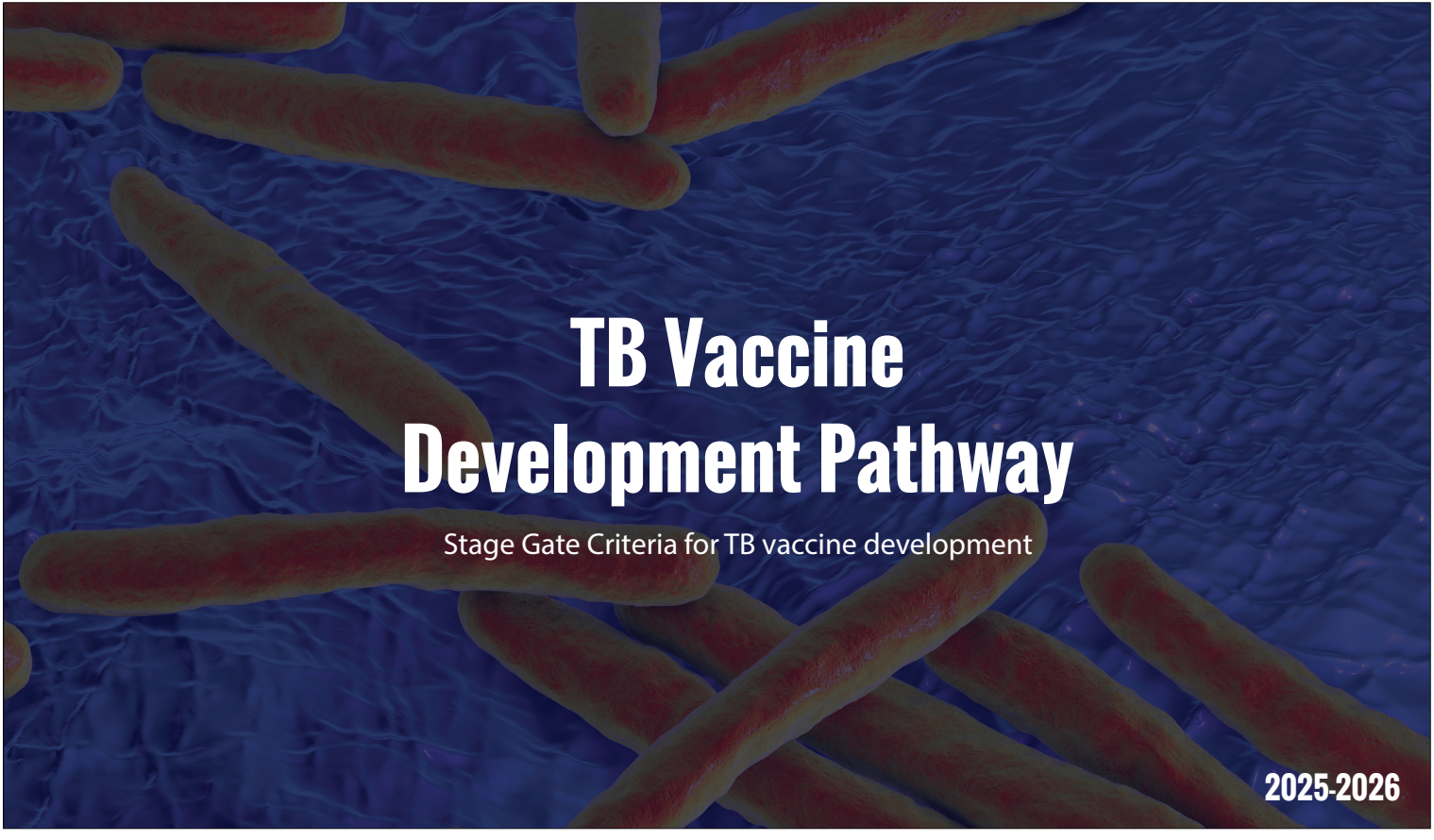

TB Vaccine Development Pathway

Stage Gate Criteria for TB vaccine development

2025-2026

TBVI

Colophon

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Stakeholders:

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About the TB Vaccine Development Pathway

Achieving Global Health impact with a vaccine encompasses everything from a brilliant idea for a new or improved vaccine to improving the lives of people worldwide.

This road can be split in two with the milestone of a marketed vaccine in the middle: the development of a vaccine product and the implementation of the new vaccine. This tool is a guidance for the first part: developing a vaccine against TB.

The development of a TB vaccine can be divided into stages, from discovery to implementation. The decision to move a vaccine candidate to the next stage is difficult, and even more so for TB vaccines because of the lack of a correlate of protection, of predictive animal models, of precedence for obtaining marketing authorisation, and the restricted amount of funding available.

The TB Vaccine Development Pathway is built on the importance of a diverse TB vaccine pipeline and of individual vaccine candidates to be advanced rationally to manage the global pipeline in the most nimble and resource-efficient way and to address the unique challenges of TB. Therefore, the TB Vaccine Development Pathway serves as a guidance tool for developers, helping them consider all the functions of development and facilitating the efficient advancement of TB vaccines to its next stage of development.

Stage gate criteria

The TB Vaccine Development Pathway uses a stage gate criteria approach. In this approach, activities are defined and performed for each stage of the development process. The gate presents a list of criteria for the vaccine candidate to progress to the next stage, or not. The stage gate criteria are intended to help developers and funders make investment decisions for the next stage of development.

Since their first publication in 2012, the stage gate criteria for TB vaccine development have been thoroughly revised with input from a wide range of stakeholders several times to include new knowledge and insights emerging from the field

For the corresponding web tool, please visit www.tbvacpathway.com

Vaccine development is a complex and long endeavour that requires multiple expertise, management of activities running in parallel, and decision points. The Stage Gate approach is a project management methodology that assists in the management of such large, long and complex projects. The Stage Gate approach organises a project along two elements: (1) the stages, which describe packages of activities that occur in parallel and generate material and data, and (2) the gates that follow each stage and consist of a review of data from the preceding stage using defined criteria where possible. These defined stages and gate criteria help to assess progress and decide whether to advance a project to the next stage, stop, hold or recycle it. This methodology is applied by the TB Vaccine Development Pathway.

The TB Vaccine Development Pathway is laid out in a series of tables which describe the stages and gate criteria for the development of a vaccine against TB disease from discovery and initial stage of the design of the vaccine (Stage A), to launch and implementation in vaccination programmes (Stage J). The development of a TB vaccine candidate is guided by its Target Product Profile (TPP) which outlines the expected characteristics of the vaccine in terms of intended use, indication, target population, route and immunisation schedule, safety and efficacy attributes and stability

requirements. The TPP is a critically important tool for an effective and coordinated management of all functions involved in the development of a TB vaccine and evolves as the development progresses across the successive stages. While the TB Vaccine Development Pathway is organised by stages and gates, its management is structured by 'functions' or 'expertise' needed to execute activities. The management is integrated, meaning that these functions work together or in sequence, based on activities as the development of vaccine candidates progresses.

Specific considerations

1. TB specific considerations

TB vaccine development is facing two key challenges that currently preclude effective and efficient prioritization of vaccine candidates to advance into the clinic: 1) the lack of accepted or validated immune correlates or surrogates of protection and 2) the lack of a validated animal model(s) that predicts TB disease and outcomes in humans. This has an impact on pre-clinical screening of potential candidates and on optimisation of the vaccine formulation and regimen, since even lengthy and costly protection experiments in animal models have not yet been validated to predict clinical efficacy. The lack of an established immune correlate also hampers the development of an appropriate, qualified assay to measure potency which would accelerate and harmonise product characterisation and Quality Control.

Measurement of antibody responses has provided the tool to monitor the quality and quantity of the adaptive immune response for many vaccines, but not for BCG. There is no consensus on what the protective antigen(s) against TB are, nor is the mechanism of protection against TB disease fully understood. Hence, the assessment of the immune responses to a TB vaccine candidate should be guided by the nature of the vaccine and broadened to include measurement of innate and adaptive immune responses, both humoral and T-cell mediated responses. This provides a greater technical and financial challenges, as preclinical results will not reduce the risks for further development to the same extent as for vaccines for which a correlate of protection exists.

The TB Vaccine Development Pathway tool addresses and provides guidance for such TB vaccine-specific challenges.

2. Vaccine technology specific considerations

In the field of vaccinology, new technological platforms have emerged, each with specific challenges for development (Pollard et al., 2021)[1] . Two classical vaccine platforms stay close to the original pathogen, either as an inactivated or a modified live version that causes no disease. Thereare several examples of attenuated and inactivated vaccines against viral diseases (*e.g. MMR and IPV*), whereas there are fewer examples for bacterial pathogens. BCG is a rare example of a marketed live attenuated vaccine and whole-cell pertussis is one of the few licensed inactivated vaccines. For TB, vaccines based on several different platforms are in advanced stages of clinical development, with an overview available in the TB vaccine pipeline[2]. Besides live attenuated or inactivated vaccine candidates, there are TB subunit vaccine candidates that comprise selected *Mtb* antigens delivered by a variety of platforms. These include classical adjuvanted protein vaccines, viral vector-based vaccines and mRNA and DNA encoded vaccines.

Protein subunit vaccines combine pathogen-specific antigens with an adjuvant as a supportive immunostimulant. Examples are the Hepatitis B subunit vaccine, bacterial toxoid vaccines e.g. Tetanus and Diphtheria, and conjugate vaccines e.g. pneumococcal vaccines. For TB, several protein subunit vaccines are in advanced stages of clinical development, including single recombinant polypeptide antigens and multiple, fused proteins combined with liposomes and Toll-like Receptor specific adjuvants.

Recombinant viral vector vaccines use a replicating or non-replicating (abortive) viral vector as a carrier for antigens of a pathogen and production of the antigens is induced in cells infected with the viral vector. They aim to induce an adaptive response against the pathogen specific antigens, while also providing some innate immune stimulation. An example is the recently licensed adenovirus vector-based COVID-19 vaccine. For TB, several candidate vaccines based on viral vectors, including Modified Vaccinia Ankara (MVA) adenoviruses, and influenza virus are in early stages of clinical development.

The DNA/RNA vaccines contain the genetic information of a pathogen specific antigen which is then produced by target cells inoculated with the DNA or mRNA. Progress has been made in the delivery of DNA (electroporation). However, the licensed mRNA vaccines for COVID-19 have provided a major incentive for TB vaccines based on mRNA formulated into lipid nanoparticles (LNP). The mRNA/LNP platform provides flexible vaccine design and generally induces strong T-cell and antibody responses. This includes candidates in clinical development and multiple preclinical projects aiming to enter clinical testing in the near future.

3. TB vaccine target population considerations

Information is given for specific TB vaccine target populations and indications for which there may be different types of vaccines or distinct approaches or requirements for the development pathway. Two main target populations have been listed below. This guidance refers to, and is aligned with, the Preferred Product Characteristics (PPCs) for different TB vaccines prepared by the WHO.

1) Adolescent/ adult populations

Adolescents and adults with pulmonary TB are the primary sources of *Mtb* transmission, and modelling predicts that vaccination of these two populations would have greater and more rapid impact on the TB epidemic than improved neonatal vaccines (Harris et al., 2016)[3]. A recent SAGE[4] recommendation stated that additional data be collected to inform the use of new TB vaccines for adolescents and adults in those with and without evidence of *Mtb* exposure at the time of vaccination. In addition, in high-incidence sites little efficiency gain is expected in only enrolling participants with a positive IGRA for the efficacy evaluation (Cobelens et al., 2025)[5]. Further, vaccines should be safe for use in HIV-infected and other subpopulations such as pregnant individuals and individuals who are breastfeeding. Vaccination ideally aims at preventing TB disease whether it results from progression, reactivation of an old (re-)infection or new infection. The clinical evaluation of a vaccine is driven by the sponsor's chosen target indication and target population(s), as well as by considerations such as budget, pricing and implementation strategies. The relevant WHO PPC is described in section 6 of the document WHO Preferred Product Characteristics[6] for New Tuberculosis Vaccines, and WHO Evidence Considerations for Vaccine Policy (ECVP)[7] development for TB vaccines intended for adults and adolescents.

2) Neonates/ infant populations

New TB vaccines for neonates could either be in the form of a replacement for neonatal BCG or a booster vaccination administered to infants with the aim to improve current BCG vaccination, providing greater and longer protection (prevention of disease) and having a safety profile at least as safe as BCG. Therefore, the benchmark for the development stages and functions is BCG, in contrast to vaccines for adults and adolescents for which no vaccine and thus no benchmark is yet available. Benefits of a BCG replacement vaccine should be evaluated in Phase 3 clinical studies. Information and recommendations on the preferred product characteristics can be found in section VII of the document WHO Preferred Product

Characteristics for New Tuberculosis Vaccines [6].

Of note:

- Other priority populations identified by the WHO ECVP[7] that are at increased risk of TB or have specific safety concerns include: immunocompromised and immunosuppressed individuals, including people living with HIV, pregnant and breastfeeding individuals, malnutrition (underweight or morbid obesity), people deprived of liberty and other high-risk priority populations (e.g., migrants, refugees, homeless people, people living in high-risk congregate settings, people with unhealthy alcohol use or substance misuse, miners, and people living in high-density areas). Vaccine developers may consider the inclusion of these priority populations in clinical trials testing new TB vaccine candidates. However, although these are populations that are important to vaccinate, they may be targeted at some point only after a recommendation has been made to vaccinate other priority populations.

- Therapeutic vaccines are deployed as an adjunct to chemotherapy in any age group to improve treatment efficacy in individuals who currently suffer from TB disease. The development pathway for therapeutic TB vaccines is substantially different from prophylactic indications, in particular the design of clinical studies. The target outcomes of therapeutic vaccines are to improve success of treatment, particularly for multi-drug resistant TB, or to decrease or prevent relapse. Shortening the duration of drug treatment and/or reducing the number of drugs necessary to cure TB disease should also be considered. Because of these multiple possible outcomes, there will be a number of aspects of the development pathway which differ compared to prophylactic vaccines. Notably, clinical trial designs will need to evaluate safety, define optimal timings and dosage in relation to drug treatment and ensure that standard chemotherapy is not adversely affected by vaccination. More information is available in the WHO PPC for therapeutic vaccines [8]. Therapeutic vaccines will not be discussed further in this document.

4. Animal Model Considerations

Because of various limitations and bottlenecks in clinical experimental medicine and trials (ethics, costs, capacity), preclinical evaluation of vaccine prototypes and/or candidates is relevant and pertinent at different stages of the vaccine development process. Pre-clinical studies in animals can

help in guiding vaccine platform and antigen selection, in generating data on preclinical safety, or in estimating optimal formulation, dose, route, and/or immunisation interval. Further, animal models can help provide proof-of-concept for efficacy. **Importantly, no single animal model is validated as predictive for clinical outcome and there is no legal or regulatory framework that dictates the use of certain (animal) models at a specific stage or for a specific purpose.** Thus, a product developer has considerable freedom whether or not to include preclinical animal studies into a product development plan, based on a product specific risk-benefit assessment.

Models are typically used to simplify 'real world' (here: clinical) complexity to leverage our knowledge base and/or relieve a resource-limited clinical development path. As all models inherently have their limitations, this guidance document aims to reflect - in a non-exhaustive manner - on some major species and modelling conditions that can support and facilitate the development of TB vaccines.

1) Considerations for the Mouse model:

Mice represent the most widely used animal model for TB vaccine testing. Typically, inbred mouse strains (limiting host variability and reducing the number of animals needed for a study), such as C57Bl/6 or Balb/c mice, are immunized and subsequently infected with an aerosolized *Mtb* dose of 50-100 CFU and protection is assessed by measuring the lung bacterial burdens between 28-42 days post-infection. In this model, BCG immunization typically reduces the lung bacterial burden by ~1 log, when assessed at these timepoints. However, the protection conferred is transient and usually dissipates by 3-4 months post-infection and outcomes of these studies have not correlated well with results from human efficacy trials. This might be improved by adapting the mouse strain and/or challenge strain used:

Mouse strains:

Mice have fewer MHC molecules than humans; the most commonly used strain (C57Bl/6) has only a single MHCII molecule, thus some antigens may not be protective in a given mouse strain simply because it lacks epitopes capable of binding the MHC molecules of that strain. Testing immunogenicity in a variety of mouse strains with different MHC haplotypes (e.g., C57Bl/6, Balb/c, and C3H) could reduce this risk. Subsequent efficacy testing could then use strains in which the vaccine is confirmed to be immunogenic. One consideration would be to use an F1 strain (e.g., C57Bl/6 x Balb/c) between two strains that are immunogenic to increase the number of MHC molecules capable of presenting antigens and to optimize the breadth of the T cell response, more akin to the breadth that would occur in humans. Another potential benefit of F1 strains is that

they are heterozygous at most loci, reducing the propensity for extremes of immunologic phenotypes in some inbred strains (e.g., C3HeB/FeJ mice). Diversity outbred mice have been used in some experimental TB vaccine studies, however, because each mouse is genetically unique, large numbers of mice are needed, and F1 mice may represent a balanced approach which introduces some genetic diversity, while requiring animal numbers which are feasible.

Challenge dose considerations for mice:

The human infectious inoculum is thought to be only 1-3 CFU and there is growing evidence that a more physiologic challenge dose may offer several advantages for TB vaccine testing in a variety of animal models. In mice, a challenge dose of 1-3 CFU enables assessment of: prevention of *Mtb* dissemination to the contralateral lung, prevention of detectable infection, as well as overall Mycobacterial lung and spleen burden, for example. Moreover, the immune mechanisms may be different from those that reduce bacterial burdens in response to a supraphysiologic challenge dose. As a result, the hierarchy of vaccine efficacy may differ in response to a physiologic compared to a supraphysiologic challenge dose. There are two disadvantages of using a 1-3 CFU challenge dose: 1) it requires more mice and is therefore more expensive, and 2) it is currently not routinely performed by most labs and may require using a TB vaccine testing service with this capacity.

2) Considerations for the Guinea pig model:

The outbred Dunkin–Hartley strain of guinea pig is the most commonly used, although inbred strains are available. The typical route of infection with *M. tuberculosis* is by the aerosol route. Guinea pigs are very susceptible to tuberculosis (TB) and disease is induced with very low doses of *M. tuberculosis*. The progression of the disease that follows infection of guinea pigs with *M. tuberculosis* displays many features of human TB including well defined granulomas with central necrosis enclosed by lymphocytes, macrophages, and multinucleate giant cells and a fibrotic capsule. Different infection and readout regimens allow the guinea pig models to test a range of vaccines and endpoints.

Even with recent efforts, there remain few immunological assays to interrogate immune responses in guinea pigs compared to other animal species. Research continues to identify antibodies which could be used in such assays. Despite this, much progress has been made in using histopathological analysis and immunohistochemical techniques to quantify host response to infection following vaccination.

Vaccine candidates that have previously demonstrated efficacy in mouse models can be further evaluated for protective efficacy in the guinea pig model if testing across different species is expected to be of value for the preclinical package.

3) Considerations for the NHP Model

NHP provide the closest proxy to humans by phylogeny, are naturally susceptible to extremely low dose *Mtb* infection (<10 CFU is commonly used for vaccine testing) and display TB disease symptoms across the range that is reflective of human infection and clinical disease phenotypes. The exceptional cross-reactivity of primate-specific reagents for investigating host disease and immunity and the notable resemblance of BCG efficacy in many if not all of its aspects, including prevention of extra-pulmonary TB dissemination and variable protection depending on the cohort under investigation, adds system validity to NHP for TB vaccine R&D, though even this model is not validated as predictive for clinical outcome. For harmonisation and standardisation, many NHP vaccine researchers gathered in the NHP research community under the Collaboration for TB Vaccine Discovery (CTVD) have agreed to use a single source barcoded *Mtb* strain Erdman (BEI resources)[9] for infectious challenge experiments. In rhesus macaques in particular, *Mtb* Erdman can be considered highly virulent, thereby posing a rather stringent test for protective vaccine performance. Though standardization can be useful, other *Mtb* strains, however, could provide different insights and are being used and reported as well.

NHP strains

Macaque species (*Macaca spp*), including rhesus macaques (*M. mulatta*) and cynomolgus macaques (*M. fascicularis*, or long-tailed macaques) are the most common species used in TB vaccine R&D. Of these, rhesus over cynomolgus monkeys are more prone to develop TB disease upon (low dose) *Mtb* infection. However, there are genotypic (or so-called spectrotype) differences within each of the two species, attributable to limiting founder population characteristics (e.g. Mauritian *M. fascicularis*) or natural geographic barriers contributing to genetic drift (e.g. Indian versus Chinese-type rhesus). Moreover, environmental factors relating to NHP husbandry conditions (nurture) add to the spectrum of the outcome of TB vaccination and infection modelling. Depending on the breeding and housing conditions, exposure to non-typical non-tuberculous mycobacteria (NTM) can be expected. NHP are typically available from specialized breeding centres and/or licensed suppliers that are mostly well equipped to warrant the quality of outbred NHP colonies and/or their housing conditions.

Ethical restrictions

The use of NHP in biomedical research can face restrictions, depending on the cultural and/or legal environment. Legal frameworks sometimes prohibit the use of NHP unless there is no suitable alternative model to answer a specific research question. Positive indicators for vaccine efficacy from evolutionarily 'lower vertebrates' (most typically mice or guinea pigs) are often required for ethical approval to progress into NHP studies.

4) Challenge strains in preclinical models.

Mostly, 2 different laboratory strains are used: H37Rv and Erdman, and in addition several clinical strains are used (table 2 in Pozo-Ramos and Kupz, 2025)[10], such as the more virulent HN878 strain (Manca et al., 2001)[11]. In addition, a triple-kill-switch (TKS) strain was developed for safe use in human challenge models that might also be used preclinically (Wang et al., 2025)[12]. Although *Mtb* is genetically highly conserved, it is important to be aware that antigen expression can differ markedly between strains (Solans et al., 2014)[13]. Moreover, as culturing strains in different labs can lead to phenotypic and genetic variation, as with the different existing BCG sub-strains (Zhang et al., 2016)[14], it is recognised that quality control is important. For example, when *Mtb* (or BCG) is cultured *in vitro*, including propionate and omitting Tween-80 in growth medium can enhance an essential virulence lipid (PDIM) and prevent attenuation of pathogenicity. PDIM-positivity was shown to be easily screened with a vancomycin assay (Mulholland et al., 2024)[15].

5. Clinical trial considerations:

Clinical trial endpoints:

1) Prevention Of Disease (POD):

Developing a POD TB vaccine targeted at adolescents and adults is a global health priority. In addition to reducing individual level TB related morbidity and mortality, modelling suggests that a Prevention Of Disease (POD) TB vaccine targeted at adolescents and adults would have the greatest public health impact by preventing infectious pulmonary TB and reducing *Mtb* transmission at a population level (Harris et al., 2016)[3] Recent phase 2b/3 efficacy trials of M72/AS01E and MTBVAC have focused on powering the trial in the Interferon Gamma Release Assay (IGRA) positive participants to maximise incident TB case accrual and reduce trial size and duration. However, since risk of progression to TB disease is highest soon after *Mtb* infection, it might be possible to include IGRA-negative individuals in a cost-effective trial design, if it were conducted in very high *Mtb* transmission settings. The regulatory and policy evidence considerations for IGRA negative participants are discussed.

The benefits and risks of innovative approaches to reduce the size, duration and cost of phase 3 trials that are considered in this document, including the use of composite asymptomatic (using chest Xray and microbiological confirmations as confirmation of disease) and symptomatic TB endpoints, enrolling a mixed IGRA positive and negative study population, integrated trial phases and adaptive designs.

2) Prevention Of Infection (POI)

The purpose of a POI TB vaccine is to prevent sustained TB infection occurring among *Mtb* unsensitised individuals and thereby reduce the risk of developing pulmonary TB disease. POI studies enrol healthy participants and have conversion of IGRA responses as a surrogate clinical endpoint. Of note, infection can occur without IGRA conversion and those with a converted IGRA may have cleared the infection.

3) Prevention Of Recurrence (POR)

The aim of a POR TB vaccine administered to patients with pulmonary TB at the end of treatment, is to reduce the risk of TB treatment failure and TB recurrence. POR studies enrol patients who recently completed TB treatment and have recurrent TB disease over a defined period as a surrogate clinical endpoint.

Of note: POI and POR TB vaccine trials were previously used as a strategy to avoid going into large, costly phase 3 TB vaccine efficacy trials. However, this approach of using POI or POR to provide a so-called 'pre-proof of concept ('pre-POC) for a POD licensure indication carries risks, as neither alternative endpoint is a true surrogate or correlate for POD. A pre-POC trial with a POI endpoint may fail to indicate protection for a vaccine that would be protective in a POD trial if the vaccine's mode of action is largely through preventing disease in people already *Mtb* infected. Conversely, a pre-POC trial with a POI endpoint may indicate protection for a vaccine that would not be protective in a POD trial if the vaccine's mode of action is largely through preventing against infections that would not progress to disease. To know that a vaccine will protect people from developing active TB disease and avert cases and deaths, it must be demonstrated that a vaccine candidate shown to prevent infection does so in individuals who, without vaccination, would have developed active TB. A negative result in a pre-POC POR trial could lead to termination of a candidate that, if tested, might have demonstrated POD.

The findings of recent efficacy trials using either POI or POR designs have lowered expectations that the findings of POI or POR trials would accelerate entry into large POD licensure trials by providing a pre-POC efficacy signal in a smaller, shorter and less expensive efficacy study. Although a prior POI trial of BCG revaccination in IGRA-negative adolescents showed 45% vaccine efficacy against the secondary endpoint, sustained IGRA conversion through six months (Nemes et al., 2018)[16], a larger trial intended to validate this result in a wider age range at multiple sites in South Africa showed no efficacy against sustained IGRA conversion (Schmidt et al., 2025)[17]. Another POI trial using DAR-901 conducted in Tanzania also did not show efficacy (Munseri et al., 2020)[18].

Similarly, two recent POR trials, of the protein-subunit vaccine H56:IC31 (Borges et al., 2025)[19] and the live attenuated, recombinant BCG vaccine

VPM1002 (unpublished), failed to show that vaccination of TB patients at the end of treatment protects against recurrent TB disease. Although these negative POR results may be vaccine-specific and studies of immune correlates of risk are ongoing, it is likely that POR efficacy will be considered too high a bar to fund more trials using this design as a means to de-risk a POD trial in the short-medium term.

Based on current insights, references to POI and POR 'pre-POC' trials in the TB vaccine development pathway have therefore been removed from the document.

List of functions:

Function 1:	**Project Management**
Function 2:	**Business, Legal, Intellectual Property (IP)**
Function 3:	**Product Characterization and Quality**
Function 4:	**Production Process**
Function 5:	**Preclinical Safety***
Function 6:	**Preclinical Immunogenicity***
Function 7:	**Preclinical Protection, Efficacy***
Function 8:	**Regulatory**
Function 9:	**Clinical Development and Operations***
Function 10:	**Clinical Safety ***
Function 11:	**Clinical Immunology***
Function 12:	**Clinical Protection, Efficacy***
Function 13:	**Market, Access and Implementation**

*these functions are revised in this current version.

TB VACCINE **DEVELOPMENT PATHWAY**

Stage Gating criteria tables

Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model

Gate A: Progress to proof of concept (PoC) studies in animals

Function	Stage A: main activities	Gate A: criteria required
1. Project Management	• Draft the Target Product Profile (TPP) with indication, target population, etc. • Set activities, deliverables and criteria to pass Gate A	• TPP with primary indication prepared • Activities, deliverables and criteria to pass Gate A agreed and finalised
3. Product Characterization & Quality	• Screen and select antigen(s), adjuvants, other excipients and delivery system • Characterise vaccine candidate. In particular, demonstrate antigen expression and purity (e.g. proteins)	• Antigens, adjuvants, other excipients, delivery system selected • Characterisation tests defined and characteristics of the vaccine candidate documented
4. Production Process	• Select expression system and lab-scale production process for generating pre-clinical material • Select specific strain	• Suitable expression system and process that can produce target product quantity and quality selected • Specific strain(s) selected and history recorded
5. Pre-Clinical Safety	• Identify *in vitro* and *in vivo* models to test for safety • Test preclinical safety elements relevant to candidate	• Safety tests identified • Safety evaluated; no evidence to suggest lack of safety
6. Pre-Clinical Immunogenicity	• Evaluate immunogenicity • Compare to benchmark, if applicable	• Evidence of relevant immunogenicity to antigens in at least one *in vitro* or animal model • Above baseline and/or benchmark (if applicable) responses to antigens preferred
7. Pre-Clinical Protection, Efficacy	• Demonstrate protection (usually in a small animal *Mycobacterium **tuberculosis*** (Mtb) infection model) • Compare to benchmark, if applicable	• Protection in a small animal Mtb infection model demonstrated • Protection statistically better than a relevant benchmark, if available

Stage B: Perform PoC studies in animals

Gate B: Progress to Pre-Clinical

Function	Stage B: main activities	Gate B: criteria required
1. Project Management	• Update the Target Product Profile (TPP) • Prepare an integrated Product Development Plan (PDP) including market information available • Set activities, deliverables and criteria to pass Gate B	• TPP revised • The PDP is drafted. It describes and integrates the main strategy across all functional areas, timeline and high-level estimated cost. • Activities, deliverables and criteria to pass Gate B agreed and finalised
2. Business, Legal, IP	• Describe Intellectual Property (IP) status • Secure funding for the whole stage • If necessary, identify potential partners to support development	• No major IP obstacles identified or strategy for resolution in place • Funding secured • As necessary, viable partners identified; Material Transfer Agreement (MTA) and other agreements established
3. Product Characterization & Quality	• Document vaccine product stability • Select assays to monitor product quality, including an assay for potency	• Initial product stability defined • Feasible assays for product quality attributes selected, including for potency
4. Production Process	• Demonstrate feasibility of process at lab scale	• Process demonstrated to be feasible at lab scale

5. Pre-clinical Safety	• Expand testing to confirm the general safety attributes of the vaccine candidate(s)	• Evidence of safety properties in one or more *in vitro* and / or *in vivo* models, confirming and expanding on tests performed in Stage A • Where relevant, safety in immunocompetent and immunocompromised animals demonstrated being as safe or safer than BCG
6. Pre-clinical Immunogenicity	• Confirm and characterise immunogenicity • Develop hypothesis for immunological mechanism of action; choose model and designstudy with appropriate outcomes, sample size, read-outs, data analysis plan, etc.	• Confirmed consistent immune response to antigens in at least one (animal)model • Hypothesis for immunological mechanism of action defined; synopsis of study in advanced model available
7. Pre-clinical Protection, Efficacy	• Confirm robust protection, e.g. in a small animal *Mycobcterium tuberculosis* (Mtb) infection model in an independent lab or second animal model/ species • Review immunogenicity and protection data in small animals Decide on use of NHP study. If yes, design study and prepare read-outs to evaluate protection	• Protection statistically better than a relevant benchmark, if available, reproduced independently in same species or confirmed in a second animal model • Immunogenicity and protection data support proposed mode of protection, and support the NHP,or another advanced model, study design • Read-outs for NHP, or other model, ready
8. Regulatory	• Identify regulatory path and potential barriers	• Regulatory strategy outlined, issues identified, and mitigation defined
9. Clinical Development and Operations	• Draft an initial Clinical Development Plan (CDP) • Look for existing epidemiology data in target population	• CDP drafted and clinical evaluation feasible • Existing epidemiology data identified and reviewed

Stage C: Perform Pre-Clinical evaluations

Gate C: Progress to preparation for Phase 1, First-In-Human

Function	Stage C: main activities	Gate C: criteria required
1. Project Management	• Review the Target Product Profile (TPP) • Update the Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate C	• TPP revised, if necessary • PDP updated to include (a) details by functional area to prepare for First-in-Human (FIH) and other Phase 1 studies; (b) summaries of data collected to date; (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate C agreed and finalised
2. Business, Legal, IP	• Establish acceptable Intellectual Property (IP) position • Secure funding for the whole stage	• Freedom to operate investigated and an acceptable level of risk demonstrated • Funding secured
3. Product Characterization & Quality	• Optimise and finalise vaccine composition and route of administration • Develop release assays and stability tests • Prepare batch release	• Vaccine characteristics critical for vaccine immunogenicity (e.g., antigen sequence, adjuvant, delivery system, route of administration) finalised • Target Bill of Testing (BOT) defined with target specifications for final product, drug substance (potency), excipients, impurity profile and product composition • Quality control (QC) tests selected and their feasibility demonstrated, incl. for potency/ relevant biological activity, identity, purity, and stability

4. Production Process	• Develop and assess feasibility and reproducibility of manufacturing process at pilot scale (e.g. multiple pilot scale runs). If needed, minor revisions to process can be applied, within process specifications and TPP • Fix the process at pilot scale • Evaluate real-time and accelerated stability on a pilot-scale lot of a Drug Product (DP) • Identify a Good Manufacturing Practices (GMP) facility • Calculate estimation of production costs for the antigen and formulated vaccine product	• Reproducibility acceptable; quantity and quality of product meets pre-defined feasibility criteria (TPP) • Process at pilot scale fixed. • First stability data meets pre-set feasibility criteria (TPP) • GMP facility identified • Production costs estimated
5. Pre-clinical Safety	• Design pre-clinical safety and toxicology studies as required according to regulatory guidelines	• Synopsis protocols for safety and toxicology studies prepared as relevant for the vaccine
6. Pre-clinical Immunogenicity	• Confirm immunogenicity against relevant benchmark • Expand immunogenicity (Th1, Th17, γδ T cells etc.) to explore mechanism in same species used to demonstrate efficacy	• Immune response against relevant benchmark established • Immune mechanisms and breadth of immune response explored
7. Pre-Clinical Protection, Efficacy	• Confirm protection or Proof of Concept (PoC) (*Note:* the (animal) models for evaluation should be justified based on candidate's proposed mechanism of action)	• Protection from Mtb challenge statistically better than BCG and/or relevant benchmark using primary endpoint in 2 (animal) models, as demonstrated by a read-out with high statistical power for the group size
8. Regulatory	• Identify regulatory path and possible barriers • Consult Regulatory Authority (RA) with questions for scientific advice in a pre-Phase 1 meeting	• Regulatory input/scientific advice obtained • Regulatory risks assessed; no major roadblocks to product and clinical development indicated

9. Clinical Development and Operations	• Plan the pathway to FIH and anticipate subsequent Phase 2 • Draft Synopsis of Phase 1 • Engage with communities where clinical research will be conducted • Update the CDP	• Pathway to FIH and subsequent Phase 2 established • Phase 1 synopsis drafted • Community engagement programme initiated • CDP updated
10. Clinical Safety	• Define the safety endpoints for Phase 1	• Safety endpoints for Phase 1 defined
11. Clinical Immunology	• Define the primary and exploratory immunogenicity endpoints based on putative mechanism of immune protection ("potential immune correlates") for Phase 1	• Plan drafted to develop assays to measure primary and exploratory immunological endpoints

Stage D: Perform GMP and toxicity studies and prepare Clinical Trial Application

Gate D: Progress to First-In-Human/Phase1

Function	Stage D: main activities	Gate D: criteria required
1. Project Management	• Update the Target Product Profile (TPP) and Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate D	• TPP and PDP updated • Activities, deliverables and criteria to pass Gate D agreed and finalised
2. Business, Legal, IP	• Develop a first business plan based on market assessment • Secure funding for the entire stage including Phase 1	• First business plan available • Funding secured
3. Product Characterization & Quality	• Release batch for the toxicology studies • Qualify assays related to critical quality attributes (CQA, product) and critical process parameters (CPP) • Release seed lots and banks • Release drug substance (DS) and drug product (DP) for FIH/Phase 1 • Optimise buffer formulation and generate stability data on DS and DP	• Batch for toxicology studies released • Critical assays qualified • Seed lots and banks released • Clinical DS and DP meet specifications and are released. Equivalence to batch used for toxicology confirmed • Stability data on formulated vaccine sufficient to support clinical trial

4. Production Process	• Complete technical transfer to GMP manufacturer and develop manufacturing process (pilot and/or Phase 1 scale) for production of (DS) and formulation of (DP) • Manufacture Good Manufacturing Practices (GMP) Master and Working seeds and banks • Produce a batch for toxicology studies (pre-GMP or GMP) • Qualify process for safety-related aspects (adventitious agents, mycoplasma, sterility) • Produce GMP Clinical Trial Material (CTM) for FIH, in sufficient quantity to support FIH/Phase 1, Toxicology, QC, archives and possibly Phase 2 • Estimate Cost of Goods (CoGs)	• Manufacturing process at Phase 1 scale locked • Master and Working seeds and banks produced under GMP, released for cGMP • Batch for toxicology studies produced with a process equivalent to the process used in GMP • Safety-related aspects of the process qualified • FIH CTM produced under GMP, in sufficient quantity. • Preliminary estimation of CoGs available
5. Pre-Clinical Safety	• Perform toxicology studies using DP from GMP run (or equivalent) • Perform safety studies such as bio-distribution, persistence and for Genetically Modified Organism (GMO) requirements, as relevant for the vaccine	• Safety and toxicology profile of the DP acceptable • Bio distribution, persistence and GMO requirements met, as relevant
8. Regulatory	• Prepare FIH Clinical Trial Application (CTA) with protocol, Investigator's Brochure (IB), Chemistry, Manufacturing and controls (CMC). • Submit CTA to National Regulatory Authority (NRA) and Ethics Committee (EC) for approvals • Draft Company Core Data Sheet (CCDS)	• CTA prepared • CTA submitted to NRA and EC for approvals • CCDS drafted

9. Clinical Development and Operations	• Prepare operations for FIH/Phase 1 (including completion of protocol, identification of principal investigator (PI), study site, etc.) • Community engagement: educate on need for TB vaccines and clinical trials, obtain community input into Phase 1 design. • Draft synopsis for subsequent Phase 2a, aiming at selection of doses, route, etc.	• Operations for FIH/Phase 1 prepared • Input from the community obtained • Draft Phase 2a synopsis prepared
10. Clinical Safety	• Review and approve local and systemic adverse events to be monitored during the Phase 1 studies	• Safety endpoint approved
11. Clinical Immunology	• Develop primary and exploratory clinical immunological assays and qualify performance of primary assays	• Clinical immunological assays optimised and qualified
13. Market, Access and Implementation	• Based on TPP, identify potential list of targeted countries (early, middle and late adopter countries) considering income (low, average, high) • Collect epidemiological, burden of disease data and market data in targeted countries for a preliminary, formal market assessment	• Initial list of targeted countries established • Preliminary formal market assessment available for targeted countries

Stage E: Perform First-in-Human/Ph1

Gate E: Progress to Ph2

Function	Stage E: main activities	Gate E: criteria required
1. Project Management	• Update the Target Product Profile (TPP) • Update the Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate E	• TPP updated with data from Phase 1 • PDP updated to include (a) details by functional area to prepare for phase 2; (b) marketing aspects ; (c) summaries of data collected to date, (d) updated timelines and budget • Activities, deliverables and criteria to pass Gate E agreed and finalised
2. Business, Legal, IP	• Refine the business plan with new data • Evaluate partners, in particular for clinical development and commercialisation • Refine IP position and IP strategy • Identify and secure funding for the whole stage	• Business plan refined • Viable partners identified; agreements established • IP position and strategy are acceptable • Funding is secured
3. Product Characterisation and Quality	• Fine tune (if needed) quality control (QC) assays • Qualify and/or validate QC procedures • Characterise newly produced drug substance (DS) and drug product (DP) • Perform stability studies	• QC assays refined (if needed) • Plan to ensure validation of QC procedures established • DP and DS pass the tentative product specifications recorded in the Target Bill of Testing (BOT); impact of changes and deviations on DS and DP are documented • Stability data sufficient to support clinical trial

4. Production Process	• Optimise process, as necessary. For well-characterised product as confirmed by Critical Quality Attributes (CQA); for less defined product, optimisation within existing specified ranges • Document changes and deviations • Manufacture Good Manufacturing Practices (GMP) Phase2 Clinial Trial Material (CTM), if necessary • Define strategy for the scale-up of the process (including formulation) up to commercial batches, perform and validate the scale up as relevant • Update Cost of Goods estimation	• Process performing according to the preset procedures and specifications. • Process changes and deviations documented. • GMP Phase2 CTM available • Process (including formulation) finalised at relevant scale by process and scale up validation according to strategy (and including risk assessment) • Estimated CoGs updated
8. Regulatory	• Obtain approval for First-in-Human (FIH)/Phase 1 • Update CCDS with new data • Propose a regulatory pathway for global licensure, aligned with CMC, clinical and marketing • Prepare and submit CTA for Phase 2a	• FIH CTA approval obtained • CCDS updated • Proposed regulatory pathway approved • Phase 2a CTA submitted

9. Clinical Development and Operations	• Conduct Phase 1 (including FIH) • Prepare operations for subsequent Phase 2a • Prepare plan and obtain funding for engaging communities in the Phase 2a studies in line with Good Participatory Practice (GPP) guidelines • Obtain community input into Phase 2b trial design • If necessary, prepare a plan to obtain adequate epidemiology data in target population for Phase 2b (or integrated Phase 2b/3) • Draft synopsis for Phase 2b • Update CDP	• Phase 1 completed • Protocol(s) and operations for Phase 2a prepared • Community input Phase 2b obtained • Plan for collecting adequate epidemiology study data for Phase 2b developed • Synopsis for Phase 2b prepared • CDP updated
10. Clinical Safety	• Analyse FIH/Phase 1 safety data, for target population and dose relevant for Phase 2a	• Safety profile of selected doses or regimen of FIH/Phase 1 supports subsequent Phase 2a
11. Clinical Immunology	• Analyse FIH/Phase 1 to • characterise immune responses using primary and exploratory endpoints • Prepare a collection and storage plan for relevant bio-specimens from Phase 2a based on primary and exploratory immunogenicity	• From FIH/Phase 1, evidence of sufficient immune response based on primary endpoints at vaccine dose level(s) that is/are safe • Potential biomarkers for Phase 2a identified; plan for their evaluation prepared • Biobanking plan established
12. Clinical Protection, Efficacy	• Define endpoints for efficacy in a Phase 2b/3	• Endpoints and necessary assays for first efficacy trial defined
13. Market, Access, Implementation	• Refine market analysis in targeted countries	• Market analysis refined

Stage F: Perform Ph2a studies

Gate F: Progress to Ph2b Efficacy

Function	Stage: main activities	Gate: criteria required
1. Project Management	• Update the Target Product Profile (TPP) • Update the Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate F	• TPP updated with data from product characterization and from Phase 2 • PDP updated to include (a) details by functional area to prepare for efficacy studies; (b) summaries of data collected to date and (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate F agreed and finalised
2. Business, Legal, IP	• Review business plan with first market forecast and estimate of Cost of Goods (CoGs). • Consolidate IP • Identify and secure funding for the whole stage	• Business plan reviewed with market forecast and CoGs • Acceptable IP status to support commercialisation confirmed • Funding secured
3. Product Characterisation and Quality	• As in previous Stage	• As in previous Gate
4. Production Process	• Increase scale of the process, if required, for commercial batches • Update Cost of Goods	• Commercial scale-up process determined • Cost of Goods updated

8. Regulatory	• Obtain approval for Phase 2 CT • Consult national regulatory authority (NRA)/ World Health Organisation (WHO) /European Medicines Agency (EMA) for scientific advice, including alignment on endpoints leading to Marketing Authorisation • Refine regulatory strategy for global licensure • Update CCDS with new data • Prepare and submit Phase 2b CTA	• Phase 2a CTA approved • Scientific advice obtained and alignment on endpoints established • Regulatory pathways updated • CCDS updated • Phase 2b CTA submitted
9. Clinical Development and Operations	• Complete operations and conduct subsequent Phase 2a study(ies) • Prepare protocol and operational plans for Phase 2b • Collect adequate epidemiology data in target population and in the countries of clinical studies • Prepare plan and obtain funding for engaging communities in the Phase 2b studies in line with GPP guidelines • Provide and discuss results of earlier trials and obtain community input into Phase 2b-3 trial design. • Update CDP including synopsis for Phase 2b-Phase 3	• Phase 2a completed; data available and analysed • Draft protocol and operation plan for Phase 2b available • Adequate epidemiology data at sites of Phase 2b available • Plan for engaging communities in the Phase 2b study and funding in place • Community engaged on trial design • CDP updated
10. Clinical Safety	• Analyse all safety data from Phase 2a and combine with all data from earlier studies	• Safety profile of the dose selected for Phase 2b acceptable

11. Clinical Immunology	• Analyse all immunogenicity data from Phase 2a • Select dose for Phase 2b • Perform validation of primary immunological assays • Review potential biomarkers from previous studies and identify assays for Phase 2b (including immunogenicity and correlate analyses) • Prepare operations for immunological assays and sample collection/storage. • If relevant, prepare plans for non-interference study (ies) with co-administered vaccine(s)	• Data from Phase 2a indicate significant immune responses and dose-response pattern allows selection of a dose • Immunogenicity at the dose selected for Phase 2b acceptable • Validation of assays confirmed • Potential biomarkers reviewed, plan for analyses established and primary endpoint immunological assays identified • Operations for immunoassays prepared • Plans for non-interference study prepared, if relevant
12. Clinical Protection, Efficacy	• Confirm efficacy endpoints of Phase 2b	• Efficacy endpoints for Phase 2b confirmed
13. Market, Access and Implementation	• Based upon market analysis, conduct forecasting in targeted (low-, middle- and high-income) countries, and document that the product is viable • Establish a multidisciplinary 'Access Team' that will enable development of a comprehensive value proposition for TB vaccine/vaccination • Develop understanding of all relevant international (WHO, GAVI, etc.) and national stakeholders requirements • Prepare international and national stakeholders mapping, including civil society and TB-affected communities to secure early community engagement and initiate engagement	• Initial forecasting in targeted countries developed, and supports a viable product • The 'Access team' is created with capacity and expertise available to develop value proposition activities • Processes and requirements of selected national & international stakeholders understood • Map of stakeholders available and engagement underway

Stage G: Perform Ph2b Efficacy
Gate G: Progress to Ph3

Function	Stage G: main activities	Gate G: Criteria required
1. Project Management	• Update the Target Product Profile (TPP) • Update the Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate G	• TPP updated with efficacy data from Phase 2b • PDT updated to include (a) details by functional area to prepare for Ph 3 and registration studies; (b) summaries of product data collected to date and (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate G agreed and finalised
2. Business, Legal, IP	• Review business plan with supply versus demand • Revise IP and needs for acquisition from third-party • Secure funding for the whole stage	• Business plan with supply and demand updated • Acceptable IP status and strategy to support commercialisation confirmed • Funding secured
3. Product Characterisation and Quality	• Confirm specifications of final formulation, drug product (DP) • Confirm criteria and specifications of DP manufactured for consistency, and define the Bill of Testing (BOT) • Compare drug product (DP) used in different studies, as relevant • Continue stability testing • Define and validate final Quality Control (QC) analytical methods and assays, for the release of batches and final product	• Specifications for DP confirmed • Criteria and specifications for consistency runs are finalised and the BOT is defined • Comparability of products used in different clinical studies is available • Stability acceptable • QC assays are validated

4. Production Process	• Plan manufacturing CTM batch for Phase 3 • Develop commercial strategy, establish final commercial-scale manufacturing process • and scale up manufacturing to commercial level • Process validation: demonstrate that ranges for given specifications are valid • Plan manufacturing runs for consistency • Validate facilities and equipment used • Confirmation of cost of goods at commercial scale	• Plan for manufacturing Phase 3 CTM available • Manufacturing strategy defined, process and manufacturing scaled and established at commercial level • Plan for consistency runs finalised • Process validation: specifications for process at relevant scale proven • Facilities and equipment validated • Cost of goods at commercial scale are within acceptable range
8. Regulatory	• Obtain approval Ph2b • Refine regulatory strategy for global licensure, including WHO prequalification (WHO-PQ) • Present Phase 2b data and design of Phase 3 to relevant regulatory authorities and WHO • Draft labels for launch • Update CCDS with new data	• Phase 2b CTA approved • Registration strategy determined, including WHO-PQ • End of Phase 2b meeting with NRA and EMA/ WHO held; Phase 3 design agreed to by relevant regulatory authority • Labels drafted • CCDS updated

9. Clinical Development and Operations	• Complete operations and conduct Phase 2b • Draft protocol for Phase 3 • Draft protocol for evaluation of clinical consistency (safety and immunogenicity) as a nested study within Phase 3 or a separate study • Prepare operational plans for Phase 3, including selection of countries, study sites, etc. • Ensure epidemiology data are available at all study sites. • Prepare plan and obtain funding for engaging communities in the Phase 3 efficacy trial in line with Good Participatory Practice guidelines • Provide and discuss results of earlier trials and obtain community input into Phase 3 trial design. • Update CDP	• Phase 2b completed and data available. • Protocol for Phase 3 drafted • Protocol for clinical consistency study drafted • Operational plans for Phase 3 prepared • Epidemiology data available at all study sites • Plan and funding in place for engaging communities in the Phase 3 efficacy trial • Community engaged on trial design • CDP updated
10. Clinical Safety	• Analyse all safety data from earlier trials, including Phase 2b • Draft Risk Management Plan (RMP) for Phase 3 and update active surveillance if needed/ justified • Draft plan to assess safety in priority populations. • Consider safety in case of concomitant administration of other vaccines	• Safety profile acceptable in target population • RMP for Phase 3 drafted and active surveillance updated • Plan drafted for safety in priority populations • Plan drafted for safety upon concomitant administration of other vaccines (if considered relevant)

11. Clinical Immunology	• Analyse all immunogenicity data from earlier trials, including Phase 2b for their consistency • Analyse Phase 2b data for potential correlates of protection (CoP) • Develop a plan to incorporate biomarkers / CoP into Phase 3 • Conduct and complete non-interference studies with other vaccines used concomitantly	• Immune responses in target populations in Phase 2b consistent with earlier trials • Phase 2b data analysed • Biomarker plan for Phase 3 established • Non-interference documented
12. Clinical Protection, Efficacy	• Demonstrate protective efficacy against the primary case definition endpoint	• Evidence of efficacy from Phase 2b or interim analysis consistent with minimal (predefined) TPP criteria
13. Market, Access and Implementation	• Update market assessment in potential early (also middle and late) adopter countries • Define Health Economics Outcomes Research (HEOR) activities to support health economics (HE) rationale (cost-effectiveness, health and budget impacts, willingness to pay, etc.) in early (middle and late) adopters countries, aiming to build evidence for a full value proposition and meet requirements from stakeholders • Identify complementary studies and/or protocol evolution (Phase 3) to close data gaps in early (mid, and late) adopters • Initiate interactions with major stakeholders (countries, communities, WHO, GAVI, etc.)	• Market assessment updated • HEOR activities defined • Complementary studies and/or protocols evolution (Ph3) to close data gaps identified • Interactions with major stakeholders initiated

Stage H: Perform Ph3 and analyse Ph3 data

Gate H: Progress to preparation of Market Authorization Application (MAA)

Function	Stage H: Main activities	Gate H: Criteria required
1. Project Management	• Update Product Development Plan (PDP) • Set activities, deliverables and criteria to pass Gate H	• PDP updated to include (a) details by functional area to perform Phase 3 and prepare for registration; (b) summaries of product data collected to date and (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate H agreed and finalised
2. Business, Legal, IP	• Consolidate the business plan with market assessment, forecasts, COG and initial pricing • Strengthen IP • Secure funding for the whole stage	• Business plan consolidated • IP obstacles to commercialization resolved • Funding secured
3. Product Characterisation and Quality	• Release Good Manufacturing Practices (GMP) Phase 3 and consistency batches • Document consistency between batches • Evaluate stability data against TPP	• No major out-of-specs for the product as listed in the Bill of Testing (BOT) • Consistency of batches documented • Stability studies completed and data support TPP
4. Production Process	• Manufacture Clinical Trial Material (CTM) for Phase 3 • Prepare consistency batches of vaccine (final formulation, at market scale) for Phase 3 • Document consistency between batches and confirm consistency of process	• Phase 3 material produced with no major out-of-specs for the production process • Consecutive consistency runs completed and product batches for Phase 3 testing available • Consistency between batches documented, confirming process consistency

8. Regulatory	• Submit CTA and obtain approval for Phase 3 • Update CCDS with new data	• CTA for Phase 3 submitted and approval obtained • CCDS updated
9. Clinical Development and Operations	• Finalise plan for community engagement for Phase 3, in line with GPP guidelines • Complete operations and conduct Phase 3 • Perform safety, immunogenicity and efficacy data analysis • Document consistency of the various lots • Prepare clinical study report (CSR) • Initiate planning for Phase 4 studies	• Community engagement plan in place for Phase 3 • Phase 3 completed • Safety, immunogenicity and efficacy data analyed • Product consistency established • CSR is available • Draft Phase 4 plan established
10. Clinical Safety	• Evaluate all available safety data against TPP • Draft a post-licensure RMP, including evaluation in specific priority populations (i.e. HIV infected individuals)	• Pre-licensure safety is acceptable and meets TPP • Post-licensure RMP is drafted, and includes post_licensure safety evaluation study for target population and priority populations
11. Clinical Immunology	• Analyse Phase 3 immunogenicity data • Develop an investigational plan to identify correlates of protection (CoP) based on Phase 3 immunogenicity and efficacy data • Collect samples for banking	• Immunological endpoints analysed • CoP plan developed and evaluated • Samples collected
12. Clinical Protection, Efficacy	• Evaluate clinical efficacy against TPP • Establish plan for phase 3 extension, if needed	• Protective efficacy meets TPP • Plan for phase 3 extension established, if needed

13. Market, Access and Implementation	• Complete market assessment • Refine pricing strategy based on Health Economics and Outcome Research (HEOR) data • Develop a core value dossier for international stakeholders and early (priority), mid and late (option) adopters • Develop an initital market plan • Consult and engage national and international stakeholders, communities and civil society including demand generation and education. • Develop dialogue to include new TB vaccine in GAVI's "Vaccine Investment Strategy" (VIS)	• Market assessment completed • Pricing strategy refined • Core value dossier developed • Initial market plan available • National and international stakeholders consulted • GAVI consulted for the TB vaccine to become part of the VIS

Stage I: Register vaccine with relevant Regulatory Authorities

Gate I: Obtain MA and Progress to launch

Function	Stage I: Main activities	Gate I: Criteria required
1. Project Management	• Update PDP • Set activities, deliverables and criteria to pass Gate I	• PDP updated to include (a) details by functional area to obtain MAA approval and prepare for launch; (b) summaries of all product data collected and (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate I approved
2. Business, Legal, IP	• Update the business plan with supply, demand, and market assessments • Seek support from investors and partners, as needed. • Confirm the business strategy and develop a detailed operational plan • Secure funding for the whole stage	• Business plan updated with validated market assessments • Investors and partners established, as needed • Business strategy confirmed, and operation plan detailed • Funding secured
4. Production Process	• Finalise CMC section of the MAA dossier • Manufacture commercial lots in launch facility • Secure capacity, equipment, resources, raw material for sustainable manufacturing and delivery of required amount of vaccines	• CMC section of the MAA dossier completed • Commercial lots manufactured • All elements for manufacturing secured

8. Regulatory	• Prepare and submit Marketing Authorisation Application (MAA) dossier to Competent Authorities for approval • Engage dialogue with Official Medicines Control Laboratory (OMCL) for the official batch release of commercial batches	• Marketing Authorisation delivered by Competent Authorities • Dialogue with OMCL engaged, with transfer of QC testings to OMCL
9. Clinical Development and Operations	• Finalise clinical section of the MAA dossier • Update protocol and update operational plans for Phase 4 • Provide and discuss results of previous trials, and obtain community input into Phase 4 trial design	• Clinical section of the MAA dossier finalised • Protocol and operational plan for Phase 4 updated • Community engaged on trial design
10. Clinical Safety	• Finalise post-marketing Risk Management Plan (RMP), including evaluation of safety in priority populations (for example PLWH) • Phase 4 safety study drafted	• Post-licensure RMP finalised and approved
11. Clinical Immunology	• Conduct assays on samples collected in Phase 3 to identify correlates of protection and/or risk	• Immunological assays performed, in search for CoP
12. Clinical Protection, Efficacy	• Finalise post-licensure evaluation plan for Phase 4 effectiveness under field conditions, inlcuding concomitant vaccines, if relevant	• Evaluation plan for post-licensure effectiveness, including administration of concomitant vaccines finalized and approved

13. Market, Access and Implementation	• Update market assessment based on Phase 3 data • Finalise pricing strategy as per HE outcome • Finalise value proposition and core value dossiers with priority to early adopters • Finalise market access plan • Further execute HEOR activities to close data gaps in early adopter countries • Continue to consult and engage national and international stakeholders • Identify and test options for introduction in National Immunization Programs (NIP) and for funding of early adopters in low, middle and high income targeted countries	• Market assessment updated • Pricing strategy finalised • Core value dossier for international stakeholders and early (priority), mid and late (option) adopters finalised • Market access plan finalised • Complementary studies to close data gaps implemented; data to build rationale of HEOR available • Stakeholders, including communities and civil society engaged • Option identified to support introduction in NIP and funding in targeted countries

Stage J
Launch

Stage J: Launch

Gate J: Implement vaccination programs

Function	Stage J: Main activities	Gate J: Criteria required
1. Project Management	• Update PDP • Set activities, deliverables and criteria to pass Gate J	• PDP updated to include (a) details by functional area to launch and implement vaccination programs; (b) summaries of additional product data collected and (c) updated timelines and budget • Activities, deliverables and criteria to pass Gate J approved
2. Business, Legal, IP	• Monitor closely the implementation of the business plan, with focus in early adopter countries • Validate demand and supply • Expand business with new opportunities	• Monitoring in particular in early adopter is effective • Demand and supply validated • Business expanded
4. Production Process	• Operate routine manufactory • Set a Quality Management System for trouble shooting, including CAPA	• Manufacturing plant operating at initial commercial scale • QMS in place
8. Regulatory	• Register with additional NRAs • Submit WHO prequalification following stringent NRA MAA or EMA Article 58 positive opinion	• NRA additional registrations obtained • WHO prequalification obtained

9. Clinical Development and Operations	• Complete operations and conduct Phase 4 studies	• Phase 4 studies conducted
10. Clinical Safety	• Execute pharmacovigilance plan in Phase 4 studies	• Pharmaco-vigilance in Phase 4 studies executed
12. Clinical Protection, Efficacy	• Evaluate vaccine effectiveness in Phase 4 studies • Conduct additional co-administration studies, as required	• Vaccine effectiveness Phase 4 studies evaluated • Additional co-administration studies conducted
13. Market, Access and Implementation	• Obtain SAGE recommendations and GAVI programmatic commitment • Obtain national immunization program (NIP) recommendations • Obtain funding for early adopters countries where vaccine is launched • Prepare potential private market • Launch in early adopters countries	• SAGE recommendation obtained, GAVI funding secured • NIP recommendations obtained • Funding obtained in early adopters countries • Private market, where relevant, prepared • 1st commercial launch achieved

List of Abbreviations

BCG	Bacillus Calmette–Guérin
BOT	Bill Of Testing
CCDS	Company Core Data Sheet
CDP	Clinical Development Plan
CL	Clinical
CMC	Chemistry, Manufacturing, and Controls
CoGs	Cost of Goods
CoP	Correlates of Protection
CPP	Critical Process Parameters
CRC	Clinical Research Centres
CSR	Clinical Safety Report
CTA	Clinical Trial Application
CTM	Clinical Trial Material
CQA	Critical Quality Attributes
DP	Drug Product
DS	Drug Substance
EC	Ethics Committee
ECVP	Evidence Considerations for Vaccine Policy
EMA	European Medicines Agency
FIH	First In Human
GAVI	Global Alliance for Vaccines and Immunisation
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GPP	Good Participatory Practice
HEOR	Health Economics and Outcome Research
KOL	Key Opinion Leader
IB	Investigational Brochure
IP	Intellectual Property
LNP	Lipid NanoParticle
MAA	Marketing Authorisation Application
MTA	Material Transfer Agreement
Mtb	Mycobacterium tuberculosis
NHP	Non-Human Primate
NIP	National Immunization Programs
NRA	National Regulatory Authority
OMCL	Official Medicines Control Laboratory
PDP	Product Development Plan
PI	Prinicipal Investigator
PLWH	People Living With HIV
PM	Project management
PoC	Proof of Concept
POD	Prevention of Disease
POI	Prevention of Infection
POR	Prevention of Recurrence
PPC	Preferred Product Characteristics
QC	Quality Control
QMS	Quality Management System
RA	Regulatory Authority
RMP	Risk Management Plan
SAGE	Strategic Advisory Group of Experts on Immunization
SGC	Stage Gate Criteria
TB	Tuberculosis
TBST	*Mtb* antigen-based skin test
TPP	Target Product Profile
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WHO-PQ	WHO prequalification process

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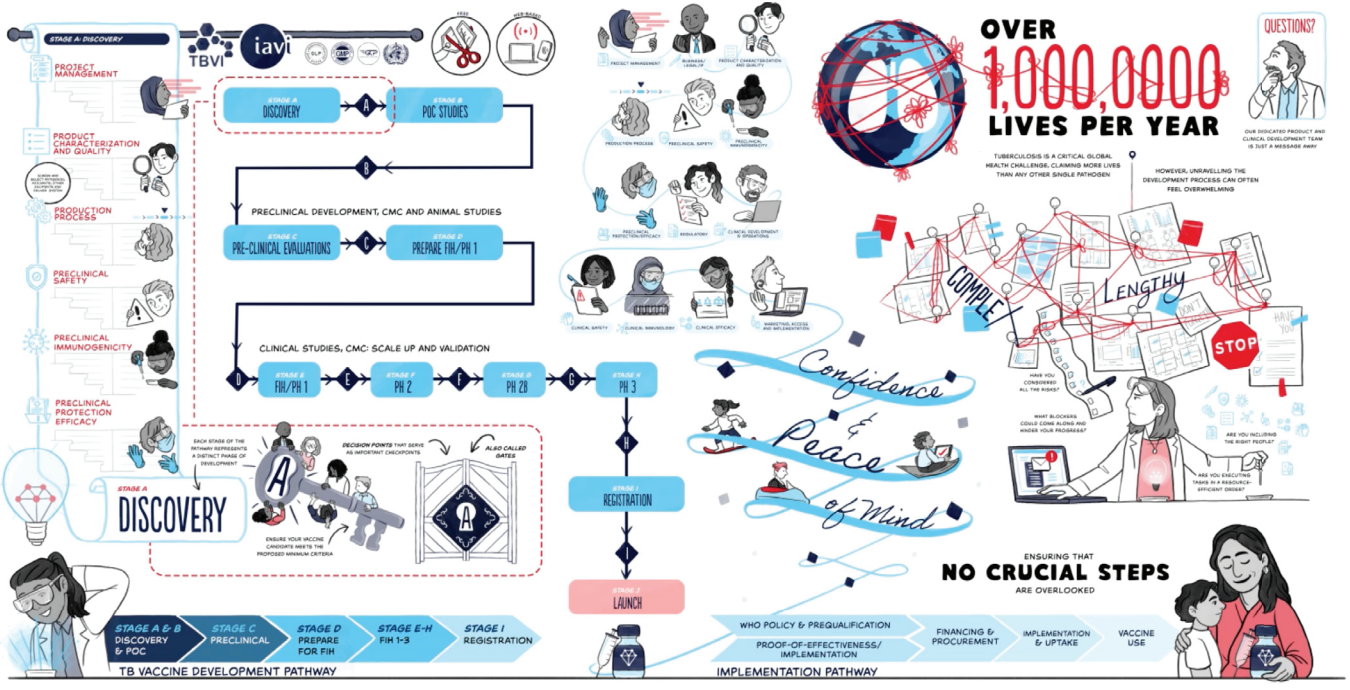
STAGE A: DISCOVERY
PROJECT MANAGEMENT
PRODUCT CHARACTERIZATION AND QUALITY
PRODUCTION PROCESS
PRECLINICAL SAFETY
PRECLINICAL IMMUNOGENICITY
PRECLINICAL PROTECTION EFFICACY
TBVI
iavi
STAGE A DISCOVERY
STAGE B POC STUDIES
PRECLINICAL DEVELOPMENT, CMC AND ANIMAL STUDIES
STAGE C PRE-CLINICAL EVALUATIONS
STAGE D PREPARE FIH/PH 1
CLINICAL STUDIES, CMC: SCALE UP AND VALIDATION
STAGE E FIH/PH 1
STAGE F PH 2
STAGE G PH 2B
STAGE H PH 3
STAGE I REGISTRATION
STAGE J LAUNCH
STAGE A
DISCOVERY
EACH STAGE OF THE PATHWAY REPRESENTS A DISTINCT PHASE OF DEVELOPMENT
DECISION POINTS THAT SERVE AS IMPORTANT CHECKPOINTS
ALSO CALLED GATES
ENSURE YOUR VACCINE CANDIDATE MEETS THE PROPOSED MINIMUM CRITERIA
STAGE A & B DISCOVERY & POC
STAGE C PRECLINICAL
STAGE D PREPARE FOR FIH
STAGE E-H FIH 1-3
STAGE I REGISTRATION
TB VACCINE DEVELOPMENT PATHWAY
OVER
1,000,0000
LIVES PER YEAR
TUBERCULOSIS IS A CRITICAL GLOBAL HEALTH CHALLENGE, CLAIMING MORE LIVES THAN ANY OTHER SINGLE PATHOGEN
HOWEVER, UNRAVELLING THE DEVELOPMENT PROCESS CAN OFTEN FEEL OVERWHELMING
COMPLEX
LENGTHY
STOP
HAVE YOU CONSIDERED ALL THE RISKS?
WHAT BLOCKERS COULD COME ALONG AND HINDER YOUR PROGRESS?
ARE YOU INCLUDING THE RIGHT PEOPLE?
ARE YOU EXECUTING TRIALS IN A RESOURCE-EFFICIENT ORDER?
Confidence & Peace of Mind
QUESTIONS?
OUR DEDICATED PRODUCT AND CLINICAL DEVELOPMENT TEAM IS JUST A MESSAGE AWAY
ENSURING THAT
NO CRUCIAL STEPS
ARE OVERLOOKED
WHO POLICY & PREQUALIFICATION
PROOF-OF-EFFECTIVENESS/ IMPLEMENTATION
FINANCING & PROCUREMENT
IMPLEMENTATION & UPTAKE
VACCINE USE
IMPLEMENTATION PATHWAY

TBVI