A Global Framework to prepare for Country Introduction of New TB Vaccines for Adults and Adolescents

Executive Summary
Tuberculosis (TB) is a major cause of ill health and one of the leading causes of death worldwide. For this reason, a United Nations convened a High-Level Meeting in 2018 committing countries to accelerate efforts to end the TB epidemic, with TB vaccines as a cornerstone of reaching future targets.

In support of this commitment by Member States, WHO seeks to advance the development and deployment of new TB vaccines to prevent TB disease, with a focus on adolescents and adults in whom 90% of TB disease occurs. TB prevention in this target population, who are the main transmitters of pulmonary TB disease, is likely to have a significant impact not only on reducing TB transmission generally but also on infants, children, and other high-risk populations. However, in most countries there is no established immunization platform for vaccine delivery for adults and adolescents.

Although new TB vaccines are still in the development phase, anticipating and addressing the challenges of vaccine delivery must start now, in parallel and at risk, to assure implementation of successful vaccines as rapidly as possible. This framework intends to facilitate the planning, investments, and preparation for rapid introduction and scale-up of TB vaccines for adults and adolescents, as they become available, such that new vaccines are available with sufficient, sustainable and timely supply; accessible, with equitable delivery aimed at all who could benefit, and accepted, so that end-users, health care workers, and policy makers’ requirements are met. It supports and is aligned with the vision of WHO’s End TB Strategy, to “achieve a world free of TB, with zero deaths, disease and suffering due to the disease” through rapid and equitable access to and distribution of new adolescent and adult TB vaccines. This document deliberately focuses on activities at a national level while also highlighting the global and regional activities needed to accelerate equitable introduction and scale-up.
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Acronyms

AIGHD  The Amsterdam Institute for Global Health and Development
BCG   Bacille Calmette-Guérin
CHAI The Clinton Health Access Initiative
COVID-19 Coronavirus disease of 2019
ECVP Evidence Considerations for Vaccine Policy
EDCTP The European and Developing Countries Clinical Trials Partnership
EPI Expanded programme on immunisation
FVVA Full Value of Vaccines Assessment
Gavi The Global Alliance for Vaccines and Immunization
HIV Human immunodeficiency virus
HPV Human papillomavirus
HWs Healthcare workers
IAVI The International AIDS Vaccine Initiative
IP Intellectual property
MDR-TB Multidrug-resistant tuberculosis
MoF Ministry of Finance
MoH Ministry of Health
MoI Ministry of Industry
Mtb Mycobacterium tuberculosis
NIS National Immunization Strategy
NITAG National Immunization Technical Advisory Group
PAHO The Pan American Health Organization
PDVAC Product Development for Vaccines Advisory Committee
PHC Primary health care
PPC Preferred Product Characteristics
PQ Prequalification
R&D Research and Development
RITAG Regional Immunization Technical Advisory Group
SAGE Strategic Advisory Group of Experts on Immunization
TB Tuberculosis
TPT Tuberculosis preventive treatment
UN The United Nations
UNICEF The United Nations Children’s Fund
WHO The World Health Organization
1. Background and context

Approximately one-quarter of the world’s population, or 2 billion people, have been infected with Mycobacterium tuberculosis (Mtbt). Of those infected, 5-10% will progress to active tuberculosis (TB) disease over their lifetimes. In 2021 alone, nearly 10.6 million people developed active TB disease, and 1.66 million died. (1)

TB is a disease mainly affecting populations living in under-resourced conditions, often with TB risk factors such as malnutrition, HIV, and diabetes, and with limited access to health care services and access to TB diagnosis and care. Bacille Calmette-Guérin (BCG), the only available TB vaccine, is effective at preventing severe forms of TB disease in young children but has limited efficacy in preventing pulmonary TB disease in adolescents and adults, who are the main transmitters of Mtbt. Without effective new vaccines, which would be added to existing tools for TB control, a world free of TB will not be possible within the timeframe of the End TB goals.

In 2018, a United Nations High-Level Meeting set key targets and commitments to accelerate efforts to end the TB epidemic, which all Member States endorsed. (2) To help achieve these targets, WHO seeks to advance the development and deployment of new TB vaccines to prevent TB disease in adolescents and adults in whom 90% of TB disease occurs. As several innovative TB vaccine candidates intended for use in adolescents and adults are either currently in or about to enter Phase III clinical trials,(1) a vaccine for the prevention of TB disease in adolescents and adults could be available in the near term.

Preventing pulmonary TB disease in adolescents and adults, given their overwhelming contribution to Mtbt transmission, is also likely to significantly impact the incidence of TB in those who might be unvaccinated, including infants, children, older adults, and other target populations, for example, people living with HIV and diabetes. (3) New effective TB vaccines will also help address drug-resistant tuberculosis (DR-TB), which remains a significant public health problem, by directly reducing the incidence of drug-resistant tuberculosis (DR-TB), and also by reducing the empiric use of antibiotic treatment for non-specific respiratory tract infections in people with undiagnosed TB. (4) TB is not just a public health emergency but also an economic one. The disease places a significant burden on healthcare systems and impedes economic development, particularly in low- and middle-income countries. By investing in TB control efforts, including new, effective TB vaccines, countries can reduce the burden of the disease and save lives while promoting economic growth and prosperity.

Rapid introduction and coverage scale-up of new TB vaccines will require a significant upfront investment, nationally and globally, to capacitate the readiness, introduction, programme delivery platform and monitoring, in parallel with the planned or ongoing efficacy trials. Pivotal efficacy studies are conducted in high-burden countries, many of which are not dependent on funding from global donors for vaccine purchases. Stakeholders in these settings, in particular, need to consider how to introduce new TB vaccines as they become available, potentially in parallel with the formulation of a WHO global policy recommendation. In addition, vaccine manufacturers are seeking clarity on the anticipated demand, use case and acceptability for TB vaccines for adults and adolescents, and guidance on the evidence that will need to be generated to ensure vaccine uptake.

This framework aims to guide countries and global stakeholders in preparing for the introduction and coverage scale-up of new TB vaccines for adolescent and adult populations as new vaccines become available. Building from past experiences with new vaccine introductions of novel products and target age groups, advance preparation and planning, at risk, is essential to achieve effective and equitable vaccine rollout. Notably, the framework leverages and is linked to recent guidance (Evidence
Considerations for Vaccine Policy) that addresses expectations for TB vaccine product attributes and evidence needs to inform development and policy at a global level as shown in Figure 1.

The framework also supports the work of the new WHO TB Vaccine Accelerator Council, envisaged to serve as a coordinating body “to facilitate the licensing and use of effective novel TB vaccines catalysing high-level alignment between funders, global agencies, governments and end users in identifying and overcoming barriers to TB vaccine development”.(5)

Figure 1. WHO guidance on TB vaccines

1. Rationale for the framework

As vaccine candidates approach regulatory approval and policy recommendations for programmatic use, ownership by and early engagement of country-level stakeholders is critical to prepare the pathway for rapid introduction, coverage scale-up, and impact of new TB vaccines, for six primary reasons:

- New TB vaccines for adults and adolescents could become available for use within the next 3-5 years;
- The prioritization of these new TB vaccines will be important to assess in the context of existing TB control interventions such as BCG vaccination and improved TB preventive treatment (TPT);
- Planning and preparation for TB vaccine introduction and scale-up for adolescents and adults will be complex, take time, and require adequate training and resourcing;

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1 See WHO Preferred Product Characteristics (PPC) for new TB vaccines intended for adults and adolescents, 2018; AIGHD/EDCTP Global roadmap for research and development of tuberculosis vaccines, 2021 endorsed by WHO PDVAC in 2020 with an advise that WHO should engage in the development of guidance for downstream aspects, including commercialization, policy development, financing and implementation; WHO Full Value Proposition for New TB Vaccines, 2022; WHO Principles and considerations for adding a vaccine to a national immunization programme: from a decision to implementation and monitoring, 2014.
• In-country awareness of the potential impact of an effective vaccine for adults and adolescents needs to be built early at the population level;
• Consideration of how a new vaccine could complement existing strategies/interventions for TB prevention and control will be essential to acceptability and readiness;
• Producing adequate vaccine supply requires a robust assessment of country-level demand and financing.

This framework supports and is aligned with the vision of WHO’s End TB Strategy, to ‘achieve a world free of TB, with zero deaths, disease and suffering due to the disease’ through rapid and equitable access to and distribution of new adolescent and adult TB vaccines. (5) This document deliberately focuses on activities at a national level while also highlighting the global and regional activities needed to accelerate equitable introduction and scale-up.

The general considerations for national vaccine introduction are well-described in WHO’s Principles and considerations for adding a vaccine to a national immunization programme: from the decision to implementation and monitoring (7). However, the public health need, infrastructure, and processes for vaccine introduction vary by country and context, including the regulatory, policy, financing and procurement environment. The framework thus identifies specific goals and milestones required to facilitate the rapid introduction and scale-up of new TB vaccines for adolescents and adults, aiming for an accelerated, coordinated, integrated, people-centred, equity-driven, and evidence-based approach.

Given the objective of this framework to raise awareness of the potential impact of TB vaccines for adults and adolescents, and to understand how they might be used in different contexts when they become available, the primary stakeholders that need to be engaged include national stakeholders, including government ministries (in particular, Health, Finance, Education and Industry), parliamentarians and politicians (who appropriate budgets), civil society (including those who represent TB patient and survivor groups), National Immunization Technical Advisory Groups (NITAGs), National TB Programmes, National Immunisation Programmes, academic institutions, and professional societies. Importantly, this document also seeks to guide global actors, including product developers and manufacturers, non-profit organisations, philanthropic organizations, donors and funders, academic institutions involved in TB vaccine research and implementation, UN agencies, and the broader TB community.

The framework assumes new TB vaccines will meet the attributes and criteria described in WHO’s Evidence Considerations for Vaccine Policy (ECVP) for new TB adult and adolescent vaccines to support equitable introduction in all countries and, in particular, meet the requirements for the low-and middle-income country introduction (publication pending, link to initial draft that was circulated for public consultation is here). Therefore, this framework should also be read in conjunction with the WHO ECVP document, which provides more guidance on target populations, potential implementation strategies and regulatory processes.

2. Development process

In response to the need for guidance to prepare for global access to new TB vaccines for adults and adolescents, the WHO convened a series of five workshops in 2022, which collectively included approximately 150 expert stakeholders. The workshops were convened around five proposed strategic pillars, namely:
1. Understanding the public health need for a new TB vaccine at the country level (including an exploratory discussion on evidence that could inform introduction decision-making)
2. Regulatory strategy
3. National, regional, and global policymaking
4. Manufacturing scale-up and commercialization
5. Financing, supply, and access.

These workshops aimed to identify the key activities and additional research required to facilitate late-stage product development, commercialization, access, and implementation of new TB vaccines for adolescents and adults.

In the context of, and as an outcome of, these workshops, the following WHO technical guidance documents are now (or will soon be) publicly available:

- The WHO ECVP for Tuberculosis Vaccines Intended for Adults and Adolescents related to strategic pillars 2 & 3.
- The WHO commissioned Full Value of Vaccines Assessment (FVVA) for New Tuberculosis Vaccines (8) related to strategic pillars 1, 3 & 4.

Following the five workshops, a WHO Expert Advisory Group was established and convened at WHO Headquarters in December 2022 to review the outputs. The group prioritized the need for this country-level framework, that describes critical activities to prepare for decision-making and subsequent rapid introduction, scale-up, and impact of new TB vaccines for adults and adolescents.

In addition to the work with the expert group to develop a draft framework, consultations were conducted in early 2023 for broader input from policymakers at the national and regional level, civil society representatives, the vaccine industry, and TB programme managers. This draft framework is being issued for public consultation and is being circulated to immunization and TB programme managers and advisory groups and is being considered by WHO’s Product Development for Vaccines Advisory Committee (PDVAC) and Strategic Advisory Group of Experts on Immunization (SAGE).

3. Structural elements

In alignment with the WHO End TB Strategy, the country-level framework envisions a world free of TB, with zero deaths, disease and suffering due to TB. Through its three goals, each with three milestones (Section 4), it seeks to facilitate rapid introduction and scale-up of new TB vaccines for adults and adolescents. The framework also outlines global and regional enablers (Section 5) that need to occur in parallel to the country level activities described, to ensure equitable introduction and scale-up.
4. Goals, key milestones, and activities

The framework outlines three goals with milestones and activities required to facilitate readiness at the country level.

The activities identified are intended as illustrative (rather than exhaustive) and will differ by country. To enable accelerated, coordinated, integrated, people-centred, equity-focused, and evidence-based introduction and scale-up, planning of these activities at the country level needs to start early, after clinical proof-of-concept has been demonstrated to inform strategies for and investment in late-stage product development, regulatory approval, and implementation research.

Goal 1: New vaccine available: Sufficient, sustainable, and timely supply

Rapid introduction and scale-up require that any newly approved TB vaccine be available in the country with sufficient, sustainable, and timely supply. Activities to guarantee vaccine availability must be initiated in advance of efficacy studies to engage commercial manufacturers, support regulatory approval, policy recommendation for use, affordable procurement, and ensure that adequate and appropriate data are obtained as part of clinical trials or pre-implementation research to support efficient decision-making on adoption and rollout.
Figure 3. Milestones and illustrative activities to support Goal 1

M1.1 Robust vaccine estimates for country demand

Given that TB vaccines for adults and adolescents are a new product requiring a novel delivery platform, the demand for such a vaccine at the country level is unclear. National epidemiological data should inform both the burden of disease and the size of key target populations, as well as drive alignment on the critical product attributes, such as expected efficacy, schedule, and duration of protection (as described in the WHO ECVP for TB vaccines). An early understanding of the acceptability and feasibility of delivery and prioritization of the intervention relative to alternatives for TB and vaccines for other diseases, within the country’s epidemiological and primary healthcare system context is needed to assess the potential demand (the number of doses needed in short, medium and long term) in a sustainable manner and the public health impact. The demand assessment should be based on the preferred vaccine attributes that impact the ease of delivery and cost-effectiveness within the country’s delivery system. These modelled outcomes need to be discussed with country TB and immunization programme managers and other stakeholders to determine potential demand forecasts for vaccines in the context of anticipated product attributes and implementation strategies.

To date, vaccine impact modelling of new TB vaccines based on WHO-preferred product characteristics, has been conducted at both a global level and for selected countries in priority populations, where robust epidemiology data are available.\(^2\) (12) As more country-specific epidemiology data becomes available, this modelling can be expanded; the models that have been developed are open source and are available to countries for their use (Ishtm-tbmg/tbvax-pub:

\(^2\) For models, see e.g., Harris RC, et al. Potential impact of tuberculosis vaccines in China, South Africa, and India (9); Harris RC, et al. Cost-effectiveness of routine adolescent vaccination with an M72/AS01E-like tuberculosis vaccine in South Africa and India (10); Portnoy A, et al. The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study (11). Other ongoing work includes also the Clinton Health Access Initiative (CHAI) analysis of TB vaccine demand in South Africa, China, India, Nigeria and Indonesia; the International AIDS Vaccine Initiative (IAVI) market sizing assessment; Smart4TB activities to inform country readiness, population and country prioritization, vaccines implementation evidence, and TB vaccine acceptability; and the Wellcome Trust and MM Global Health Consulting market assessment.
Where resources or data are inadequate to conduct this work, countries may consider using neighbouring countries or regional data to infer demand.

**M 1.2 National policy pathway for new TB vaccine defined and evidence gaps identified**

Policy pathways for new adult and adolescent TB vaccines should be determined during – and ideally before - Phase III studies to identify the key stakeholders who must be engaged, and who will set the "goal post" including what data and evidence are required to enable rapid decision-making on adoption. The WHO ECVP for TB vaccines describes the considerations for policy at a global level, and can serve as a framework for policy recommendation by national immunization technical advisory groups (NITAGs), TB programmes, and other stakeholders within the primary healthcare system. It is critical to determine what evidence is required for policy recommendation and to assess how this aligns with the data that will be generated as part of the regulatory package to avoid a delay in recommendation for use following regulatory approval. Any critical evidence gaps could be addressed through parallel clinical studies or pre- or early implementation research in a few pilot/early adopter countries, for example, to assess the feasibility of deploying vaccines for adults through the TB control programme, HIV control programmes, antenatal clinics and workplaces. Decision-making on TB vaccine introduction should be taken in context of immunization planning and closely linked to national health strategy.

**M 1.3 Procurement plans in place**

The timely introduction of new TB vaccines for adults and adolescents requires anticipation and dialogue between manufacturers and procurers on mechanisms, expected volumes, and pricing before regulatory approval so that procurement can be rapidly executed once the decision to introduce a vaccine is in place.

In the case of self-financing countries, procurement agreements will be heavily influenced by vaccine prices, availability of vaccines and national tendering processes. They may also be influenced by whether or not there is a requirement for in-country efficacy data or a preference for new TB vaccines to be manufactured in-country. The concepts and considerations described in the WHO Full Value of Vaccines Assessment and ECVP for TB vaccines can assist countries in determining prioritization of TB vaccines, taking into consideration the benefits that would accrue from vaccination, such as health impact; value for money; equity and social impact; economic impact; and implementation feasibility. If a country aims to engage a global procurement partner, like UNICEF Supply Division or PAHO Revolving Fund, procurement principles also need to be determined upfront.

There is a global shift towards vaccine production and the access landscape with less reliance on global mechanisms and a greater focus on regional and national manufacturing and procurement strategies.(13) Countries may want to leverage these developments to provide greater flexibility and control over procuring new TB vaccines.

**Goal 2: New vaccine accessible: Equitable delivery aimed at all who could benefit**

The decision to adopt a new vaccine and its regulatory approval in a country is a critical step for vaccine access. **Rapid introduction and rollout require that a country has a clear plan for how that vaccine will be delivered to those most in need**, regardless of socio-economic status, location, or other factors that may limit access. The most viable and cost-effective delivery strategies will likely differ by country and need to be individually determined while mindful of financing requirements.
M 2.1 Vaccine implementation strategy defined

Routine immunization programmes were established 50 years ago to vaccinate young children and have evolved considerably since then to include older children, adolescents, pregnant women, other adults and the elderly. However, in many countries established immunization platforms or implementation strategies for delivery vaccines to adolescents and adults remain limited or weak. There are limited established immunization platforms or implementation strategies for delivering vaccines to adolescents and adults. For example, countries may choose to deliver TB vaccines through the primary health care (PHC) system or focus on delivery through EPI clinics, child and adolescent primary care programmes, workplaces, or schools. It is essential to establish clear expectations about which government department(s) are responsible for leading the immunization co-ordination and scale-up. Multiple parts of the healthcare system and other ministries (e.g. education) will need to be engaged and coordinated to determine the optimal delivery strategy/ies for the country, long before the vaccine is considered for implementation. The optimal delivery strategy (e.g. routine immunization, campaign approach, school vaccination, TB programme, primary health care services, HIV programme) will be based on defined target population and vaccine characteristics, such as cold-chain requirements or the number of doses required.

The most relevant delivery experience to adults and adolescents is the delivery of COVID-19 vaccines (14) for adults and adolescents and human papillomavirus (HPV) vaccines for adolescents. As such, countries should review what lessons can be applied to TB vaccine implementation from these programmes. While adolescents are a key target population, adult vaccine introduction will likely occur first, as there may be limited safety and efficacy data on young adolescents (under 15 years) at the time of first implementation.

The WHO ECVP for TB vaccines identifies populations that will be targeted initially, based on data expected to be included in the regulatory dossier, followed by safety and immunogenicity and/or effectiveness studies in other populations to support expanded policy. Therefore, countries will need short-, mid-, and longer-term strategies to ensure equitable vaccination of all target populations and conduct robust implementation research that may include pilot implementation and studies to...
establish acceptability, achievable coverage, and potential impact to inform current and future strategies.

**M 2.2 Delivery systems in place**

Once an implementation strategy is proposed/selected, as described in 2.1, countries will need to define and cost delivery including number of health care workers needed and trained, data monitoring and recording systems, infrastructure, logistics and supply chain.

Selected countries will also need to work with manufacturers to put in place phase IV surveillance systems and impact evaluations (including for post- implementation vaccine effectiveness studies). Pharmacovigilance plans will need to be developed before implementation to establish a baseline against which vaccine safety assessment can be meaningfully measured. Risk management plans should also be developed to address regulatory and public concerns and provide early awareness regarding any evolution in the safety profile of new TB vaccines.

**M 2.3 Sustainable financing strategy in place**

Countries’ decision to introduce TB vaccines should be included in their National Immunization Strategy (NIS) which identifies sources of financing for the immunization programmes.

Significant financing, including funding for vaccine procurement and the in-country costs for the delivery, will be required for national introduction and continuous scaled up rollout of TB new vaccines, particularly for a novel target population. Allocation of additional resources to the PHC system or to essential package of services may be required for effective and sustained delivery of the vaccines to a new population target. The case for investment in establishing a new TB vaccine for adults and adolescents within the healthcare system, the so-called willingness-to-pay, will require that countries assess the full value that encompasses the vaccine price and projected costs of introduction and rollout, as compared to public health, economic and broader benefits at both an individual and population level, and in the context of other interventions for TB control as well as other vaccines that could be introduced. The allocation of resources for TB vaccine should be decided as part of the National immunisation Strategy (NIS).

Policymakers and budget holders will need to be engaged early in evaluating and assessing evidence needed for decision making on vaccine introduction and deployment. For countries unable to finance TB vaccines from their national budgets alone, a dialogue will need to take place with potential external donors, such as Gavi, the Vaccine Alliance; the Global Fund, the World Bank, and bilateral aid agencies (e.g., USAID). Countries will also need to consider and plan for the private sector healthcare system’s role in financing procurement and delivery.

**Goal 3: New vaccine accepted: Policymakers, end-users, and health system requirements met**

COVID-19 has shown that unless and until the vaccines are accepted by the people who are expected to deliver and receive them, scaling up coverage in an equitable manner will not be possible. **Having a vaccine available and accessible does not mean it will be adopted by communities or populations at risk, particularly in the case of a new target population.** For that reason, much work needs to be done upfront with a full range of stakeholders, from policymakers to health workers, TB survivors and eligible patient groups (including in- and out-of-school adolescents) to position these vaccines for uptake. New TB vaccines must "fit" within health systems and be wanted by the people they serve. Country’s PHC and HIV systems, for example, should be leveraged and affected communities should be engaged in decision making.
Scaling demand will also require addressing vaccine confidence, which significantly hindered COVID-19 vaccine uptake in many countries and communities. **National programmes will need to work closely with stakeholders to understand and address specific areas of concern**, including through robust and targeted communication strategies.

![Figure 5. Milestones and illustrative activities to support Goal 3](image)

### M 3.1 Vaccine Value Defined at Individual and Community Levels

Adopting new TB vaccines and building vaccine confidence will require "buy-in" from all stakeholders, from political leadership, policymakers to front-line health workers, target populations to TB survivors. At the individual level, ensuring uptake and increasing coverage will require clearly articulating vaccine safety and efficacy and the benefits of an additional intervention over and above what is already available. This is why it is critical to involve communities in the decision-making process. Healthcare workers must be confident that delivering this vaccine is worth the effort. At a community level, new TB vaccines for adults and adolescents will reduce transmission and therefore risk of infection and disease, as well as potentially having other impacts such as reducing anti-microbial resistance. Policymakers and donors will need to understand and quantitate how these benefits trade-off against the cost of procuring and delivering the vaccine in a ‘value-for-money’ assessment that also considers the investment in other, alternative interventions for TB, other vaccines or other health issues. Assessing the “vaccine value” will require an in-depth analysis of the drivers and trade-offs specific to each group of stakeholders.

### M 3.2 Community Engaged

People- and user-centred design is an effective strategy to enable better programming and build community-based champions. Engaging the range of stakeholders, from community groups to professional associations to private providers to opinion leaders, begins before the planning of Phase III studies so that gaps in knowledge, awareness, preferences, and perception of TB vaccines can be identified and addressed, including in pivotal studies. Building on successful experience with HIV medicines, engagement can include developing community advisory boards focused on national
adoption and engaging priority populations, particularly adolescents and their parents and caregivers. The COVID-19 experience underscored that engagement of health workers from the start is crucial.

**M 3.3 Robust communication strategy in place**

Introduction and coverage scale-up will require early identification and addressing of gaps in knowledge, awareness, and perception of TB vaccines across the range of stakeholders who need to be engaged in the policy and implementation process. On the policy front, analyses should be developed on the burden of TB within a country, to identify the priority target populations and potential delivery strategies, and the potential impact a new TB vaccine could have at an individual and societal level, on the healthcare system and for the economy more broadly. On the individual and community levels, communication messages should be developed, based on evidence, to address and to alleviate specific concerns, including vaccine hesitancy, and highlight attributes seen as of highest value.

Some audiences may have limited knowledge of TB, and in particular the need and potential benefit of a vaccine for adults and adolescents, or the imminent availability of these vaccines as an essential method of TB control. Therefore, it is vital that, even before Phase III studies, materials are developed and made accessible to multiple audiences at different levels, e.g., senior policymakers, healthcare workers, schools and workplaces, and broader communities, addressing their specific questions and concerns.

Regarding communications strategies, countries can leverage their experience with COVID-19 vaccination. Particularly important will be to identify and address the issues that led to vaccine hesitancy and engage early in the development process to pre-emptively address misconceptions as they start circulating. Robust, quickly reactive communication strategies are also essential during implementation of the vaccine, including explaining any emerging safety issues that may become evident after the vaccine has been introduced and is widely used.
5. Integration of goals, milestones, and activities

Each milestone is underpinned by multiple activities, some of which are supporting other goals and milestones (Figure 6). Many of these activities are inter-related, for example, assessing demand will require a clear understanding of perceived value and acceptability by the community, and implementation research will inform both the policy pathway and the implementation strategy.

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<td>Engage tri-partite and other national stakeholders to develop a robust demand forecast ✓ ✓ ✓ ✓ S, M</td>
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<tr>
<td>National policy pathway defined, and evidence gaps identified</td>
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<tr>
<td>Define milestones for data and evidence requirements to inform policy decisions ✓ ✓ ✓ ✓ S</td>
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<td>Gather evidence needs for policy in parallel with clinical development for a blockchain regulatory dossier, streamlines processes for rapid approval ✓ ✓ ✓ ✓ S</td>
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<td>Conduct pre-implementation research ✓ ✓ ✓ ✓ S, M</td>
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<td>Measurements in place</td>
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<td>Establish dialogue between manufacturers, regulators, and procurement partners ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<tr>
<td>Secure pricing and volume commitments from manufacturers ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<tr>
<td>Assess the role of local and regional manufacturers ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Vaccine implementation strategy defined</td>
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<td>Define risk-robustity population ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<td>Agree on interactions between primary health care, TB, HIV and SRH and school health programs ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<tr>
<td>Assess health system readiness and address needs—open gaps in implementation and access ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<td>Build on lessons learned from strategies from COVID-19 and HIV ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Plan and conduct implementation research/field studies to inform vaccine rollout ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<td>Supply systems in place</td>
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<td>Define infrastructure and supply chain requirements, and bureaucracy streamlining strategies ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Work with manufacturers to put in place post-licensure surveillance ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Sustained financing strategy in place</td>
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<td>Assess the willingness to pay for new TB vaccines ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<td>Secure budget/funding for procurement and delivery ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Engage with financial and the private sector ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Identify innovative financing solutions ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Value of new TB vaccine defined, at individual and community levels</td>
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<td>Assess perceived value and acceptability ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<td>Articulate benefits and potential harms to anticipate feedback, raise stakeholder buy-in ✓ ✓ ✓ ✓ ✓ ✓ ✓ M</td>
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<td>Communities engaged</td>
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<td>Conduct subnational identification mapping ✓ ✓ ✓ ✓ ✓ ✓ ✓ S</td>
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<td>Assess knowledge and perceptions through focus groups and other community outreach ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<td>Use information gathered to inform communications strategy ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<td>Provide support and information to promote engagement ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<tr>
<td>Robust communication strategy in place</td>
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<tr>
<td>Identify key audiences and champions ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<tr>
<td>Develop targeted materials; address vaccine hesitancy ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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<tr>
<td>Integrate communication strategies with data-generating activities such as pre and post-launch clinical trials and pharmacovigilance activities ✓ ✓ ✓ ✓ ✓ ✓ ✓ S, M</td>
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Figure 6. Interlinkages between the goals, milestones, and illustrative activities
6. Global and regional enablers for the introduction

Beyond the goals and milestones described to accelerate country introduction and scale up, several factors are influenced by the regional and global environment, where a series of ‘enablers’ need to be coordinated and integrated to achieve global supply, policy, financing, and procurement to support introduction across all countries that choose to introduce new TB vaccines for adults and adolescents, to achieve global vaccine impact (Figure 7).

Rapid and equitable introduction and rollout of new TB vaccines across multiple countries cannot occur without i) ensuring that vaccines are designed to ‘fit’ within the programs that are intended to deploy them, ii) alignment on the expectations for data to support regulatory approval and policy recommendations, iii) adequate supply and manufacturing capacity, and iv) sustained global/regional financing and political engagement. These global and regional factors allow (or hinder) countries to achieve accelerated, integrated, coordinated, people-centred, equity-driven, and evidence-based TB vaccine introduction and scale-up.

Figure 7. Illustrative linkages between country framework and regional/global enablers

i) Programmatic suitability

Early consensus on the anticipated delivery strategies for vaccines informs the requirement for optimal vaccine presentation. It also enables manufacturers to develop a vaccine that is acceptable for use by national programmes. In this regard, country preferences, driven by the initial assessment of a country delivery system and preliminary implementation plans, need to feed into the vaccine development process. These attributes are described in WHO preferred product characteristics(3), the WHO ECVP for TB vaccine intended for adults and adolescents, and guidance on requirements for WHO prequalification(15) to guide vaccine manufacturers. Furthermore, pre-implementation research is vital in helping understand the "real-life" use of the vaccine in a range of contexts that countries have regarding prioritized populations, TB and immunization programmes, and health systems.
ii) Regulatory and Policy

Given the specific requirements that some countries’ national regulatory authorities may have for population-specific data (e.g., country-, sex-, and age-specific data, data on women and adolescents), early engagement between national programmes, national regulatory and manufacturers needs to take place before the design of the pivotal efficacy studies. Harmonized regulatory pathways, i.e., alignment of data expectations, approval processes and timelines across the national regulatory agencies of multiple target countries, are key enablers to accelerating a TB vaccine supply. Synchronizing a collective regulatory review entails clarity on the roles and timing of entities responsible for safety and efficacy reviews and licensing at the global and regional level, particularly for high-burden countries.

Notably, the data required by global policymakers and financing agencies for introduction are usually beyond the requirements for regulatory approval and rely heavily on factors such as cost-effectiveness and feasibility of use; the evidence needed for global policy bodies such as WHO’s SAGE and financing agencies must be clarified and data collected as part in the pivotal efficacy study or generated in parallel, to accelerate introduction.

iii) Supply and manufacturing

An affordable, reliable, and sufficient supply of TB vaccines is a prerequisite for effective vaccine introduction and scale-up at the country level. To this end, diversified vaccine production, including regional manufacturing capacity, is important in lowering the risk of supply shortages and securing equitable distribution. Overall, early collaboration between regulators, regional and global policymakers, manufacturers, potential regional and global procurement agencies (e.g., PAHO, UNICEF), and vaccine and TB procurement and programme financiers (e.g., Gavi, The Global Fund) can facilitate the development of initial access, intellectual property (IP), and procurement agreements and pooled procurement arrangements to enable country preparedness and equal distribution of vaccines.

iv) Financing and political engagement

From vaccine development to country implementation, strong political will and buy-in across the stakeholders are drivers of success and an enabler of the availability of adequate funding. Achieving universal access will require sufficient and sustained public sector financing from investments in research and development to lower end-user costs to investment in delivery systems for the poorest and most marginalized. To this end, high-level advocacy, including engagement of G7 and G20 countries, is critical for an equitable TB vaccine introduction. Furthermore, clarity on the roles of funding partners (e.g., Gavi, the Global Fund, the World Bank, bilateral donors), procurement partners (e.g., PAHO, UNICEF), their potential financing instruments (e.g., advance market commitments, volume guarantees, vaccine independence initiative), and potentially other sources of domestic and donor funding is needed early on to enable countries to define the priority populations and plan the procurement and delivery while also providing manufacturers with a risk mitigation measures for investment.

7. What is needed next?

This framework identifies the essential activities and considerations that will apply to every country as it evaluates the potential impact and feasibility of deploying new TB vaccines for adult and adolescents. Much of the planning for uptake at both the global and country levels will depend on and be driven by the countries, the level of engagement of key voices within the TB community, and the timely initiation
of planning. However, the vaccine cost-effectiveness/cost-benefit will depend on the country’s context, including epidemiology, the strength of its immunization system and TB programme, the maturity of the regulatory agency and the requirement for efficacy data in the domestic population. Therefore, it is strongly recommended that countries considering early introduction seek the support to implement this framework. Their experience can also inform modifications on subsequent iterations of this guidance.
References


15. WHO. Vaccines Prequalification [Internet]. 2023 [cited 2023 Mar 1]. Available from: https://extranet.who.int/pqweb/vaccines