billion is needed annually for TB prevention, diagnosis, treatment and care to achieve the global target agreed at the UN High Level-Meeting on TB in 2018 *(15)*, and $10 billion is needed between 2023 and 2030 to accelerate the development of new vaccines, with $52 billion being needed for vaccination once new vaccines are available *(16)*.

The only available TB vaccine, Bacille Calmette-Guérin (BCG), is effective at preventing severe disease in young children when administered at birth or soon after. However, the existing BCG vaccines have variable efficacy in adolescents and adults, and have had limited impact in preventing pulmonary TB disease, the main route of onward transmission to and infection of susceptible individuals *(17)*. Similarly, the availability of effective drug treatment regimens and diagnostics has not controlled the TB epidemic. The availability of one or more novel and effective TB vaccines is deemed essential to achieve the 2035 End TB targets *(18)*.

TB vaccine research and development (R&D) has recently been stimulated by data from two clinical efficacy studies: revaccination with BCG reduced the rates of sustained Mtb infection in adolescents by 45% *(19)*; and M72/AS01E, an adjuvanted protein vaccine, demonstrated 50% efficacy in the prevention of pulmonary TB disease in adults aged 18 to 50 years of age *(20)*. These efficacy signals were unprecedented and have catalysed investment in advanced clinical TB vaccine studies.

Although WHO declared TB a global emergency in 1993 *(12)*, TB does not currently meet the criteria for a Public Health Emergency of International Concern (PHEIC), and TB vaccines are currently not considered eligible for the WHO Emergency Use Listing (EUL) procedure. This situation is not expected to change within the period in which the leading TB vaccine candidates could be licensed.

2.1 Current drug treatment options and opportunities for new TB vaccines

Despite significant recent advances in TB preventive treatment (TPT), diagnostics, and therapies for both drug-sensitive and drug-resistant TB, the rates of diagnosis and subsequent treatment fall far short of what is required to control the TB epidemic by 2035. TPT is a critical component of the WHO End TB Strategy, and WHO guidelines target specific risk groups. The efficacy of currently available TPT ranges from 60% to 90% and, while progress has been made, implementation is not optimal *(21)*. In 2021, the WHO estimated a treatment coverage rate of 61%, down from 69% in 2019 due to the COVID-19 pandemic, and similar to the treatment coverage rate of 59% in 2015 *(11)*.

The emergence and spread of multidrug-resistant TB (MDR-TB) makes TB infections significantly more difficult and costlier to treat. In 2021, drug-resistant Mtb accounted for an estimated 3.6% of first-time diagnoses and 18% of cases previously treated for TB. Only one third of those who develop drug-resistant TB each year are estimated to be enrolled in appropriate treatment programmes *(11)*. These significant gaps resulted in increased mortality, compounded by the impact of the COVID-19 pandemic on TB services, especially in the case of MDR-TB. The molecular mechanisms of drug resistance in Mtb are not likely to affect susceptibility to immune-based control approaches, so vaccine-induced protection against drug-resistant TB is likely to be equivalent to that against drug-sensitive TB.

Achieving the 2035 End TB goals will require an accelerating decline in global TB incidence rates from the 2% per year decline recorded in 2015 to an estimated 17% decline in incidence per year after 2025 *(13)*. Achieving these goals will be challenging, given issues such as access to care, the duration and complexity of treatment regimens, side effects of treatments, difficulties in adherence to treatment, low efficacy of second-line drugs, and drug–drug interactions with antiretroviral therapies.

New TB vaccines offer multiple potential advantages, including reductions in Mtb transmission through prevention of TB disease, less antimicrobial resistance resulting from the indiscriminate use of antibiotics for treatment of TB symptoms, and reductions in the health and socioeconomic consequences of the disease. To attain the 2035 End TB goals, currently available tools need to be supplemented by improved TB vaccines, which may be now within reach.

"New TB vaccines offer multiple potential advantages, including reductions in Mtb transmission through prevention of TB disease"

2.2 Adolescents and adults as a priority target population for new TB vaccines

Transmission of Mtb occurs after aerosolization of Mtb from persons with active pulmonary TB disease. Ninety percent of TB disease occurs in adolescents and adults, and adults constitute the major transmitters of Mtb. Mathematical modelling indicates that **a vaccine that effectively prevents disease in already infected persons will be the most important short-term driver to reduce TB disease incidence and transmission of new infections** *(22)*.

While WHO has developed TB vaccine PPCs for adolescents and adults, as well as for new TB vaccines with improved efficacy and durability of effect for infants *(10)*, modelling indicates that it would take many years for an infant vaccination strategy to have any significant impact on the TB epidemic. By contrast, mass vaccination of adolescents and adults with a vaccine having 40% efficacy for a prevention of pulmonary disease endpoint would achieve the same impact on the epidemic 20 years earlier than an infant vaccine with 80% efficacy and lifelong durability of effect *(23)*. A vaccine that prevents active pulmonary TB disease in adolescents and adults will also prevent Mtb transmission to infants, young children, and adolescent and adult TB contacts. For this reason, **WHO specifies that vaccines which prevent active pulmonary disease in adolescents and adults is a key strategic goal and is actively facilitating their development *(10)***.

People living with HIV (PLHIV) have a 2- to 20-fold higher risk of developing TB disease than HIV-uninfected individuals *(24)*. Impaired immunity due to HIV infection, even in those receiving antiretroviral therapy, may affect their ability to mount both innate and adaptive immune responses. A recent publication suggests that trials of TB vaccine candidates should include PLHIV, with careful assessment of safety, immunogenicity and efficacy, so that new vaccines can be recommended in this priority population as soon as feasible *(24)*.

Pregnancy[1] may increase the risk of Mtb infection and progression to disease in the mother, and the risk is greatest within the first 90 days after pregnancy *(25)*. Maternal TB disease is associated with adverse pregnancy outcomes, including increased maternal, foetal and neonatal morbidity. As a general principle, women of childbearing potential would be immunized with any new class of TB vaccine for adults prior to pregnancy. However, if not previously immunized, pregnant women are an important population for vaccination to protect both mother and child.

1 To facilitate readability, the terms "pregnant woman" and "mother" are used throughout this document to refer to all pregnant adolescents and adults at risk of TB, including cisgender women, transgender men, non-binary and gender-fluid individuals, and intersex individuals born with a female reproductive system.

3. Vaccine development status and product development considerations

3.1 Status of vaccine candidates targeting adolescents and adults

As of mid-2023, several candidate TB vaccines targeting adolescents and adults are in clinical development (updated annually and reported in the WHO Global TB report) *(11)*, with some either in or approaching proof-of-concept or pivotal efficacy studies. Candidate TB vaccines include inactivated whole cell vaccines, live attenuated vaccines, recombinant BCG and adjuvanted protein vaccines. mRNA-based candidates are also entering clinical development. Candidate vaccines are addressing one or more of three different indications: prevention of disease (POD), prevention of infection (POI), and/or prevention of recurrence (POR). **The focus of this ECVP is limited to vaccines that prevent active pulmonary Mtb disease (i.e., POD) in adolescents and adults who have been infected, as modelling has identified this as the key strategic goal.**

At present, the only candidate vaccine for which prevention of TB in adults has been demonstrated in a clinical study is the adjuvanted recombinant protein vaccine **M72/AS01$_E$**. In a phase IIb placebo-controlled efficacy study (NCT01755598), 3575 HIV-uninfected adults with evidence of prior Mtb infection were randomized to M72/AS01$_E$ or placebo in South Africa, Kenya and Zambia. The vaccine demonstrated efficacy of 49.7% (95% confidence interval, 2.1 to 74.2) for the prevention of pulmonary TB disease followed up for 3 years *(20)*.
A multicountry phase III licensure study based on a POD endpoint has begun.

Enrolment has been completed in a phase III study (CTRI/2019/01/017026) of 12 721 participants in India to evaluate the efficacy of **VPM1002** (a recombinant BCG) and **MIP** (heat-killed *Mycobacterium indicus pranii*; also referred to as **Immuvac**) in preventing pulmonary and extra-pulmonary TB in healthy household contacts of newly diagnosed pulmonary TB patients.

An ongoing placebo-controlled phase III trial of **Gam*TBvac***, a protein subunit vaccine, in just over 7000 HIV-uninfected participants with no evidence of previous Mtb infection, is being conducted in the Russian Federation to determine efficacy in preventing TB (NCT04975737).

A phase III licensure study in adults and adolescents, based on a POD endpoint, is currently being planned for **MTBVAC**, a live attenuated Mtb vaccine and a phase 2b study has begun (NCT06272812).

> "The focus of this ECVP is limited to vaccines that prevent active pulmonary Mtb disease."

3.2 Clinical development considerations for TB vaccine candidates targeting prevention of disease

There are currently **no established correlates of immune protection for TB vaccines**. In addition, there are **no reliably predictive animal models** or **controlled human infection models** that could be used to de-risk progression from early safety and immunogenicity studies to large and costly phase III trials. Consequently, there is significant interest in identifying populations in which small, rapid and cost-effective studies could be conducted to provide either early evidence of efficacy or of biological activity to support progression to pivotal POD efficacy studies.

Recruitment in populations where TB disease occurs at a higher rate than in the general population will markedly reduce study sample size and shorten study duration, reducing costs and development time *(26)*. Use of POI and POR endpoints could facilitate smaller and shorter studies to generate data to de-risk progression to phase III POD studies. These high-risk populations are also the ones most likely to benefit from vaccine introduction, so such focused studies are considered ethical.

Once proof-of-concept is established, that is, indication of efficacy in a phase IIb trial, there is a need for well designed phase III field efficacy studies in high-risk target populations across a range of epidemiological settings, with clearly defined microbiological and clinical endpoints. Although there is no standardized microbiological endpoint, the type and number of microbiological tests to define a POD endpoint needs to be carefully considered and will also be determined by the objectives of the trial, for example, efficacy against undiagnosed, subclinical TB disease *(27)*. Such studies must include comprehensive biobanking to facilitate evaluation of potential correlates of protection, in order to accelerate the development of next-generation candidates.

4. Regulatory considerations to facilitate policy decisions

Elucidation of the optimal regulatory approval pathway requires early and ongoing discussions between developers and national regulatory authorities (NRAs). Initial licensure of new TB vaccines is likely to occur in high-burden countries, as the pivotal efficacy studies will be conducted there and because these countries have the greatest clinical need.

Regulatory strategies for initial licensure will be specific to each product, and will depend on the countries that the clinical studies are conducted in and the maturity of their NRAs. **WHO prequalification (PQ)** will be essential for UN procurement, rapidity of authorization by a broad number of NRAs and for facilitating approvals in countries that do not have a mature NRA, and also to support vaccine policy, financing and procurement. A dossier can be submitted for WHO PQ only when a vaccine product has been approved by an NRA operating at WHO maturity level 3 or higher, specifically for vaccines. Countries with less established NRAs may rely on WHO PQ or a reliance model/collaborative procedure with other agencies for approval.

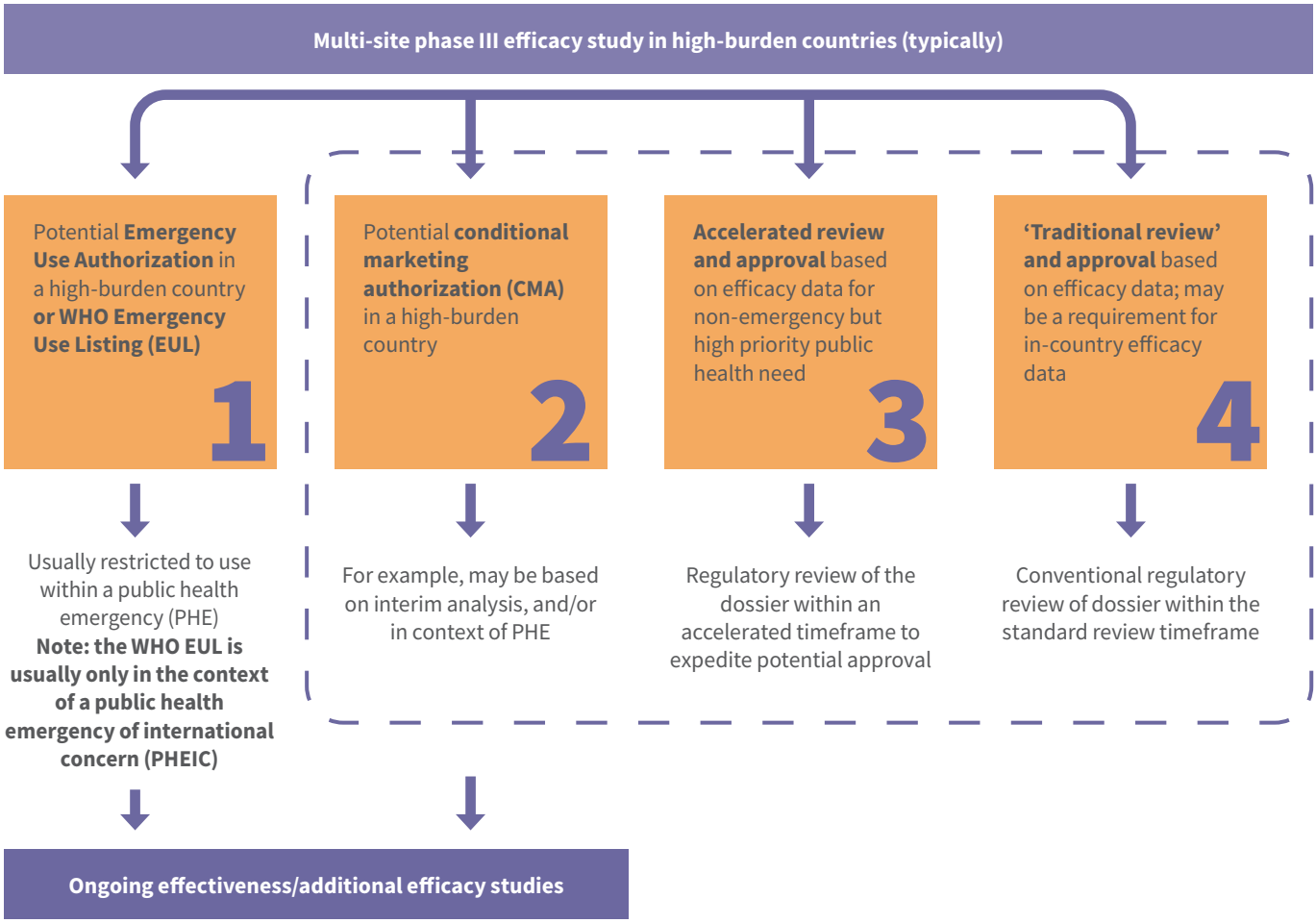
Joint or harmonized reviews between NRAs are an important consideration for approvals for multi-centre studies where each country lacks sufficient sample size for stratified precise outcomes. This mechanism might accelerate vaccine approvals for clinical trial authorizations and regulatory approval in all high-burden countries, and should be discussed before or during pivotal studies for the registration dossier.

Potential routes for new TB vaccine approval are summarized in Fig. 1 below. The pathways that are considered applicable to new TB vaccines are shown in the dashed box. All pathways described can leverage a harmonization mechanism, such as those associated with the African Vaccine Regulatory Forum (AVAREF) or International Coalition for Medicines Regulatory Authorities (ICMRA).



Dr Adam of WHO and Dr Geoffrey of Mashuuru Hospital go through a tally sheet at a vaccination desk in Mashuuru Hospital in Kajiado on 4 August 2023.
Photograph courtesy of © WHO / Billy Miaron

Fig. 1. Potential regulatory strategies for new TB vaccine approval. The potential approval pathways for new TB vaccines are outlined in the dashed box.



1. *The WHO Emergency Use Listing (EUL) procedure or the US Food and Drug Administration (FDA) Emergency Use Authorization (EUA):* TB is not categorized as a Public Health Emergency of International Concern (PHEIC), and is currently not considered eligible for the WHO EUL or FDA EUA pathway. There are no surrogate markers or correlates of protection for TB vaccines to support rapid licensure (e.g., FDA accelerated pathway).
2. *Conditional marketing authorization (CMA):* Some NRAs offer conditional approvals based on less comprehensive data than requested for full authorization, facilitating earlier use of a vaccine. This generally requires a commitment to completion of safety and efficacy studies and/or post-licensure studies.
3. *Accelerated review and approval:* Early discussions with NRAs may provide opportunities for expedited review and approval period (distinct from the EUA or EUL pathways described in strategy 1) where there is high public health need. Data requirements are the same as for the traditional pathway (strategy 4), but review and approval timelines are accelerated.
4. Traditional regulatory review: Longest route to licensure, but this and strategy 3 are the most likely to support a broad policy recommendation. Clinical studies with endpoints that measure protection from symptomatic disease with microbiological confirmation are currently considered the optimal route to regulatory approval for TB vaccines.

The accelerated scenarios for approval of new TB vaccines include pathways 2 and 3, which can operate synergistically (that is, expedited review and approval of a dossier for conditional marketing authorization). WHO PQ can follow or occur in tandem with national regulatory approval, depending on the pathway selected (see Table 4), and as long as initial global policy requirements are met (see Tables 1, 2 and 5).

Developers are advised to consult relevant regulators directly to obtain further advice on the licensure requirements for their specific candidates.

"Developers are advised to consult relevant regulators directly to obtain further advice on the licensure requirements for their specific candidates."

5. Stakeholder roles and engagement across the product development-to-uptake continuum for new TB vaccines

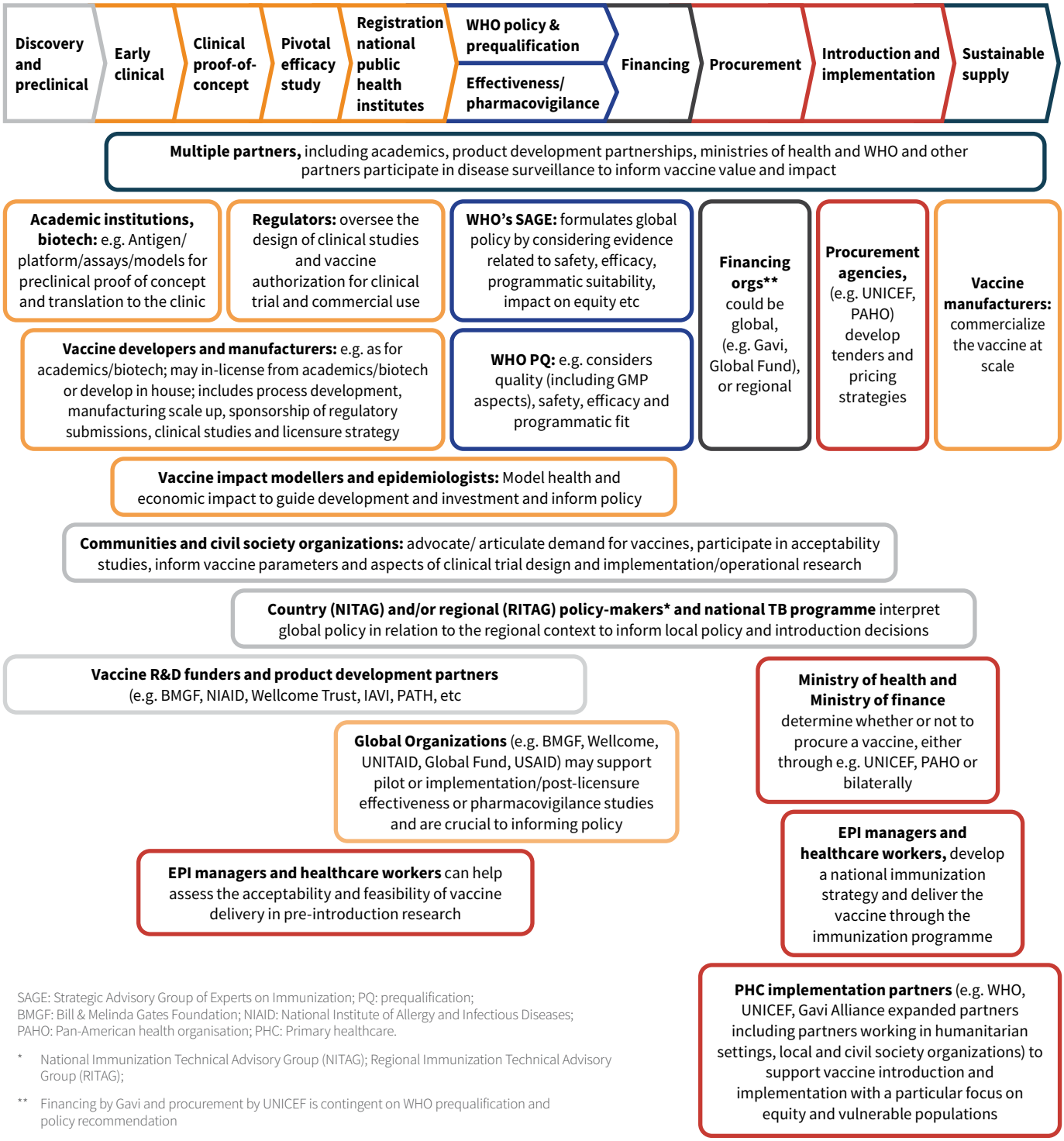
The product development-to-uptake continuum for new TB vaccines requires the integration of various related but discrete activities, and the engagement and coordination of multiple stakeholders, including those in TB control programmes. Fig. 2 provides an overview of these major stakeholder groups, and outlines areas of engagement across the continuum. **Fig. 2 is not intended to be exhaustive or representative of every region, but it illustrates some of the roles of stakeholders, and emphasizes the need for timely engagement of late-stage actors,** such as policy-makers, civil society organizations and end-users. This will help catalyse dialogue on the factors that will determine feasibility of introduction and implementation, since these factors will critically influence product parameters and evidence needs, which themselves must be considered during earlier phases of development.

"The product development-to-uptake continuum for new TB vaccines requires the integration of various related but discrete activities..."



Nurse Rosemary Raikekeni stands for a photo with her team during a visit to bring vaccines and other essential health services to residents of remote Kuvamiti village in East Guadalcanal, Solomon Islands, on 17 May 2023.
Photograph courtesy of © WHO / Neil Nuia

Fig. 2. Outline of the process for product development-to-uptake of a new TB vaccine intended for global use



SAGE: Strategic Advisory Group of Experts on Immunization; PQ: prequalification; BMGF: Bill & Melinda Gates Foundation; NIAID: National Institute of Allergy and Infectious Diseases; PAHO: Pan-American health organisation; PHC: Primary healthcare.

* National Immunization Technical Advisory Group (NITAG); Regional Immunization Technical Advisory Group (RITAG);

** Financing by Gavi and procurement by UNICEF is contingent on WHO prequalification and policy recommendation

Exemplar roles of stakeholders are described in the rectangular boxes, beneath the chevrons. While this pathway is presented as a series of sequential steps, it is integrated and iterative. Understanding the data requirements for later-stage policy and procurement could impact the earlier development strategy.

6. Tables

The primary aim of this document is to inform all stakeholders of the data and evidence that is anticipated to be needed to inform and support global and national policy decision-making related to TB vaccines for prevention of disease in adults and adolescents.

Five tables cover the following parameters:

- Table 1. Vaccine product-related parameters
- Table 2. Vaccine delivery-related parameters
- Table 3. Vaccination of other target populations
- Table 4. Regulatory strategy considerations for initial licensure
- Table 5. Implementation considerations

HIGH-PRIORITY parameters, in red, are attributes and/or policy considerations that are expected to be critical for stakeholders such as global, regional and country-level decision-makers, and for vaccine developers, manufacturers and funders.

MEDIUM-PRIORITY parameters, in blue, are attributes and/or policy considerations for which data and evidence are likely to be important for licensure or policy considerations.

Tables 1, 2 and 3 stratify the attributes and data that are expected to inform either of the following.

- **Initial policy (IP) recommendations** for the priority target population(s). These requirements should therefore be considered in the design of a pivotal licensure study and any pre-introduction studies. Developers should be aware that most of this evidence is expected to be obtained from licensure studies or other studies carried out in parallel.
- **Expanded policy (EP) recommendations** to address gaps in and expand upon initial policy recommendations. Data and evidence to support expanded policy can be obtained after introduction, through post-approval studies.

Table 1 covers vaccine product parameters for primary populations of interest, who are those considered the highest priority target populations. Table 3 focuses on other target populations that may not be included in initial policy recommendations, where different delivery mechanisms may be required, and decision-making may require data from additional studies.

Table 1. Vaccine product-related parameters

	Parameters (high priority, medium priority)	Preferred vaccine product attributes	Data expected	Rationale
T1.1	**Disease indication** *(condition that the vaccine is intended to prevent, e.g., (severe) disease, infection, transmission)*	Prevention of active pulmonary TB disease (POD). See T1.4 for preferred efficacy.	**IP:** Data demonstrating POD.	Mtb infection results from inhalation of Mtb aerosolized from the lungs of persons with active pulmonary TB. Prevention of active pulmonary TB will have the most rapid impact on the TB epidemic, due to reduced transmission *(23)*.
T1.2	**Priority population(s)** *(the populations who will be the primary recipients of the vaccine after licensure)*	Adults and adolescents (12–18 years of age) with or without evidence of prior Mtb infection. People living with HIV (PLHIV). Additional target populations are described in Table 3.	**IP: Safety and efficacy data** in adults with evidence of prior Mtb exposure. **Safety and immunogenicity** data in adults without evidence of prior Mtb infection. **Safety and immunogenicity** data in PLHIV . Phase III efficacy studies should not exclude people with diabetes or people with malnutrition.	Ninety percent of TB disease occurs in adolescents and adults, who represent the most common sources of Mtb spread *(28)*. PLHIV are at high risk of developing TB disease and should be included in initial policy recommendations *(24)*. Therefore, safety and immunogenicity data in these populations should be generated pre-licensure to inform initial policy considerations (see T3.1). The low incidence of TB disease in persons without evidence of prior Mtb infection would require unfeasibly large and prolonged licensure studies for efficacy *(29)*. Similarly, determining efficacy in subpopulations, such as PLHIV, and in other target populations, such as people with diabetes, will not be feasible in licensure studies. Vaccine effectiveness data in these populations should be planned for and collected in the intermediate implementation period. Vaccination should not require screening for HIV infection or Mtb infection status.

	Parameters (high priority, medium priority)	Preferred vaccine product attributes	Data expected	Rationale
			EP: Introduction in younger adolescents may depend on effectiveness data, and/or potentially correlate of protection analysis if available, from post-introduction studies. Safety and immunogenicity data in PLHIV with and without evidence of prior Mtb exposure infection.	In many settings, adolescents are at high risk of Mtb infection *(26)* and are therefore an important population for inclusion in initial policy recommendations. While it might be optimal to vaccinate before peak disease incidence, typically in young adults (18–35 years), the demonstration of efficacy against TB disease in children or younger adolescents (9–14 years of age) is not feasible, due to the relatively low incidence of TB disease in this age group *(29)*. The age range for initial licensure and policy recommendation will be driven by the age groups included in licensure studies. Strategies for, and timing of, programmatic implementation in young adolescents will be informed by evidence of effectiveness and feasibility of co-administrations with other vaccines (see T1.9)
T1.3	**Safety/reactogenicity**	A favourable safety and reactogenicity profile.	**IP:** Safety data in priority populations. **EP:** Post-introduction pharmacovigilance will be required to further characterize the safety profile in all priority and target populations to support expansion of the initial policy recommendation, and to identify any rare events not found in the registration trials.	The risk–benefit of a TB vaccine may vary in different target populations (e.g., PLHIV , people with diabetes and immunocompromised individuals).
T1.4	**Efficacy** *(percentage reduction of outcomes of interest in the vaccinated compared to the unvaccinated group under optimal conditions)*	50% or greater efficacy in preventing confirmed pulmonary TB in the priority populations described in T1.2 *(10)*.	**IP:** Data from sufficiently powered randomized, placebo-controlled studies conducted in high-burden countries, with broad inclusion criteria, in the priority populations (see T1.2). Although demonstration of efficacy in all subpopulations will not be possible, licensure studies should be broadly representative of target populations and conducted so as to provide supportive evidence for use in Mtb uninfected individuals.	It is likely that vaccine efficacy will be determined in licensure studies in people with evidence of prior infection with Mtb, to optimize sample size and duration of studies. Although ≥50% protection is preferred, a vaccine with less than 50% vaccine efficacy, if widely used in areas of high TB burden or in populations at high risk, may still prove valuable and contribute to reducing the transmission of Mtb in a cost-effective way *(23)*. However, acceptability will likely be context-specific; in lower burden settings, reduced efficacy may result in lower uptake due to a preference for other interventions (e.g., TPT), which may be more effective and familiar to end-users.
		Efficacy in preventing confirmed pulmonary TB in populations not included in initial policy recommendations, described in Table 3.	**EP:** Where efficacy data are inconclusive or unavailable for populations not included for initial policy recommendations, effectiveness data should be planned for and collected post-introduction.	Safety and immunogenicity data in populations for whom it has not been possible to determine efficacy – such as people with diabetes, people with no documented Mtb infection, and older adults – may be sufficient to support policy recommendation. This is especially the case if there is supportive, albeit inconclusive, efficacy data or correlates of protection. Where demonstration of efficacy is feasible, a vaccine with lower efficacy than that expected for the priority target populations (adults) may be acceptable, and potentially impactful and cost-effective *(23)*.

	Parameters (high priority, medium priority)	Preferred vaccine product attributes	Data expected	Rationale
T1.5	**Primary efficacy endpoints in the clinical trial**	Prevention of microbiologically confirmed pulmonary TB disease *(27)*.	**IP:** See T1.4. Case definitions should be standardized and used across efficacy studies *(27)*. Efficacy against subclinical TB is not currently practical to measure in phase III studies, and will likely not be needed for initial policy considerations.	Microbiological confirmation of symptomatic cases, for example, by obtaining samples from all participants at the end of a study, is sufficient to confirm a TB endpoint, and is the endpoint required by regulators. Guidelines on timing of sample collection and number of samples required to confirm an endpoint have been published *(27)*. Documenting vaccine efficacy against incident Mtb infection is highly desired for policy purposes, especially as it is related to recommendations for vaccine implementation without screening for Mtb infection status. Obtaining samples from all participants at the end of the study would, therefore, be highly advised to determine infection status, and would capture asymptomatic cases that would otherwise be missed.
T1.6	**Secondary and exploratory endpoints** *(endpoints not selected as the primary endpoint but providing additional insights into vaccine performance)*	Prevention of infection (POI). Prevention of drug-resistant TB disease. Reduction in number of deaths associated with/ attributable to drug-resistant TB.	**EP:** POI endpoints may be a useful tool for determining meaningful biological vaccine effect, particularly in populations where assessment of efficacy is not feasible; however, the relationship between vaccine-derived POI and the subsequent risk of disease is currently not known *(29)*. Although molecular mechanisms of drug resistance in Mtb are unlikely to impact vaccine efficacy, sensitivity testing should be conducted on Mtb isolates obtained during clinical vaccine trials.	These endpoints may enable analyses of additional aspects related to vaccine impact, which may be informative in policy considerations. These endpoints will vary between vaccine products, and their relevance may be context-specific (e.g., depending on the level of MDR-TB, HIV–TB co-infection, extent of previous exposure to Mtb within populations). WHO considers Mtb a priority pathogen target to reduce antimicrobial resistance (AMR) and has called for the accelerated development of improved vaccines *(30)*. An effective vaccine could reduce AMR by reducing the incidence of both drug-resistant and drug-sensitive TB. This would also reduce the transmission of drug-resistant TB, and may reduce selection of resistant strains, as the use of anti-TB drugs declines.
T1.7	**Target countries** *(countries where the vaccine is intended to be introduced soon after licensure)*	Suitability for use in all high-burden countries. Potential regulatory strategies are described in Table 4.	**IP:** Data should be obtained from sufficiently diverse and representative epidemiological contexts to support licensure in all high-burden countries. Licensure studies will likely not be conducted in all high-burden countries; data are likely to be available from countries with appropriate clinical trial infrastructure and regulatory oversight.	Policy-makers will need evidence of vaccine efficacy across a range of epidemiological settings, which could affect vaccine impact and therefore policy recommendations. Countries without a requirement for domestic clinical trial data or manufacturing should be enabled to approve the vaccine at the earliest possible time. Early engagement with the trial findings, and consideration of their relevance to other country epidemiological, programmatic and policy contexts is important to achieve this approval. Having adequately representative clinical trials settings will also ease WHO PQ and facilitate broader product regulatory authorization and policy decisions (see T4.1).
			EP: Data from countries with various epidemiology/target populations.	Early planning and engagement are essential to avoid a delay in regulatory and policy timelines in high-burden countries that may require domestic clinical trials and/ or establishment of local manufacturing of an approved vaccine.

	Parameters (high priority, medium priority)	Preferred vaccine product attributes	Data expected	Rationale
T1.8	**Duration of protection** *(period for which protection needs to be demonstrated for the disease indication)*	≥2 years of prevention of active pulmonary TB disease. One-year duration of protection data might be sufficient for conditional marketing approval, subject to discussion with NRAs (Table 4).	**IP:** Demonstrated efficacy against the primary endpoint (see T1.5) with at least 1-year follow-up once the number of primary efficacy endpoints have been accrued for registration.	Short vaccine efficacy durations are likely to have useful health impacts; however, national and regional technical advisory groups will evaluate efficacy durations within local contexts. There may be limited accrual of endpoints within the first 6–12 months to support assessment of efficacy, as observed in a previous POD study *(20)*. Therefore, it is likely to take at least 2 years for accrual of sufficient endpoints. An additional 12 months of follow-up, after the number of primary efficacy endpoints have been accrued, is recommended to assess rebound. Longer-term follow-up of the trial population will be needed to assess duration of protection, providing sufficient duration data for licensure of protection and assessment of possible need for booster doses (see T1.10).
		≥ 5 years of prevention of active pulmonary TB disease.	**EP:** Demonstrated efficacy against the primary endpoint (see 1.15) at least 5 years after completion of the primary immunization regimen.	Modelling indicates 5-year protection could substantially impact TB disease incidence, and could be cost-effective in high-burden countries when administered to adolescents/adults *(23)*. Longer-term follow-up studies, possibly after initial vaccine introduction, will be important in determining duration of protection, risk of rebound and any booster requirements.
T1.9	**Schedule** *(dosing regimen for the primary series)*	A schedule of one or two doses in the primary series. A requirement for more than three doses in the primary series would be less desirable.	**IP:** Dosing schedule will be determined in early clinical studies and confirmed in licensure studies. Dosing schedules including dosing intervals should be carefully considered in the context of current and projected ages of immunization and other primary health care (PHC) touchpoints.	A vaccine with more than two doses in the primary series is unlikely to be programmatically acceptable *(10)* because of challenges in implementation feasibility and low cost-effectiveness (see Table 5). While the immunization programme will be responsible for vaccine introduction, the vaccine could be deployed through other programmes within the primary health care system, in addition to, or instead of, the immunization platform.
		Compatibility with schedules for other vaccines recommended for use in the target populations (see 1.2 and Table 3).	**EP:** Safety and immunogenicity data in the target population when vaccine is co-administered with other vaccines in the intended delivery setting.	If these vaccines are deployed through the immunization programme, the acceptability, feasibility and cost-effectiveness of a vaccine may be improved when co-administered with other vaccines. Data will be needed to demonstrate that there is no interference between the TB vaccine and the co-administered vaccine.
T1.10	**Booster schedule** *(dosing regimen for booster, if required)*	Boosting no more than once every 5 years.	**EP:** Long-term follow-up studies should assess the need for and timing of boosters, e.g., based on immunogenicity and/or effectiveness data indicating waning immunity.	Requirement for a booster more frequently than once every 5 years will likely not be programmatically acceptable *(10)*. Co-administration issues may need to be considered throughout the age life-course of intended target populations (see T1.12).
T1.11	**Route of administration** *(how the vaccine is delivered)*	Injectable (intramuscular, intradermal or subcutaneous), using standard volumes of administration, as specified in programmatic suitability for WHO PQ guidance *(33)*. Needle-free approaches would be advantageous.	**IP:** Assessment of acceptability and feasibility of administration route in the intended contexts of use, and the implications on feasibility of implementation (see T5.1 and T5.2), particularly in the context of the intended delivery strategy (see T2.1).	The route of administration determines the feasibility of vaccine delivery in the intended setting, and may impact vaccine acceptability, cost-effectiveness, demand, and uptake and programmatic ease and efficiency. Other routes (inhaled, intranasal, needle-free) may be considered for development, if considered acceptable and feasible.

	Parameters (high priority, medium priority)	Preferred vaccine product attributes	Data expected	Rationale
T1.12	**Co-administration with other vaccines** *(administration of more than one vaccine on the same day, as part of the expected delivery schedule)*	Favourable safety and absence of immunologic interference with other vaccines recommended for use in the same target population and schedule.	**EP:** Data demonstrating no detrimental effect on the immunogenicity or safety of other vaccines potentially co-administered with a TB vaccine (e.g., influenza, COVID-19, human papillomavirus (HPV), measles catch-up, tetanus and diphtheria for women, especially pregnant women).	Co-administration will depend on which other vaccines are recommended within national immunization programmes, such as influenza, COVID-19, HPV, measles catch-up, tetanus and diphtheria, especially in relation to high priority populations for TB vaccination.
T1.13	**Effectiveness** *(ability of vaccine to prevent outcomes of interest in real-world settings)*	Impact of vaccine on incident TB cases (including drug-resistant TB) and mortality rates.	**EP:** Although not required for initial policy, consideration should be given to generating supporting data during the pre-licensure phase so as not to delay expanded policy recommendations, such as for use in other target populations of interest, e.g., younger adolescents, older adults and pregnant women (see also Table 4). Evidence on mortality impact should be planned for.	Efficacy data generated to support the initial policy recommendation programme needs to be supplemented with effectiveness data to support expansion to additional contexts/target populations. This also includes evidence on a range of health, economic and social impacts, particularly on mortality.
T1.14	**Efficacy/ effectiveness against variants of concern or bacterial antigenic variants**	Not relevant.		
T1.15	**Immunogenicity** *(types of immune response that the vaccine generates and their magnitude over time)*	Collection of clinical samples for determining correlates of protection and risk.	**EP:** Immunogenicity data to measure potential correlates of protection/risk will be essential for expansion of policy to populations where efficacy studies are not feasible. Identification of correlates/ surrogates of protection from samples collected from clinical studies, using standardized assays and reagents, should be prioritized *(28)*.	There are currently no established correlates of protection for TB vaccines. Identification and validation of correlates of protection would significantly accelerate the development of new TB vaccines, and would provide opportunities to generate supportive data for use in target populations that are difficult to study *(28)*.

Table 2. Delivery-related parameters

	Parameters (high priority, medium priority)	Preferential vaccine product attributes	Data expected	Rationale
T2.1	**Vaccine delivery strategy(ies)** *(how the vaccine will be delivered to the primary target population (e.g., routine, mass vaccination, school-based) and potential for integration into existing country programmes)*	Suitability for integration into in-country PHC services that include immunization programmes, TB control programmes and/or existing health care-seeking practices. Potential delivery settings for specific target populations are included in Table 3.	**IP:** Regional or country-specific data and stakeholder engagement will be required to define a feasible vaccine implementation strategy. Where feasible, pre-implementation studies should be conducted in some key high-burden countries to inform implementation strategies in other countries and epidemiological contexts, before an initial policy recommendation, to assess the feasibility of vaccine delivery/ implementation in various contexts (see Table 5). Dialogue with in-country or regional stakeholders should be undertaken to identify opportunities to integrate a TB vaccine within existing primary health care practices where adults and adolescents receive care (e.g., HIV programmes, national TB programmes, family planning and antenatal care programmes). Lessons learned should be leveraged from the introduction of other new vaccines (e.g., HPV vaccine for adolescents through school-based delivery, the malaria vaccine RTS,S/ AS01, in the context of malaria control programmes, and COVID-19 vaccines) in low resource settings.	Factors that determine the optimal and most cost-effective delivery strategy will be context-specific, and may include country epidemiology, sociodemographics and existing health care infrastructure. For example, mass vaccination may be appropriate in some high-burden countries, whereas subnational targeting of TB "hot spots" may be optimal in others. Target populations may vary in some contexts (e.g., in countries where the epidemic is predominantly in the elderly population *(31)*). There are not well established platforms for delivery of vaccines to adults and adolescents in many high-burden countries. COVID-19 vaccines have been delivered to adolescents and adults, and this experience should be carefully considered in TB vaccine introduction. Integration with school-based vaccination or other delivery settings for HPV vaccines may be a potential option; however, HPV vaccination is recommended for 9–14-year-olds, and it will be challenging to conduct POD studies in young adolescents *(32)*, so policy recommendation for this population will be based on effectiveness or a correlate of protection (see section T1.2).
T2.2	***Vaccine thermostability and storage temperature requirements*** *(how the vaccine needs to be stored, including during transportation to the point of administration)*	No requirement for storage at less than –20°C. If the vaccine presented for prequalification requires storage below +2°C during its shelf-life period, it should have a minimum period of storage above +2°C of 6 months. Vaccines and diluents that can be stored for extended periods at temperatures above +8°C and will not be damaged by freezing are preferred.	**IP:** Data in adherence with the mandatory criteria and, where possible, the preferred criteria included in WHO's programmatic suitability for prequalification guidance *(33)* on vaccine thermostability and storage temperature. All data will be required at the time of WHO PQ .	Stability of all vaccine components above –20°C is a mandatory requirement of WHO's current guidance on programmatic suitability for prequalification *(33)*. Thermostability criteria for prequalification vary from mandatory to preferred and should be considered during product development to avoid complex and costly reformulation *(33)*. Developers should avoid complex cold chain and storage condition requirements that reduce the feasibility of implementation and jeopardize safe administration of vaccine.
T2.3	**Presentation** *(including vial size, cold chain storage volume for secondary packaging, diluents, formulation (e.g., liquid, freeze-dried), and vaccine vial monitor; may include reference to application devices (e.g., jet injector))*	Single component/ready-to-use formats (e.g., liquid). Non-campaign setting: ≤10 doses per vial. Campaign setting: ≥10 doses per vial, in compliance with WHO multi-dose vial policy *(33)*. The vaccine presented for prequalification should be packaged in standard vial sizes and materials that can be disposed of appropriately in the field using standard procedures. Developers are strongly advised to refer and adhere to the mandatory requirements for programmatic suitability for pre-qualification (ref), including guidance on dose volume and the need for antimicrobial preservative in ready-to-use, multi-dose presentations.	**IP:** Data consistent with the mandatory criteria and, where possible, the preferred criteria included in WHO's programmatic suitability for prequalification guidance *(33)* on vaccine presentation. All data will be required at the time of WHO PQ .	Development of a vaccine that is not appropriate for programmatic use may delay uptake until a cost-effective and programmatically acceptable presentation is available, presenting a risk to vaccine manufacturers and reducing the impact of the vaccine. To simplify administration, multi-component vaccines should be in formats that minimize (1) the number of steps, (2) potential for error during preparation and administration and (3) cold chain requirements. Vaccine presentation determines the feasibility of vaccine delivery in the intended setting and may impact vaccine acceptability (see T5.2) and uptake. Given that vaccine delivery costs are a significant proportion of the total cost to immunize, the number of doses per vial need to be appropriate for the intended delivery setting; this minimizes storage and transportation costs as well as vaccine wastage.

Table 3. Vaccination of other target populations

Other target populations are populations that are important to vaccinate but may be targeted at some point after a recommendation has been made to vaccinate the priority populations listed in Table 1. They are categorized below as high or medium priority. For each target population, details are provided of important clinical considerations, whether the population is a priority for initial or expanded policy, and of proposed delivery strategy.

	Target population	Clinical considerations	Proposed implementation strategy	Rationale
T3.1	**Persons living with HIV (PLHIV)** *(diagnosed, infection controlled by antiretroviral therapy (ART))*	Priority population (see Table 1). Safety data from PLHIV should be available for all TB vaccine candidates, including live attenuated vaccines, to support initial policy recommendations. Careful safety evaluations will be required for live attenuated vaccine candidates *(10, 24)*.	**IP:** Routine vaccination strategies for PLHIV could include integration with ART programmes.	TB is the most important cause of death in PLHIV, who are 18 times more likely to develop active TB disease than people without HIV *(24)*. As HIV is prevalent in many TB high-burden countries, PLHIV are a priority target population *(24)*. HIV screening prior to TB vaccination would be a significant barrier to rapid vaccine introduction approaches *(10)*. Therefore, TB vaccines must be demonstrated to be safe in PLHIV for initial policy recommendation.
T3.2	**Persons living with HIV** *(not on treatment or infection poorly controlled by ART)*	Demonstration of safety is needed to avoid HIV screening prior to TB vaccination in many settings. Studies on PLHIV who are not on ART will be challenging because of the ethical requirement to provide treatment. Data may have to be extrapolated from individuals where ART is failing.	**EP:** Safety/ effectiveness studies and/or delivery strategies could be conducted through ART clinics.	Safety data in this target population, which is at very high risk for TB disease, is essential to enable administration of TB vaccines without any need for pre-screening for HIV, and prior to initiation of rapid vaccine introduction.
T3.3	**Persons with diabetes**	Persons with well controlled diabetes should be eligible to be included in vaccination campaigns, and therefore should be included in clinical trials.	**IP:** Routine vaccination strategies should include integration with PHC for diabetes to ensure easy and timely access to vaccination.	Diabetes adversely affects TB incidence and TB mortality *(34)*. While a specific policy recommendation for those with diabetes may be based on evidence accumulated in effectiveness studies, this target population will likely not be included in the pivotal efficacy study, and numbers may be sufficient to support initial policy.
T3.4	**Immunocompromised and immuno-suppressed persons**	Safety and immunogenicity data in these populations should be collected post-licensure once vaccine efficacy has been demonstrated. Live-attenuated vaccine candidates must be sensitive to first-line anti-TB treatment, in case dissemination occurs in those who are severely immunocompromised.	**EP:** Via primary health care facilities managing these patients.	These are important populations at higher risk of TB disease or potentially at risk of adverse effects from live vaccines. Efficacy studies in the specific groups within this population are unlikely to be feasible; therefore, discrete safety studies in groups of interest will be required for expanded policy. An immunological correlate of protection will be important to infer clinical benefit. Examples include transplantation patients and those on corticosteroids or anti-TNF therapy. Immunocompromised individuals may be excluded from live attenuated vaccine clinical studies due to the risk of possible dissemination of live vectors. An assessment of potential efficacy in these populations may become more feasible once a correlate of protection is established; however, the immunological threshold for protection may differ in these groups.
T3.5	**Malnutrition** *(underweight or morbid obesity)*	Individuals with malnutrition should be eligible to be included in rapid vaccine introduction strategies and, therefore, should not be excluded from clinical studies.	**IP:** Rapid vaccine introduction strategies to include persons with malnutrition.	WHO estimates that undernutrition contributes to twice the number of TB cases as HIV globally *(35)*. Body mass index should not be an exclusion criterion in trials, other than for exceptional cases requiring medical intervention per country/professional organization guidance. While this policy recommendation is expected to be based on evidence accumulated in effectiveness studies, this target population will likely not be excluded in the pivotal efficacy studies, and numbers may be sufficient to support initial policy.

	Target population	Clinical considerations	Proposed implementation strategy	Rationale
T3.6	**Persons who have previously had TB disease**	Because of the high risk of recurrence, people who have a history of TB disease are likely to be included in efficacy studies. Even if excluded, it is likely that people with a prior history of TB will be enrolled due to poor recall of past medical history.	**EP:** Rapid vaccine introduction strategies to include persons who have previously had TB.	The high prevalence of persons who have previously had TB in high-burden countries and who are at elevated risk of recurrence or reinfection make this a high-priority population for safety evaluation in clinical studies and vaccination. Screening for prior Mtb infection should not be required for TB vaccination. This target population will likely continue to be monitored through effectiveness studies. Demonstration of effectiveness against TB disease in the general population will likely result in a policy recommendation to vaccinate persons who have previously had TB.
T3.7	**Persons with current disease** *(i.e., active pulmonary disease with a positive microbiological diagnosis)*	Studies, where vaccine is administered concurrently with TB treatment as an immunotherapeutic and prevention of recurrence, may be conducted concurrently with licensure, or shortly after, to support policy recommendations.	**N/A** Not applicable as the vaccine is indicated for prevention of disease.	The therapeutic use of a TB vaccine would require tracking of an immunotherapeutic endpoint. It would therefore be assessed as a separate indication. Persons with active TB disease are expected to be excluded from pre-licensure POD studies. Data collected during implementation from persons with active TB, who are inadvertently vaccinated, will likely be informative for expanded policy recommendations on the safety of vaccinating individuals with active TB.
T3.8	**Persons with severe allergic reactions to vaccine components/ similar vaccine platforms**	Vaccine contraindicated in this population.	N/A as the vaccine is contraindicated.	These persons are excluded from clinical trials; therefore, this will be a contraindication in initial vaccine label and policy recommendations.
T3.9	**Other high-risk target populations** *(e.g., migrants, refugees, homeless people, people living in high-risk congregate settings, people with unhealthy alcohol use or substance misuse, miners, people living in high-density areas)*	These are all priority populations. Efficacy studies will be conducted in communities with a high incidence of TB disease, and should include populations at risk of both disease and complications from the disease. All clinical studies should include diverse representation of genders, race and ethnicity that represent the intended population for vaccine implementation. Consideration should be given to collecting demographic and socio-economic data during clinical studies to define the characteristics of the study populations.	**IP:** Early consideration should be given to identifying these populations and determining strategies to provide rapid access to vaccines once licensed.	These target populations are all at significantly elevated risk of TB disease. Most participants in TB vaccine trials are considered vulnerable, live in poor, crowded areas and will likely be a well represented subset of the licensure study population. Policy recommendations for target populations such as prisoners, migrants and refugees are a priority, and the available safety and efficacy data will be used to inform policy-making.
T3.10	**Pregnant women*** * To facilitate readability, the terms "pregnant woman" and "mother" are used throughout this document to refer to all pregnant adolescents and adults at risk of TB. including cisgender women, transgender men, non-binary and gender-fluid individuals, and intersex individuals born with a female reproductive system.	Vaccine development programmes should consider inclusion of pregnant women at the earliest opportunity, based upon a benefit–risk analysis. Early developmental and reproductive toxicology (DART) studies and evaluation of pregnancy data from similar vaccine platforms are important. If pregnant women are excluded from a clinical development plan, this should be thoroughly justified *(36)*. Even if excluded from efficacy studies, it is likely that some pregnancies will occur during the course of the study, and data should be collected from such pregnancies *(36, 37)*. Currently available standardized tools should be used to collect maternal and neonatal outcome data post-licensure *(36, 38)*.	**EP:** Once sufficient safety data are available, pregnant women should be included in the policy recommendation and early implementation strategy. Delivery of vaccines to pregnant women could be considered at ante-natal clinics to ensure adequate follow-up.	Pregnant women are an important population for vaccination to protect both mother and child. Pregnancy may increase the risk of Mtb infection and progression to disease in the mother, and maternal TB disease is associated with adverse pregnancy outcomes, including increased maternal, fetal and neonatal morbidity *(25)*. Prevention of TB disease in mothers will reduce transmission of Mtb to neonates and young infants.

	Target population	Clinical considerations	Proposed implementation strategy	Rationale
T3.11	**Lactating women*** * To facilitate readability, the term "women" is used throughout this document to refer to all gender-diverse lactating people at risk TB, including cisgender women, transgender men, non-binary, gender-fluid and intersex individuals born with a female reproductive system.	Lactating women should not be excluded from vaccination strategies unless there are specific safety concerns associated with a particular vaccine (e.g., CMV-vectored TB vaccines). Vaccine development programmes should consider inclusion of lactating women at the earliest opportunity by generating appropriate pre-clinical data and utilizing historical pregnancy data from similar vaccine platforms.	**IP:** Rapid vaccine introduction strategies	Prevention of TB disease by vaccination is important in this group as TB disease may have adverse effects on the infant, due to a mother being unwell or through exposure to TB drugs in breast milk *(25)*. People are at elevated risk of TB disease in the post-partum period.
T3.12	**Neonates** (less than 1 month)	N/A; not a relevant target population for this class of vaccines.		
T3.13	**Infants** (less than 1 year)			
T3.14	**Children** (1–9 years)			
T3.15	**Adolescents** *(12–18 years)*	Priority target population (see Table 1).	**EP:** Rapid vaccine introduction strategies for younger adolescents could include integration with other adolescent PHC activities and, potentially, school-based delivery of HPV vaccine.	Younger adolescents may not be included in initial phase III efficacy studies, but consideration should be given to effectiveness evaluation as soon as is feasible post-licensure. See T1.2.
T3.16	**Adults** *(18–64 years)*	Priority target population (see Table 1).	**IP:** Rapid vaccine introduction strategies for adults could include all PHC programmes, such as screening for TB or other disease, and/or approaches used by the immunization programme for rapid scale-up of introduction, such as integration with COVID-19 vaccine delivery.	Initial policy recommendations may be limited to a narrower age range, dependent on the data available from efficacy studies, which will recruit from populations with the greatest incidence of disease. See T1.2.
T3.17	**Persons older than 65 years**	Safety and immunogenicity should be evaluated in this age group to support policy recommendations in all regions. The evaluation of TB vaccines in people older than 65 years of age might differ by region.	EP: Persons older than 65 should be included in Rapid vaccine introduction strategies, particularly in regions where burden of disease is prevalent in older age groups *(31)*.	In countries such as China *(31)*, where the TB epidemic is driven by disease in older people, an efficacious vaccine delivered to older adults will be crucial to maximize population-level impact. This group may therefore be a target for initial policy-setting. Immunogenicity may be lower in this age cohort. The impact of this on vaccine efficacy will need to be evaluated in post-licensing studies.

Table 4. Regulatory strategy considerations for initial licensure to help facilitate policy review

There are three major stages to achieve global vaccine regulatory approval as a basis for global introduction.

1. Initial regulatory approval, for which there are various pathways described in section 4.
2. WHO prequalification (PQ) to (a) support regulatory approvals by other NRAs and (b) enable financing by agencies such as Gavi and procurement by agencies such as UNICEF. WHO PQ requires regulatory approval by an NRA with WHO Listed Authority (WLA) at maturity level 3 or higher.
3. Subsequent NRA approvals, which may be in countries where the clinical efficacy study has not been conducted, to support broad implementation. In this case, WHO PQ and the regulatory reliance mechanisms described below become important enablers.

	Regulatory strategy for initial licensure	Regulatory considerations	Rationale
T4.1	**National regulatory authority (NRA) for initial approval and marketing authorization and the NRA maturity level** *(39)*	A variety of regulatory pathways are available, including national and/or collaborative procedures (see section 4). Product registration strategies should prioritize consultations with NRAs prior to submission of a phase III trial protocol for approval, both to ensure that local requirements are met and that seamless filing for approval in high-burden countries occurs. Some countries may require clinical evidence in local populations or domestic manufacturing for licensure. Those countries that do not require domestic manufacturing for regulatory approval, or have domestic manufacturing in place at the time of regulatory review, are likely to lead early approval activities. WHO PQ requires initial regulatory approval with a WHO listed authority (WLA) at maturity level 3 or higher for vaccine production, and which will enable and facilitate timely regulatory approval in a range of countries via a reliance model *(39)*.	Regulatory strategies for initial approval will be context-specific and require early consideration and discussion with NRAs and supra-national bodies such as WHO and collaborating NRAs, particularly in the case of expedited regulatory strategies (see T4.3). Global policy recommendations and WHO PQ inform national decision-making in many lower-income countries. A strategy should be developed to enable WHO PQ (and the requisite global policy recommendation) as soon as feasible after initial regulatory approval in the first country (see T4.2).
T4.2	**WHO prequalification (PQ) strategy**	Any TB vaccine should be WHO prequalified to support purchasing by United Nations agencies. This typically follows, or occurs in tandem with, preparation for a WHO policy recommendation for use. Consideration should be given to the use of the European Medicines Agency's (EMA's) M4-all *(40, 41)* or Swissmedic's Marketing Authorization for Global Health Products (MAGHP) procedures *(42)*, whereby WHO PQ and non-EU regulatory authorities, particularly NRAs of the countries targeted for initial licensure and use, collaborate in assessment of a regulatory dossier. Eligibility for this procedure will be decided in consultation with WHO. In regions with a high burden of TB, consideration should also be given to the use of regional regulatory structures for collective review by NRAs from high-burden countries.	The EMA M4-all process is an established pathway to ensure early engagement and alignment of LMIC NRAs and WHO PQ, ultimately accelerating licensure in high-burden LMICs that do not have a mature regulatory agency and WHO PQ for UN agency procurement. WHO PQ is also a prerequisite for financing by Gavi.
T4.3	**Accelerated regulatory approval** *(e.g., conditional marketing (or use) authorization (CMA or CUA) (43), emergency use mechanism, or other accelerated or parallel pathway)*	Early discussions should be held with NRAs to explore potential expedited regulatory approval pathways, in order to establish feasibility and requirements for accelerated or conditional use authorization. These discussions should take place before phase II studies, in order to inform end-point selection and trial design. Some NRAs or regional regulatory authorities offer conditional marketing or use authorization, including the EMA and the South African Health Products Regulatory Authority (SAHPRA), based on less comprehensive clinical data than are required for full approval, where the benefit of immediate availability of the vaccine outweighs the risk. The criteria/conditions for any conditional use authorization will vary between NRAs. The US FDA's accelerated and Emergency Use Authorization (EUA) (44) pathways are not currently considered feasible for TB vaccines. TB vaccines might meet the requirements for a US FDA priority review, where the FDA's goal is to act on an application within 6 months (compared to 10 months under standard review).	The US FDA's accelerated pathway is based on a surrogate marker of efficacy, which is not available for TB. The US FDA's EUA is applicable when there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of US citizens. TB vaccines are not categorized as eligible for this pathway. FDA priority review accelerates the review process. Designation of a product as "priority" does not alter the scientific/medical standard for approval, or the quality of evidence necessary, or affect the length of the clinical trial period.

	Regulatory strategy for initial licensure	Regulatory considerations	Rationale
T4.4	**WHO Emergency Use Listing (EUL)** *(45)*	The WHO EUL is not an applicable pathway for TB vaccines.	The WHO EUL procedure could become a potential route following the declaration of a PHEIC, under the International Health Regulations (IHR) (2005) *(45)*. Although the WHO declared TB a global health emergency in 1993 *(46)*, TB does not currently meet the criteria for a PHEIC. This situation is not expected to change within the period that the leading candidates could be licensed.
T4.5	**Joint or harmonized review strategy (e.g., African Vaccine Regulatory Forum (AVAREF)** *(47)*, **International Coalition of Medicines Regulatory Authorities (ICMRA))** *(48)*	Mechanisms exist for joint or harmonized reviews of clinical trial design and regulatory approval, for example through AVAREF, which will become part of the African Medicines Agency (AMA) when procedures are established, and the South-East Asian Regulatory Network (SEARN). These should be used to accelerate approvals in high-burden countries. Developers should engage with NRAs early in development to improve the likelihood of harmonized advice and product specifications. In addition to EMA's M4-all and Swissmedic's MAGHP described in section T4.2, developers could consider using the WHO–EMA Collaborative Registration Procedure (CRP). This aims to facilitate registration of centrally authorized medicines in LMICs by sharing EMA assessments with NRAs. The NRA can use the assessments but retain their regulatory responsibilities and decision-making authority. Other NRAs, such as Swissmedic, may offer similar procedures.	Use of collaborative regulatory mechanisms may be a way to accelerate clinical trial conduct and regulatory approvals.



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Table 5. Implementation considerations

A lack of clarity on evidence needed for policy-making and alignment on responsibility for funding the generation of data can lead to bottlenecks in vaccine implementation, post regulatory approval. This table presents an initial view of the evidence likely to be important to inform WHO global policy, financing and introduction decisions by multiple stakeholders. It is intended to support dialogue regarding specifying and refining the data needs and expectations of different stakeholders, depending on specific contexts and policy scenarios. **Vaccine developers and/or country-level decision-makers are not expected to generate all the data described.** Rather, it is anticipated that **the data described below will be generated by multiple stakeholders**, potentially working in collaboration. WHO strongly emphasises the criticality of commitment and co-ordination of all partners, including to fund evidence generation, so as not to impede or delay as rapid vaccine rollout as is possible for products that demonstrate safety and efficacy.

This table may be informative for multiple stakeholders, including: policy-makers at the national, regional and global levels; global and regional financing agencies; civil society organizations and implementation partners; and non-governmental organizations, which often fund studies to generate this data and evidence. It may be particularly helpful for vaccine developers, as it offers additional detail on the types of data that will likely inform policy decisions. Therefore, many of the activities/types of studies described will be initiated during clinical development, and will likely be based on modelling estimates in early iterations. These initial estimates will be refined as data on vaccine characteristics become available, for example, related to efficacy and duration of protection, and as modelling estimates are supplemented with (pre-)introduction and implementation research data. For this reason, the information is not stratified by initial and expanded policy; data on many of the parameters will be necessary for initial policy-making, and need to be considered while preparing for studies that aim to support regulatory approval.

Several parameters inform the criteria, and will likely inform decisions for global and/or regional financing and initial policy introduction at the country level. Some of this evidence generation may be commissioned directly by global financing agencies such as Gavi and/or the Global Fund. If available, this information may also be helpful for self-procuring countries when making their initial or expanded policy decisions.

The information below is not exhaustive. For example, additional data/evidence may be needed to facilitate delivery in fragile and/or conflict settings. Consultation across a broad range of country, regional and global partners engaged in vaccine implementation, with a particular emphasis on equity, will be needed in an ongoing manner as evidence develops and evolves.

This table represents an initial view of the evidence that is believed will be important to support decision-making. It outlines the data needs and expectations of different stakeholders, depending on their specific contexts and policy scenarios. Vaccine developers and/or country-level decision-makers are not expected to generate all data described.

	Parameter	Supportive data/ activities required	Data used to inform financing and/or procurement decisions?	Rationale and notes
T5.1	**Feasibility** *(practicality of vaccine implementation, including in high-burden countries, considering logistics, delivery and programme-related issues)*	Evidence on the ease of (1) supply chain logistics, (2) vaccine presentation (see 3.3), (3) programmatic integration into existing primary health care services (e.g., TB, non-TB, or immunization programmes), and (4) administration, i.e., ease of immunization relative to alternative TB control strategies. Product attributes that may impact the feasibility of implementation are described in Table 3. The structure and strength of local/national health care systems, particularly primary care services serving priority groups, and availability of reliable immunization service funding, may affect feasibility.	Yes – ease of supply chain integration; feasibility of vaccine schedule; potential long-term financial implications.	A vaccine will only be integrated into immunization programmes, or other health care/delivery programmes, if it is considered feasible to implement by key stakeholders. It is therefore critical to identify key immunization programme and health system needs for new vaccine introduction – including human, financial and logistic resources. Feasibility of implementation in additional target populations (Table 3) will likely be considered following an initial policy recommendation and use in the priority target population, forming part of expanded policy recommendations.

	Parameter	Supportive data/ activities required	Data used to inform financing and/or procurement decisions?	Rationale and notes
T5.2	**Values and preferences of target populations** *(the likely acceptability of the vaccine in target populations and other key stakeholder groups)*	Data from vaccine acceptability studies, which can include qualitative acceptability research and/or quantitative preference elicitation research.	Yes – need for health care worker behaviour change to vaccinate adults and adolescents; acceptability in target population.	Understanding the acceptability and vaccine preferences of the priority and target populations is essential to identify critical product characteristics, to inform potential demand estimates (see T5.3), to feed into feasibility considerations (see T5.1), and to finalize communication, pricing and delivery in different contexts.
T5.3	**Demand potential** *(likely future uptake and market size, including for high-burden countries, to inform market-shaping discussions with stakeholders such as donors, industry partners and vaccine purchasers)*	Market landscaping and demand estimates, including in different epidemiological settings, taking into account alternative vaccine use scenarios, target populations and alternative interventions.	Yes – demand forecasts across countries expected to introduce the vaccine.	It is important to start assessing likely demand during product development, particularly in high-burden countries. Forecasting will need to be iteratively revised as more information becomes available, including vaccine strategies/SAGE recommendations on use. Data to help frame demand potential include size of the target population per country, as well as capacity and timeframe for vaccine introduction (expected regulatory filing date in markets, including where phase III licensure trials were conducted). Demand will also be influenced by feasibility (T5.1), acceptability (T5.2) and value-for-money compared to other interventions (T5.7), as well as broader pricing and access strategies in high-burden countries (outlined in the text preceding the table).
T5.4	**Health impact** *(the benefit of vaccination to vaccinated individuals and to the wider population, including indirect effects)*	Estimated potential health impact, including total future deaths averted in a defined period (e.g., before 2050) and per 100 000 vaccinated. Total future cases averted in a defined period (e.g., before 2050) and per 100 000 vaccinated. Total disability-adjusted life years (DALYs) averted in a defined. period (e.g., before 2050) and per 100 000 vaccinated. Epidemiological transmission modelling studies (including transmission effect) on estimated health impact, including in high-burden settings.	Yes – total current and future deaths, DALYs, and cases averted (until 2035 and per 100 000 vaccinated).	It is critical to understand the potential health impact, namely, future mortality and morbidity averted, if a vaccine is introduced, including impacts on other health conditions. Current burden of disease data (ideally per country) will be required to calculate the benefits of introduction. Potential health impact is likely to be significant, particularly in high-burden settings, due to the high burden of TB morbidity and mortality in adolescents and adults *(23)*. Existing disease models can be utilized or built upon.
T5.5	**Broader economic impact** *(contribution of vaccine introduction to micro- and macro-economic outcomes/impacts per country)*	Estimates of potential economic impact on: **(1) Health system:** including health care sector-wide, TB and immunization programme-specific costs averted/incurred. **(2) Society:** including direct medical costs as well as indirect costs (i.e., income/ productivity losses) and costs faced by TB-affected households[2]. **(3) Macroeconomics:** including impacts on economic growth.	Yes – direct and indirect costs averted.	Collecting economic burden data for TB (direct and indirect costs per country) will input into economic evaluation and value-for-money analyses (see T5.7), thus helping to determine the potential benefits of introducing a new TB vaccine in the context of the broader health care system. It is anticipated that new TB vaccines could have significant epidemiological and economic impacts, particularly when targeted at adolescents and adults, notably contributing to economic growth in high-burden settings *(49, 50)*.

2 Additional efforts are required to achieve the End TB target on costs faced by TB-affected households. 48% (95% CI: 36–61%) of people with TB and their households are faced with total costs (including direct medical expenditures, direct non-medical payments, and indirect costs such as lost income) that exceed 20% of annual household income.

	Parameter	Supportive data/ activities required	Data used to inform financing and/or procurement decisions?	Rationale and notes
T5.6	**Budget impact** *(estimates of budgetary impact/ affordability over budget cycle period (51)).*	Estimates that include: • Short-term (1–5 years generally) annual net implementation costs (procurement, delivery depending on delivery mode from the payer's perspective), of vaccine and ancillary supplies.	Yes – total vaccine procurement and delivery cost and potential cost savings.	Budget impact assessments for health interventions or technologies are relevant for any health care priority setting decisions in a context of limited resources. Budget impact may be significant *(52)* and an important consideration for high-burden countries and, in particular, resource-constrained settings. Integration with other health or delivery programmes may increase efficiency of delivery, and thereby maximize value-for-money by reducing costs. Projected budget impact estimates should be supplemented with detailed information about input parameter values and calculations to allow the analysis to be replicated. Results should be presented in a disaggregated manner to support flexibility required by local decision-makers.
T5.7	**Economic evaluation and value-for-money *(53)*** *(comparison of the costs and benefits, relative to alternative treatment and prevention policy options)*	Estimated figures for: • Health impact of vaccine delivery depending on population coverage (number of deaths or cases averted). • Economic cost of vaccine delivery depending on population coverage (e.g., cost per person fully vaccinated). • Comparison with the estimated current costs and outcomes of alternative disease prevention or treatment interventions.	Yes – data outlined in T5.4, and optimal use of alternative interventions (prevention and treatment).	Models can be designed to address specific policy questions and are dependent on data and evidence available, or that which is expected to be needed, for decision-making. Economic models will need to be based on epidemiological/economic assumptions when used before phase III and IV trial data become available, in order to support evaluation that could inform investment decisions, e.g., to forecast potential impact and demand. Model vaccine characteristics (e.g., efficacy, number of doses per regimen and duration of protection), and resource needs for successful implementation, together with price assumptions, should encompass the full range of uncertainty, and sensitivity analyses should be performed. These models help inform the optimal allocation of limited resources, thereby producing benefits for society. Economic modelling should consider if the vaccine will be introduced in the context of other interventions or the standard of prevention/care, in a range of epidemiological and socioeconomic settings, and take into account a range of perspectives, depending on the research question (e.g., health system, societal). Decision-makers can then use modelled cost-effectiveness estimates for new vaccines to inform their decisions about introducing the new vaccine, alongside other considerations of importance to them (e.g., equity, affordability, feasibility, acceptability). These data that inform cost-effectiveness analysis may be readily available for vaccine manufacturers in high-income countries, but not necessarily to those in high-burden countries, which are typically middle or low income. Therefore, efforts should be made to generate and share this information, both with stakeholders involved in investing in vaccine development and with decision-makers in high-burden countries, so they can contextualize data to their settings.

	Parameter	Supportive data/ activities required	Data used to inform financing and/or procurement decisions?	Rationale and notes
T5.8*	**Equity and social protection impact** *(prioritizing the needs and rights of the most vulnerable, and ensuring equitable benefit from vaccines)*	Estimates of potential equity impact, including data on or estimates of: • Direct benefits of vaccination for groups at highest risk of TB (e.g., estimates of distributional impact by stratification of health impact outcomes according to risk); indirect benefits of vaccination for groups at highest risk of TB; and impact on catastrophic health expenditures. • Vaccine access and coverage across countries with different TB burdens and income levels. • Impact on vulnerable groups, including women and girls, rural and low-income populations, or individuals in fragile and conflict countries (including displaced populations).	Yes – disproportionate impact of disease on vulnerable groups such as PLHIV, and benefits of vaccination for women and girls.	It is important to understand whether vaccine introduction will impact some or all high-burden populations that may benefit most as part of the cost-effectiveness analysis, and also to consider the sustainability of the intervention. Assessments of equity/social protection impact may be qualitative due to challenges in data collection, but should be included to the extent that is possible. New TB vaccines could be an equitable intervention as long as countries include their high-burden subpopulations in implementation plans *(50)*.
T5.9	**Access and affordability** *(ensuring that a vaccine is made broadly and equitably available at an affordable price)*	An access strategy should be in place that includes the following elements: • Plans for ensuring timely access in high-burden countries, including plans for regulatory filings where necessary for vaccine access, and in countries that participated in phase III licensure trials. • Identification of barriers to access, particularly for vulnerable populations. • Commitment to an affordable pricing strategy based on principles of equity, sustainability, quality and availability. • Approach for integrating vaccine into financing and procurement platforms. • Plan for equitable distribution in priority populations in high-burden countries.	Yes – Procurement costs as per T5.6.	Regulatory engagement and filing strategy should prioritize early availability in high-burden countries and for all countries that participated in clinical studies. Sustainable supply for high-burden countries is imperative. Pricing strategy should reflect a commitment to affordability and be based on the principles of equity, sustainability and availability. A price that is too high will hinder access and discourage implementation; a price that is too low is unsustainable for manufacturers. Developers can consider several pricing models, including cost-plus pricing (price set as costs of manufacturing plus a reasonable margin, or cost of goods sold plus a mark-up) or volume-based price thresholds that take advantage of economies of scale. Some TB vaccines may have a dual market, with market demand potential in high-income countries among groups such as international travellers, incarcerated persons, members of armed forces, refugee populations and health workers. In such cases, tiered pricing may be an option. Integration into financing and procurement platforms for high-burden country access – for Gavi-eligible and non-Gavi-eligible countries – impacts feasibility (T5.1), budget impact (T5.6) and demand forecasting (T5.3), and is important for eventual accessibility.
T5.10	**Global health security impact** *(the potential benefit of the vaccine in averting biosecurity risks)*	Potential global health security impact (e.g., impact on cumulative treatments averted before 2050; and impact on drug-resistant treatment cost savings). Impact on antimicrobial resistance (AMR).	Yes – epidemic potential of disease and impact of vaccination on AMR.	New TB vaccines are likely to have significant impact on drug-resistant TB, particularly where drug resistance is common *(30, 52)*. Data are required on current levels of resistance and vaccine efficacy/effectiveness in drug-resistant populations to determine potential impact of vaccine introduction.

	Parameter	Supportive data/ activities required	Data used to inform financing and/or procurement decisions?	Rationale and notes
T5.11	**Community engagement and communication strategies** *(including addressing vaccine acceptance/ hesitancy, awareness-building, education, and demand generation)*	Communications and community engagement plans developed and supporting materials generated. Health education and promotion carried out across the country to ensure acceptance of a new vaccine.	No.	Effective communication strategies are essential and should be part of robust community engagement programmes throughout the development process. Issues and myths relating to both the disease and vaccination need to be identified and addressed before and during TB vaccine introduction and rollout.
T5.12	**Pharmacovigilance and risk management** *(detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues; prevention of untoward effects of a vaccine or immunization; planning of any additional studies designed to provide further information on safety or usage)*	Development of detailed pharmacovigilance and risk management plans prior to vaccine implementation (e.g., WHO COVID-19 vaccines safety surveillance manual *(54)*), for the collection, analysis and sharing of safety data and information on TB vaccines within and between countries. Post-introduction safety trials planned in groups that are vaccinated first to gather safety information rapidly, as well as in groups that may have been under-represented in registration trials. Development of standardized definitions and lists of adverse events of special interest (AESI) and adverse events following immunization (AEFI). A patient/user engagement framework to collect real-world data once the vaccines are routinely used in the community. Existing templates *(55–58)* for collection and dissemination of safety data and risk–benefit assessments should be used.	No.	A vaccine safety related events response plan should be prepared before a vaccine is introduced. Vaccine safety surveillance during TB vaccine introduction is essential to facilitate the early detection, investigation and analysis of AEFIs and AESIs to ensure appropriate and rapid responses to evolving safety information and risk–benefit evaluations. The use of harmonized definitions and reporting systems for AEFIs and AESI is important for rapid and timely evaluation and dissemination of data. A critical element of a risk management plan is to ensure the continued monitoring of the vaccine in use, to address any additional aspect relating to the use of the vaccine, and to address public concerns with effective communication strategies regarding the safety of newly introduced vaccines, and to address concerns arising through rumours and misconceptions.

7. References

1. Shirey, M. *Vaccine equity: a comparison of new vaccine introductions. With all the talk about vaccine equity, how long does it normally take for a new vaccine to be available?* 7 September 2022]; Available from: https://www.dropbox.com/s/r3u1fz88rewho0w/Vaccine%20Equity%20-%20a%20comparison%20of%20new%20vaccine%20introductions%20-%20TYH%2029%20April%202021.pdf?dl=0.
2. O'Brien, K.L., et al., *Mind the gap: jumping from vaccine licensure to routine use.* Lancet, 2016. **387**(10031): p. 1887-9.
3. Maxmen, A., *Scientists hail historic malaria vaccine approval - but point to challenges ahead.* Nature, 2021.
4. WHO. *Immunization Agenda 2030. Strategic Priority 7 Reaserach and Innovation*. 23/08/2022]; Available from: ia2030-draft-4-wha_b8850379-1fce-4847-bfd1-5d2c9d9e32f8.pdf (who.int).
5. WHO. *Product Development for Vaccines Advisory Committee.* 23/08/2022]; Available from: https://www.who.int/groups/product-development-for-vaccines-advisory-committee#:~:text=PDVAC%20is%20an%20independent%20standing,related%20manufacturing%20and%20delivery%20technologies.
6. WHO. *From Vaccine Development to Policy: A Brief Review of WHO Vaccine-Related Activities and Advisory Processes (2017).* Available from: https://cdn.who.int/media/docs/default-source/immunization/product-and-delivery-research/who_vaccine_development_policy.pdf?sfvrsn=20def1e4_5&download=true.
7. WHO. *WHO Coordinated Scientific Advice for health product R&D.* Available from: https://www.who.int/activities/optimizing-research-and-development-processes-for-accelerated-access-to-health-products/who-coordinated-scientific-advice-for-health-product-r-d#:~:text=WHO%20has%20developed%20the%20WHO,a%20prequalified%20status%20if%20the.
8. WHO. GUIDANCE FOR THE DEVELOPMENT OF EVIDENCE-BASED VACCINATION RELATED RECOMMENDATIONS. 23/08/2022]; Available from: https://cdn.who.int/media/docs/default-source/immunization/sage/general/guidelines-development-recommendations.pdf?sfvrsn=e455fd4b_2&download=true.
9. Kochhar, S., et al., *Building the concept for WHO Evidence Considerations for Vaccine Policy (ECVP): Tuberculosis vaccines intended for adults and adolescents as a test case.* Vaccine, 2022. **40**(12): p. 1681-1690.
10. WHO. *WHO Preferred Product Characteristics for New Tuberculosis Vaccine.* 23 August 2022]; Available from: https://www.who.int/publications/i/item/WHO-IVB-18.06.
11. WHO. *Global tuberculosis report 2022. Geneva: World Health Organization.* 2022; Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.
12. WHO. The end TB strategy.; Available from: The end TB strategy (who.int)
13. Uplekar, M., et al., *WHO's new end TB strategy.* Lancet, 2015. **385**(9979): p. 1799-1801.
14. Sahu, S., L. Ditiu, and A. Zumla, *After the UNGA High-Level Meeting on Tuberculosis-what next and how?* Lancet Glob Health, 2019. **7**(5): p. e558-e560.
15. WHO. *Tuberculosis.* 27/07/2023]; Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.
16. *Global Plan to END TB 2023-2030.* 2023(26/7/2023).
17. Martinez, L., et al., *Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis.* Lancet Glob Health, 2022. **10**(9): p. e1307-e1316.
18. Fletcher, H.A. and L. Schrager, *TB vaccine development and the End TB Strategy: importance and current status.* Trans R Soc Trop Med Hyg, 2016. **110**(4): p. 212-8.
19. Nemes, E., et al., *Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination.* N Engl J Med, 2018. **379**(2): p. 138-149.
20. Tait, D.R., et al., *Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis.* N Engl J Med, 2019. **381**(25): p. 2429-2439.
21. WHO. *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment.* 2020; Available from: https://apps.who.int/iris/bitstream/handle/10665/331170/9789240001503-eng.pdf.
22. Harris, R.C., et al., *Potential impact of tuberculosis vaccines in China, South Africa, and India.* Sci Transl Med, 2020. **12**(564).
23. Knight, G.M., et al., *Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries.* Proc Natl Acad Sci U S A, 2014. **111**(43): p. 15520-5.
24. Miner, M., et al., *Developing TB Vaccines for People with HIV: A Roadmap: Meeting Consensus Report.* 2022, Research Square.

25. Mathad JS, Yadav S, Vaidyanathan A, Gupta A, LaCourse SM. *Tuberculosis Infection in Pregnant People: Current Practices and Research Priorities.* Pathogens. 2022 Dec 6;**11**(12):1481. doi: 10.3390/pathogens11121481. PMID: 36558815; PMCID: PMC9782762.

26. Ellis, R.D., et al., *Innovative clinical trial designs to rationalize TB vaccine development.* Tuberculosis (Edinb), 2015. **95**(3): p. 352-7.

27. Garcia-Basteiro, A.L., et al., *End-point definition and trial design to advance tuberculosis vaccine development.* Eur Respir Rev, 2022. **31**(164).

28. Scriba, T.J., M.G. Netea, and A.M. Ginsberg, *Key recent advances in TB vaccine development and understanding of protective immune responses against Mycobacterium tuberculosis.* Semin Immunol, 2020. **50**: p. 101431.

29. Ginsberg, A.M., D*esigning tuberculosis vaccine efficacy trials - lessons from recent studies*. Expert Rev Vaccines, 2019. **18**(5): p. 423-432.

30. WHO, *Bacterial vaccines in clinical and preclinical development 2021 An overview and analysis.* Available from: https://www.who.int/publications/i/item/9789240052451.

31. Harris, R.C., et al., *Age-targeted tuberculosis vaccination in China and implications for vaccine development: a modelling study.* Lancet Glob Health, 2019. **7**(2): p. e209-e218.

32. Pelzer, P.T., *Potential implementation strategies, acceptability, and feasibility of new and repurposed TB vaccines.* PLOS Global Health, 2022.

33. WHO. *Assessing the programmatic suitability of vaccine candidates for WHO prequalification (revision 2014).* 2014 16 September 2022]; Available from: https://apps.who.int/iris/bitstream/handle/10665/148168/WHO_IVB_14.10_eng.pdf.

34. Restrepo, B.I., *Diabetes and Tuberculosis.* Microbiol Spectr, 2016. 4(6).

35. Sinha, P., et al., *Undernutrition and Tuberculosis: Public Health Implications.* J Infect Dis, 2019. **219**(9): p. 1356-1363.

36. Krubiner, C.B., et al., *Pregnant women & vaccines against emerging epidemic threats: Ethics guidance for preparedness, research, and response.* Vaccine, 2021. **39**(1): p. 85-120.

37. Bonhoeffer, J., et al., *Global alignment of immunization safety assessment in pregnancy - The GAIA project.* Vaccine, 2016. **34**(49): p. 5993-5997.

38. Kochhar, S., et al., *Safety assessment of immunization in pregnancy.* Vaccine, 2017. **35**(48 Pt A): p. 6469-6471.

39. WHO. *A Framework for evaluating and publicly designating regulatory authorities as WLA, WHO.* 4 September 2022]; Available from: https://www.who.int/initiatives/who-listed-authority-reg-authorities

40. Cavaller Bellaubi, M., et al., *The European Medicines Agency facilitates access to medicines in low- and middle-income countries.* Expert Review of Clinical Pharmacology, 2020. **13**(3): p. 321-325.

41. European Medicines Agency *Medicines assessed under the 'EU-M4all' procedure.* 21 September 2022]; Available from: https://www.ema.europa.eu/en/partners-networks/international-activities/medicines-assessed-under-eu-m4all-procedure.

42. Swissmedic. *Swissmedic procedure for scientific advice and Marketing Authorisation for Global Health Products (MAGHP).* 2019 16 September 2022]; Available from: https://www.swissmedic.ch/swissmedic/en/home/about-us/development-cooperation/marketing-authorisation-for-global-health-products.html.

43. EMA. *Conditional marketing authorisation.* Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation.

44. FDA. *Emergency use authorization.* Available from: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

45. WHO. *Emergency Use Listing Procedure for vaccines.* 2020 16 September 2022]; Available from: https://www.who.int/teams/regulation-prequalification/eul/eul-vaccines.

46. Nathavitharana, R.R. and J.S. Friedland, *A tale of two global emergencies: tuberculosis control efforts can learn from the Ebola outbreak.* Eur Respir J, 2015. **46**(2): p. 293-6.

47. WHO. *Overview: The AVAREF Joint Review Process*. Available from: https://www.afro.who.int/health-topics/immunization/avaref/joint-review-process.

48. ICMRA. *International Coalition of Medicines Regulatory Authorities.* 26/07/2023]; Available from: https://www.icmra.info/drupal/en.

49. Harris, R.C., et al., *Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines.* Hum Vaccin Immunother, 2016. **12**(11): p. 2813-2832.

50. Portnoy A, et al. *The potential impact of novel tuberculosis vaccines on health equity and financial protection in low-income and middle-income countries.* BMJ Glob Health. 2023, 8(7); :e012466. doi: 10.1136/bmjgh-2023-012466. PMID: 37438049; PMCID: PMC10347450.

51. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, Orlewska E, Penna P, Rodriguez Barrios JM, Shau WY. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014 Jan-Feb;17(1):5-14. doi: 10.1016/j.jval.2013.08.2291. Epub 2013 Dec 13. PMID: 24438712.

52. Weerasuriya, C.K., et al., *Affordability of Adult Tuberculosis Vaccination in India and China: A Dynamic Transmission Model-Based Analysis.* Vaccines (Basel), 2021. 9(3).

53. WHO guide for standardization of economic evaluations of immunization programmes, 2nd ed, accessed at: https://www.who.int/publications/i/item/who-guide-for-standardization-of-economic-evaluations-of-immunization-programmes-2nd-ed (5 November 2023)

54. WHO. *Covid-19 vaccines: safety surveillance manual.* 2020; Available from: https://cdn.who.int/media/docs/default-source/covid-19-vaccines-safety-surveillance-manual/covid19vaccines_executive_summary_manual.pdf?sfvrsn=7a6f8fe4_1&download=true.

55. Condit, R.C., et al., *The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of viral vector vaccines.* Vaccine, 2020. **38**(49): p. 7708-7715.

56. Kochhar, S., et al., *The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of inactivated viral vaccines.* Vaccine, 2020. **38**(39): p. 6184-6189.

57. Kochhar, S., et al., *The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines.* Vaccine, 2020. **38**(35): p. 5734-5739.

58. Kim, D., et al., *The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines.* Vaccine, 2020. **38**(34): p. 5556-5561.

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