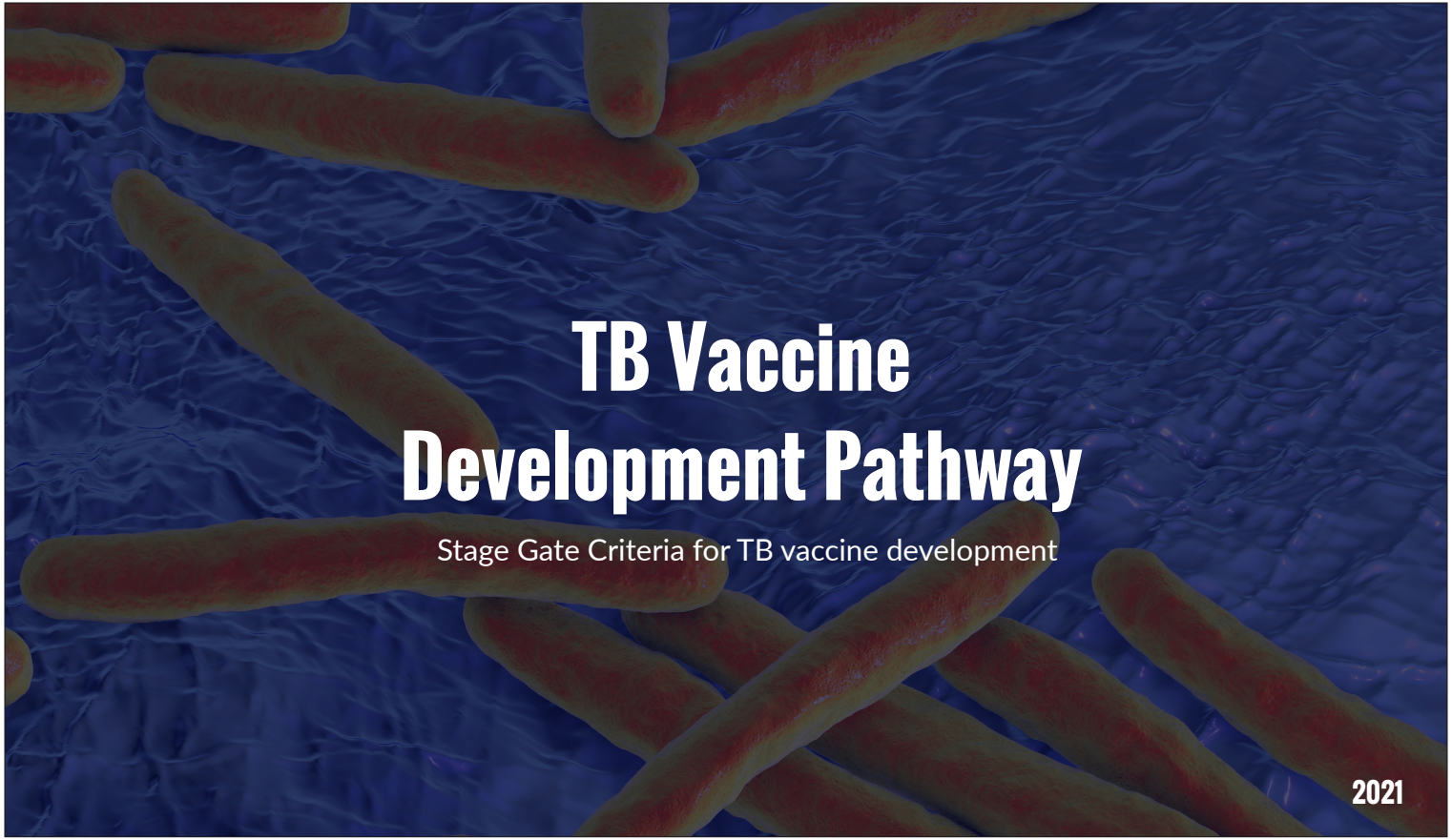

TB Vaccine Development Pathway

Stage Gate Criteria for TB vaccine development

2021

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TBVI

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Current GTBVP members are, in alphabetical order, BMGF, EC, EDCTP, EIB, EVI, IAVI, SA DST, SAMRC, TBVI and Wellcome, with NIH and WHO as observers.

GTBVP Global TB Vaccine Partnership

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Background on the TB Vaccine Development Pathway

In 2012, a generic set of Stage Gate (SG) criteria were published by TBVI and Aeras[1]. These criteria were intended to enable the evaluation of candidates from discovery to pre-clinical development (Gate1), from pre-clinical development to Phase I/IIa clinical studies (Gate2), from Phase I/IIa to Phase IIb clinical studies (Gate3), and from Phase IIb to Phase III clinical studies (Gate4) (https://www.ncbi.nlm.nih.gov/pubmed/22441156).

While the SG criteria were updated on a regular basis, they were formally revised in 2017 / 2018 by a Working Group of experts in vaccines from TBVI and IAVI. This Working Group added scientific information on TB, expanded the list of activities in the Stages and criteria in the Gates, and added Stages / Gates. The TB Vaccine Development Pathway was launched in September 2018: www.tbvacpathway.com. In 2019, the Working Group further developed criteria specific to vaccine candidates in sub-populations and indications, namely infants, adults and for immunotherapy. This was followed by a revision in 2021 based on a stakeholders review. This lead to an expansion and deepening of the SG criteria. It now includes vaccine technology specific considerations and more specific attention to market, access and implementation and community engagement.

In 2020 Tuberculosis published the article 'The TB vaccine development pathway – An innovative approach to accelerating global TB vaccine development'. This publication emphasizes the importance of a diverse TB vaccine pipeline to address the TB-specific challenges and the importance of individual vaccine candidates to be advanced rationally and that the global pipeline must be managed in the most nimble and resource-efficient way.

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

1 Aeras TB vaccine clinical programme was transferred in 2018 to IAVI. The TB vaccine programme will continue at IAVI.

About

Vaccine development is a complex and long endeavour that requires multiple expertise, management of activities running in parallel, and decision points. The Stage Gate Criteria (SGC) is a project management methodology that assists in the management of such large, long and complex projects. The SGC 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. These defined stages and gate criteria help to assess progress and decide to advance a project to the next stage, to stop, hold or recycle it. This methodology is applied by the TB Vaccine Development Pathway.

The pathway is laid out in a series of tables which describe the stages and gate criteria for the development of a vaccine against TB, from discovery and initial stage of the design of the vaccine and its Target Product Profile (TPP) (Stage A), to launch and implementation in vaccination programmes (Stage J). While the development path 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 vaccine candidates progress.

The stage gates that relate to the preclinical and clinical aspects of TB vaccine development are described under three separate functions: 'safety', 'immunogenicity' and 'protection/efficacy'. In addition, there is a separate clinical 'operations' function. The SGC per function can be directly accessed through the 'Function buttons' in the webtool. Alternatively, all of the SCG for a specific Stage is accessed through the pathway infographic.

TB specific considerations

A key challenge in TB vaccine development is the lack of accepted or validated immune correlates or surrogates of protection. This has an impact on pre-clinical screening of potential candidates and on optimisation of the vaccine formulation, since lengthy and costly protection experiments must be performed using animal models that 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.

Commonly, measurement of antibody responses provides the tool to monitor the quality and quantity of the adaptive immune response to vaccines, but BCG is a rare example of a marketed vaccine against infectious diseases for which antibodies do not provide the main mechanism of action. The measurement of the quantity and quality of the innate immune response and a T-cell mediated response provides a greater challenge, and this is a key consideration for novel TB vaccine development.

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

1) Adolescent/ adult populations

Adolescents and adults are the primary sources of *Mycobacterium tuberculosis* transmission, and modelling predicts that vaccination of these two populations would have greater and more rapid impact on the TB epidemic than neonatal vaccines (Harris et al., 2016). New TB vaccines for adolescents and adults must cover those with and without evidence of latent *Mtb* infection and be safe for use in HIV-infected populations. Vaccination aims at preventing TB disease whether it results from reactivation or new infection. In general, the specific considerations for these targeted indications are related to the clinical evaluation of the vaccines in the adult/ adolescent populations and to several factors that will influence the budget, pricing and implementation strategies. The relevant WHO PPC is described in section 6 of the document WHO Preferred Product Characteristics for New Tuberculosis Vaccines.

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 protection (prevention of disease) and having a better safety profile. Therefore, the benchmark for the development stages and functions is BCG. Benefits of a BCG replacement vaccine should be evaluated in Phase 4 clinical studies. Information and recommendations for the use of BCG can be found in the WHO Report on BCG vaccine use, and section 7 of the document WHO Preferred Product Characteristics for New Tuberculosis Vaccines, which describes the PPC for neonate/ infant TB vaccine.

3) Therapeutic vaccines

Therapeutic vaccines are deployed as an adjunct to chemotherapy in any age group. The aim of therapeutic vaccination is 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.

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**

Vaccine technology specific considerations

In the field of vaccinology, new technological platforms have emerged, each with specific challenges for development. Two classical vaccine products stay close to the original pathogen, either as an inactivated or a modified live version that causes no disease. There are 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 marketed live attenuated vaccine and whole-cell pertussis is one of the few inactivated vaccines. For TB, recombinant BCG and live attenuated *M. tuberculosis* candidates are in advanced stages of clinical development.

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, single recombinant polypeptide antigens and multiple, fused proteins combined with liposomes and Toll-like Receptor specific adjuvants, are in advanced stages of clinical development.

The 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 a specific adaptive response against the pathogen specific antigen structures, while also providing some innate immune stimulation. An example are the recently licensed adenovirus vector-based COVID-19 vaccines. For TB, several candidate vaccines based on viral vectors, including Modified Vaccinia Ankara (MVA) and adenoviruses, 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) and of mRNA formulated into lipid nanoparticles (LNP). Examples are the licensed mRNA vaccines for COVID-19. For TB, nucleic acid-based candidate vaccines have yet to enter clinical development stages.

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. P-CL (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. P-CL Immunogenicity	• Evaluate immunogenicity • Compare to benchmark, if applicable	• Evidence of relevant immunogenicity to antigens in at least one animal species • Above baseline and/or benchmark (if applicable) responses to antigens preferred
7. P-CL Protection, Efficacy	• Demonstrate protection 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 (e.g. BCG or no vaccine, or 'best-in-class' comparator)

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. P-CL 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. P-CL Immuno	• Confirm and characterise immunogenicity • Develop hypothesis for immunological mechanism of action; design the Non-Human Primate (NHP) (or other model) study with appropriate outcomes, sample size, read-outs, data analysis plan, etc.	• Confirmed consistent immune response to antigens in at least one animal species • Hypothesis for immunological mechanism of action defined; synopsis of NHP study (or another advanced model) available
7. P-CL Protection, Efficacy	• Confirm robust protection 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 and design of NHP study • Prepare read-outs to evaluate protection in NHP (or other model) study	• Protection statistically better than a relevant benchmark (e.g. BCG or no vaccine, or best-in-class) 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	• 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. P-CL Safety	• Design pre-clinical safety and toxicology studies as required by regulatory guidelines	• Synopsis protocols for safety and toxicology studies prepared as relevant for the vaccine
6. P-CL Immuno	• 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. P-CL 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 vs 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: 1. Protection vs Mtb challenge in a small animal model confirmed, 2. Protection vs Mtb challenge in a Non human primate (or justified, human-relevant, advanced animal model) confirmed

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 Clinical Development Plan (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 Immuno	• 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. P-CL 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
6. P-CL Immuno	• Not applicable, meaning that no additional data are required, on top of what was provided in the previous stage(s)	• Not applicable
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	• Safety endpoint approved	• Safety endpoint approved
11. Clinical Immuno	• 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 accepable • 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	• Submit and 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 FIH/Phase 1 • Prepare operations for subsequent Phase 2a • Provide and discuss results of earlier trials and obtain community input into Phase 2b trial design • If warranted, prepare for pre-Proof of Concept (PoC) study (e.g., Prevention of Infection (PoI) study) • If necessary, prepare a plan to obtain adequate epidemiology data in target population for Phase 2b • Draft synopsis for Phase 2b • Update CDP	• FIH/Phase 1 completed • Protocol(s) and operations for Phase 2a prepared • Community input obtained • If warranted, pre-PoC study prepared • 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	• Safety profile of selected doses or regimen of FIH/Phase 1 supports subsequent Phase 2a
11. Clinical Immuno	• Analyse FIH/Phase 1 immunogenicity data • 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 pre-PoC study (if warranted) together with endpoints for efficacy in a Phase 2b	• Endpoints for pre-PoC or first efficacy trial defined
13. Market, Access, Implementation	• Refine market analysis in targeted countries	• Market analysis refined

Stage F: Perform Ph2 (including Pre-PoC) 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) • Conduct Pre- Proof of Concept (PoC) study (if part of Clinical Development Plan (CDP)) • 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 2 studies in line with Good Participatory Practice 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 • Pre-PoC study completed • 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	• Safety profile of the dose selected for Phase 2b acceptable

11. Clinical Immuno	• Analyse all immunogenicity data from Phase 2a • Select dose for Phase 2b • Confirm 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	• If applicable, analyse pre-PoC data • Confirm efficacy endpoints of Phase 2b	• Whenever available, pre-PoC data are supportive • 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	• Submit CTA Phase 2b and obtain approval • 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 site, 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 Clinical Development Plan (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	• Safety profile acceptable in target population • RMP for Phase 3 drafted and active surveillance updated
11. Clinical Immuno	• Analyse all immunogenicity data from earlier trials, including Phase 2b for their consistency • Analyse Phase 2b data for 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	• Establish clinical Proof of Concept (PoC) efficacy	• Evidence of efficacy from Phase 2b or interim analysis consistent with minimal TPP criteria (based on predefined 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	• Prepare plan for community engagement for Phase 3, in line with Good Participatory Practice guidelines • Complete operations and conduct Phase 3 • Perform safety and immunogenicity 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 and immuno data analyed • Product consistency established • CSR is available • Draft Phase 4 plan established
10. Clinical Safety	• Evaluate pre-licensure safety against TPP • Assess the ratio of benefit-risk • Draft a post-marketing RMP, including evaluation in specific target studies (i.e. HIV infected individuals)	• Pre-licensure safety is acceptable and meets TPP • Favourable benefit-risk assessed • Post-marketing RMP is drafted, and includes post_marketing safety evaluation study and specific target studies

11. Clinical Immuno	• Perform secondary endpoints for analysis • Develop an investigational plan to identify correlates of protection (CoP) based on Phase 3 immunogenicity and efficacy data • Collect samples as per banking	• Secondary 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 • Evaluate Post Marketing effectiveness	• Protective efficacy meets TPP • Plan for phase 3 extension established, if needed • Post Marketing effectiveness data are available
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 specific target populations (for example HIV+)	• Post-marketing RMP finalised and approved
11. Clinical Immuno	• Conduct analyses for CoP establishment • Perform assays	• Analyses of CoP completed • Immunological assays performed
12. Clinical Protection, Efficacy	• Finalise post-marketing evaluation plan with Phase 4 effectiveness protocol and concomitant vaccines, if relevant	• Post-marketing effectiveness evaluation plan and 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

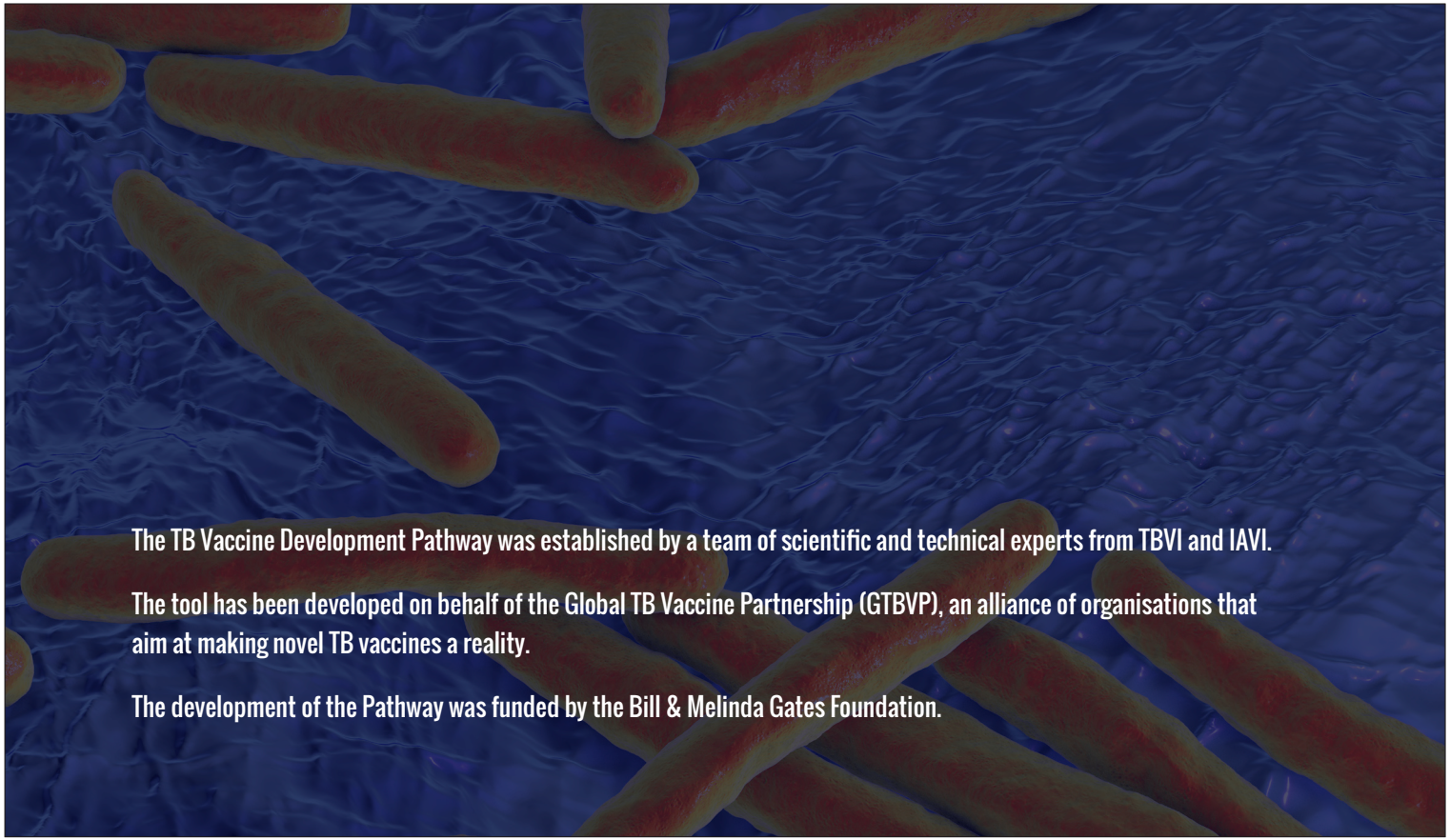
Gate J: Implement vaccination programs

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
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
EMA	European Medicines Agency
FIH	First In Human
GAVI	Global Alliance for Vaccines and Immunisation
GMP	Good Manufacturing Practice
GMO	Genetically Modified Organism
HEOR	Health Economics and Outcome Research
KOL	Key Opinion Leader
IB	Investigational Brochure
IP	Intellectual Property
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
PM	Project management
P-CL	Pre-clinical
PoC	Proof of Concept
PoI	Prevention of Infection
PI	Prinicipal Investigator
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
TPP	Target Product Profile
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WHO-PQ	WHO prequalification process



The TB Vaccine Development Pathway was established by a team of scientific and technical experts from TBVI and IAVI.

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