Ch 8. New tools

Priority actions

1. Invest, at minimum, US$ 4 billion annually to accelerate the research and development of new TB diagnostics, medicines, and vaccines. Resources need to be mobilized from governments and philanthropies, increased engagement with the private sector, and new approaches to innovative and sustainable financing.

2. Accelerate the development of new tools to prevent, diagnose, and treat TB by identifying innovative product-development pathways and improving collaboration among actors in product development. Research priorities include:

Diagnostics:

- Develop rapid and affordable non-exclusively sputum-based tests for diagnosis or triage at point of care.
- Develop accurate DST for critical medicines, including through sequencing-based tests and strategies for early detection of resistance to the drugs used in regimens.
- Improve tools for detecting TB infection (i.e., latent TB), subclinical TB and testing for risk of progression to active disease.
- Develop and harness artificial intelligence (AI) and machine learning-based tests.

Medicines:

- Advance and increase the number of new candidates with novel mechanisms of action in the clinical pipeline.
- Advance the development of new treatment regimens that will be superior to current regimens for drug-sensitive and drug-resistant forms of TB.
- Focus on treatment-shortening strategies for both TB disease and TB infection.

Vaccines:

- Diversify and broaden the pipeline of next generation TB vaccine candidates by expanding research on *Mtb* immunology and basic mycobacteriology, and develop animal models that better reflect human infection and disease.
- Provide resources and support to efficiently move a diverse range of vaccine concepts from the lab to the clinic.
- Significantly accelerate clinical development of vaccine candidates and ensure sufficient financing, resources, and capacity to advance promising candidates through efficacy trials and licensure without delay.
- Conduct research on correlates of vaccine-induced protection during vaccine efficacy trials to inform vaccine design and expedite clinical trials of future vaccine candidates.
- Work with countries and affected communities to prepare for successful licensure and roll-out of new TB vaccines once licensed (see Chapter 4).

3. Invest at least US$ 800 million in basic science research.

4. Expand the use of operational research.

5. Develop and implement digital tools.

6. Create an enabling environment for TB R&D.

7. Apply best practices in community engagement throughout the R&D process.

8. Apply access principles in rolling out and optimizing the use of new tools.

9. Strengthen advocacy for TB innovation.

Invest, at minimum, US$ 4 billion annually to accelerate the research and development of new diagnostics, medicines, and vaccines.

Investments in science and technology are crucial to tackling any disease and are an absolute necessity to reach goals of elimination of disease. For TB, a disease that primarily affects the developing world, funding has always fallen short of meeting the basic required levels needed to support research and development needs.

Without new medicines, diagnostics and effective vaccines, we will not achieve the steep reductions in incidence and mortality that we need, and millions more people will get sick or die from the disease. After years of under-investment, developing these tools will require commitment and funding from governments, the private sector, and philanthropic organizations that is on par with the urgent need for innovation. It will also require a radically transformed approach to accelerating promising medicine, diagnostic and vaccine candidates through the development pathway. R&D efforts should be needs-driven, evidence-based and guided by the core principles of affordability, efficiency, equity and collaboration.

In the UN Political Declaration on TB, UN Member States recognized the “lack of sufficient and sustainable financing” for TB research and innovation. In response, they committed to “mobilize sufficient and sustainable financing, with the aim of increasing global investments to US$ 2 billion per year in order to close the estimated US$1.3 billion gap in funding annually for tuberculosis research.”

Governments have consistently fallen far short of this commitment. In 2020, governments collectively invested only US$642 million in TB R&D (of a total US$915 from all funding sources). Adjusted for inflation, total investment in TB R&D was flat between 2018 and 2020. The commercial pharmaceutical

sector also invested very little in TB R&D, including almost nothing for vaccines. As a consequence, the effort to eliminate TB continues to suffer from an enormous gap in R&D funding.

In contrast to their support for a COVID-19 vaccine, multilateral funders such as Gavi, CEPI, and the multilateral development banks have not yet contributed significant resources to support TB R&D (TAG, 2021).

Table 1 shows annual TB funding needs for the R&D of new TB medicines, diagnostics and vaccines from 2023-2030.

Table 1. Resources needed for TB R&D, 2023-2030

Tool	Investment needed (US$ billions)
Medicines	$16,060
Diagnostics	$7,720
Vaccines	$10,000
Total	$33,780

The projected total funding required for R&D for new TB medicines, diagnostics and vaccines from 2023–2030 is US$ 33.8 billion, or an average of US$ 4.2 billion annually. These figures do not include the resources needed to implement new vaccines, nor do they include the resources needed for basic science research or the operational research required to identify the most effective ways of implementing new tools in various national contexts. See Chapter 4 for details on vaccine implementation.

The funding needs are greater than the US$2 billion funding needed in prior years. The increased need reflects the lack of investment in prior years and includes the costs of carrying out large-scale Phase 3 vaccine trials–a cost that reflects advances in vaccine R&D in recent years. Costed priorities are presented in R&D strategic frameworks for diagnostics, medicines and vaccines below. See Chapter 9 for a discussion of mobilizing resources for TB R&D.

Urgency leads to innovation

Investments, partnerships, and global multisectoral efforts have translated to remarkable impact in creating effective therapies for HIV, and the undeniable progress the world has made in vaccines, diagnosis and treatment developed for SARS-COV2. Advocacy, a sense of urgency, political will as well as substantial public and private investments proved critical to see these impressive results.

The response to COVID-19 involved unprecedented scientific innovation. The introduction of multiple vaccines in rapid time showed what is possible to achieve with a critical mass of resources and political will.

Working together, governments, the private sector and philanthropy identified new approaches and pathways to development, which allowed them to move quickly through the R&D and regulatory processes and introduce new products in record time.

The global TB R&D community must learn and leverage as much as possible from the COVID-19 response in order to transform the approach to advancing new TB medicines, diagnostics and vaccines.

The urgency is even greater now than in the past, considering the pandemic's impact on TB R&D, which include the diversion of resources (human, financial and infrastructure) and delays in TB research activities. With immense resources invested in COVID-19, scientists today face even less incentive to develop careers in TB research. New resources are critically needed to rebuild TB R&D capacity and safeguard TB innovation from potential future disruptions.

Accelerate the development of new tools to prevent, diagnose, and treat TB by identifying innovative product-development pathways and increasing collaboration among key stakeholders in product development.

The following section lays out strategic frameworks for accelerating the research and development of new TB medicines, diagnostics, and vaccines.

New diagnostics

Objective	Milestone	Major activities	Funding required 2023 – 2030 (US$ millions)
Objective 1			**417.15**

Ensure expanded and equitable access to critical knowledge and resources that enable the development of new diagnostic tools	Increase access to reference materials and digital repositories that are critical for the discovery, development and validation of new TB diagnostics	a. Facilitate sample storage and database maintenance within country of collection, reducing the need for import/export permits b. Ensure that international biobanks and digital repositories collaborate and have centralized, open-access mechanisms and dashboards so requestors can obtain samples from anywhere c. Promote highest quality in biobanking and database curation to ensure global representativeness, relevance and integrity. In compliance with patient rights, data protection laws and FAIR Data Principles[1]	62.54
	Integrate biomarker discovery and validation in well powered trials and studies collecting high quality data	Undertake research to identify and validate new non-sputum-based markers and diagnostic concepts addressing high priority use cases including pediatric TB, EPTB, HIV, subclinical TB, and to guide personalized medicine in TB	316.4
	Support assessment of MTB genetic variants to inform the development of molecular tests for the detection of drug-resistant TB	a. Expand the global knowledgebase and repositories with genomic, phenotypic, and associated metadata from MTBC samples, review for quality and standardization b. Support contributions of sequencing datasets by diverse groups (National TB Programs, academics, consortia, etc.) to expand and maintain a catalog of mutations associated with resistance to anti-TB drugs and that is updated periodically to ensure standardized and accurate interpretation of data	16

	Undertake research and consultations to support the development of person-centered diagnostic tools and solutions	a. Definition of patient charter/ethical criteria, and consensus-building on appropriate patient data utilization and data protection protocols b. Include end users (people who have experienced TB, health workers, lab technicians etc.) from conceptualization, design, evaluation, and implementation of diagnostic tools and solutions, taking into account social and gender factors c. Evaluate alternate, minimally-invasive or non-invasive, easy-to-collect or self-collected specimen methods	16.71
	Disseminate knowledge on diagnostic tools and solutions	a. Develop clearer guidelines for validation studies for new diagnostics b. Update target product profiles (TPPs) c. Develop and promote online country-specific platforms for knowledge sharing on diagnostic development, ongoing accuracy trials, and implementation research, including massive online open courses (MOOCs) and in-country “TB think-tanks”	5.5
Objective 2			**1,621.47**

Develop and evaluate a diverse portfolio of new tests and solutions	Develop fit-for-purpose diagnostics for testing strategies addressing the major diagnostic gaps in TB	Develop tests and solutions for the following: a. Fast and affordable tests to determine risk of developing active TB disease in infected, at-risk populations b. Improved TB screening tools c. Simple and affordable point-of-care diagnostics for TB detection in all patients, including EPTB, PLHIV and pediatric TB d. New tools that are based on easy-to-obtain non-sputum samples e. High-throughput centralized diagnostics f. Early detection of subclinical TB disease g. Detection of drug resistance, including both pDST and gDST sequencing-based strategies h. Treatment monitoring and tests of cure i. Multi-disease platforms and tests to differentiate between pathogens, reduce antibiotic overuse, and improve self-isolation strategies j. Digital diagnostics for relevant use cases listed above	848.93
	Conduct accuracy trials for new tests and evaluate their clinical performance in trials to guide global policy and country uptake	Carry out accuracy trials and evaluation studies for the tools a-j listed above	612.54

	Ensure that any diagnostic is a connected diagnostic, so that surveillance, reporting, and linkage to care is automated	a. Support development of standardized digital data collection tools suitable for multiple settings and transition away from paper-based data collection b. Strengthen and centralize national TB surveillance systems using digital tools and applications c. Incorporate connectivity elements such as digital readers/QR codes in the design of novel TB diagnostics to make the reporting of results digital d. Improve the timeliness of reporting diagnostic results to patients using digital tools and applications	160
Objective 3			**566.08**
Demonstrate patient benefit and predict impact within the entire health system	Predict patient and health system impact from the use of new diagnostics and solutions to improve TB detection, reduce transmission, and prevent mortality	a. Demonstrate impact of new diagnostic tools on patient important outcomes, through pragmatic implementation trials in relevant countries and settings b. Use diagnostic network optimization (DNO) and modeling to estimate the likely impact and cost-effectiveness of new technologies and innovative diagnostic strategies c. Conduct qualitative studies on end users (people who have experienced TB, health workers, lab technicians etc.) values and preferences, quality of care, and health system utilization	549.08
	Conduct market analysis and estimate the potential of new diagnostics	Update and expand existing market assessments	4

	Work with companies and regulatory bodies to streamline the process of regulation, WHO prequalification, and national and international approval	a. Quality assurance and post market surveillance b. Support and streamline processes for WHO prequalification and national regulatory processes	13
Objective 4			**5,115.12**
Ensure that WHO approved diagnostic are made available and appropriately used in relevant countries	Roll out tools and solutions, supporting transition away from smear microscopy for TB diagnosis	Procure devices and consumables for the rollout of WHO approved molecular tools and innovative solutions (new and existing) for rollout in high-burden countries	4,158

	Effectively integrate diagnostic tools within the health system, including within the private sector	a. Empower countries to develop fit-for-purpose models using DNO to optimize the placement and integration of diagnostic tools based on country contexts b. Integrate TB diagnostic services with diagnostic services for communicable and non-communicable diseases c. Incentivize the private sector, including pharmacies, medical clinics, and hospitals, to use WHO endorsed tools d. Strengthen information technology (IT) capacity to implement more advanced diagnostic technologies that use AI e. Strengthen laboratory capacity for appropriate scale-up of new tools via: i. Training (coordination, development of tools, sessions, training supervisors, reference specimen transfer) ii. Empowering in-country partners (e.g., Supranational Reference Laboratories, Centers of Excellence) to support introduction of new tools in-country and promote operational research iii. External quality assurance and accompanying measures for tools being used iv. Ongoing external and within-country assistance, including for supply management aspects	526.5

	Ensure patient-centered diagnosis and decentralization of testing where appropriate	a. Include people with TB in decision-making/policies regarding TB diagnostics b. Develop solutions for effective, rapid sample transportation c. Ensure that proper services are in place to link patients to care following their diagnosis	48
	Support rapid policy change at the country-level for implementation and facilitate in-country regulatory processes	a. Support country-specific policy change and regulatory processes (local cost-effectiveness and validation studies) b. Harmonize regulatory processes in high-burden countries with stringent regulatory systems and difficult markets to penetrate	59.62
	Sensitize stakeholders about diagnostic uptake and national diagnostic algorithms	Coordinate with advocacy groups and civil societies to organize workshops with NTPs, ministries of health, technical procurement and funding agencies, medical associations (pharmacy, chest physicians etc.), and patient representatives	35
	Scale up manufacturing and other market interventions to bring price down	a. Invest in commercialization and successful scale-up, including local diagnostic start-ups and companies to create lower-cost, innovative diagnostic solutions b. Support local manufacturers to improve scale-up c. Conduct market interventions to reduce the price of diagnostic products (e.g., pool procurement mechanisms, advanced market commitment, volume guarantee, demand forecasting, demand generation, cost of goods sold (COGS), optimization, new channels etc.)	264

	Expand next generation sequencing capacity in countries by 2030 and establish hubs for genomic drug resistance surveillance	a. Build capacity and sustainable infrastructure, and provide training and support in genomics and bioinformatics to implement next generation sequencing approaches for genomic surveillance of drug-resistant TB at the reference laboratory level b. Reinforce the mechanism to use the supranational reference laboratory network and WHO collaborating centers as the main driver to provide training, study guidance, and long-term support	24
TOTAL			**7,719.82**

New medicines

Vision: Develop shorter, more effective, and safe medicines and regimens for all age groups and populations affected by TB

Goals:

1. Introduce shorter treatment regimens (less than 4 months) for treating all forms of TB using three or four new medicines with no cross-resistance to existing medicines
2. Introduce shorter regimens for TB preventive therapy

Table 1: New medicines strategic framework

Objective	**Milestone**	**Major Activities**	**Funding Required 2023–2030** (US$ Millions)
Sustain the pipeline through basic discovery for TB medicines	One new clinical candidate entering Phase I each year	Accelerate screening and optimization of new chemical entities; validate biomarkers of treatment outcomes; develop in vitro and animal models that are more predictive of clinical efficacy; identify new drug targets	3,500

Increase trial site capacity	Increase the number of Good Clinical Practice/Good Laboratory Practice (GCP/GLP) compliant sites available for TB drug trials	Identify, maintain and develop new GCP/ GLP compliant sites, including clinical trial sites, clinical laboratory, pharmacy, and biospecimen storage capacity	900
Introduce shorter regimens for DS-TB and, where appropriate, evaluate as potential universal regimens	Complete Phase III trials of a shorter than 4-month regimen for DS-TB and assess regimens for all forms of active TB.	Conduct trials: pharmacokinetics studies, Phase I, Phase II (early bactericidal activity, serial sputum colony counting, drug-interaction studies), and Phase III to advance two to three new treatment-shortening regimens	7,200
Develop a safe, higher efficacy and shorter (4 months) regimen for MDR-TB	Complete Phase III of a shorter regimen for MDR-TB	Conduct trials: PK studies, Phase I, Phase II, and Phase III to advance two to three new treatment-shortening regimens	2,000
Improve TB treatment for children	Complete formulation development and clinical testing in children	Include children in trials as early as possible for new regimens; develop safe, reliable and user- friendly regimens for all forms of child TB early in the development process; conduct drug-interaction studies	430
Develop a safer, high-efficacy regimen for TB infection	Complete Phase III of a safer, high-efficacy regimen for TB infection	Conduct Phase III trials of new regimens for TB infection with the aim of a shorter duration of treatment with high efficacy and safety	330
Ensure adoption of new TB medicines and regimens at country level	Enhanced access of patients to newly approved medicines and regimens, especially in high- burden countries	Include new medicines and regimens in national policies and guidelines; implement mechanisms to expedite regulatory processes in countries; engage key stakeholders; conduct extensive training of health providers	1,500
Engage community and civil society in the entire process of medicine development and access	TB-affected community and civil society members have been recruited to all decision- making processes and forums along the medicine	Include TB-affected community and civil society representatives, and specifically high risk populations, in advisory committees, protocol and study design, scientific networks and other forums related to TB drug	200

	discovery and development pipeline	development to ensure adequate drug access.	
TOTAL FUNDING REQUIRED			**16,060**

New Vaccines

Vision: To develop new, more effective vaccines that will directly and safely prevent TB in all age groups and populations and are affordable and accessible to those who most need them.

Goals:

1. Develop new TB vaccines that prevent *Mtb* infection, TB disease, and/or recurrence of TB disease following successful treatment of TB, thereby interrupting TB transmission
2. Incorporate the goal of equitable accessibility throughout the TB vaccine R&D process
3. Strengthen community engagement in TB vaccine R&D

The End TB Strategy calls for a new effective TB vaccine for use by 2025. It is likely that more than one vaccine will be necessary to meet the needs of different populations and different regions. However, this goal has been rendered unachievable by chronic underfunding.

Scientific advances, particularly in the past five years, have demonstrated the feasibility of developing new vaccines to prevent TB infection and to prevent TB disease. These advances included positive results from two Phase 2b clinical trials. However, while these results were published nearly five years ago, phase III studies have not yet started due primarily to chronically inadequate resources.

The successful development and licensure of at least one new TB vaccine in this decade will require a transformation in the vaccine development pathway backed by new resources, including:

- Accelerating clinical development pathways, including but not limited to streamlining design of efficacy trials while still meeting regulatory requirements for licensure .
- Evaluating novel vaccine technology platforms (e.g. mRNA)for TB and identifying human protective antigens
- Developing animal models that reflect relevant human outcomes (i.e. resistance to infection) and are 'fit-for-purpose' to prioritize vaccine candidates for human testing
- Developing innovative financing models that will enable the rapid development and deployment of vaccines once efficacy has been established
- Investing in scale-up of manufacturing at risk and preparing the supply chain to ensure ample supply and rapid distribution of vaccines once licensed

Roadmap for the Research and Development of New Tuberculosis Vaccines

In April 2021 the European & Developing Countries Clinical Trials Partnership (EDCTP) and the Amsterdam Institute for Global Health and Development (AIGHD) launched a Global roadmap for

research and development of tuberculosis vaccines. The Roadmap identifies key barriers to TB vaccine R&D and implementation, ways to overcome them, and a shared set of priorities to guide TB vaccine R&D activities. The Global Plan's strategic framework for TB vaccine R&D has been adapted to align with this Roadmap, and funding requirements were applied to these research priorities and activities. More details and information about these activities and priorities can be found in the Roadmap.

New Vaccines Strategic Framework 2023 – 2030

Vision: To develop new, more effective vaccines that will directly and safely prevent TB in all age groups and populations and are affordable and accessible to those who most need them.
Goals: 1. Prevent TB diseases and interrupt transmission through the development of new vaccines that would prevent infection, progression, reactivation and/or reinfection 2. Incorporate and consider equitable accessibility throughout the TB vaccine R&D process 3. Strengthen community engagement in TB vaccine R&D

Strategic framework adapted from the Roadmap for Research and Development of New TB Vaccines, published by EDCTP and AIGHD, April 2021. Costing and sections in green added

Objective 1: Diversify the TB Vaccine Pipeline to increase probability of success in developing effective, new TB vaccines			
Priority	**Key Actions**	**Comments**	**Funding Required (US$ millions)**
Mechanisms and biomarkers of protection	Conduct observational clinical studies combining pathogenesis and immunology, making use of systems biology, epidemiology and modelling	Identify components of the host-pathogen interaction associated with clearance, progression to disease and subclinical disease; identify biomarkers and biosignatures of natural protection.	1000
	Study the role of non-conventional, cellular immunity, antibody responses and trained innate immunity in natural and vaccine-induced protective responses	Explore cellular responses through class-I restricted CD8+ T cells, Th17 cells and MAIT cells; B- cell and antibody responses including Fc-mediated antibody effector functions; and innate immune responses through unconventionally restricted T cells and epigenetic reprogramming of monocytes and natural killer cells. Investigate their role in human immune responses to *M. tuberculosis.*	
	Identify biomarkers and biosignatures that correlate with vaccine-induced protection	Based on data and biological samples from trials that have shown protection signals; through targeted approaches to detect cellular and/or	

		humoral immune responses and unbiased approaches including transcriptional profiling of blood cells and mycobacterial growth inhibition assays.	
Undertake novel approaches to vaccine discovery	Develop new vaccine concepts that induce a broad diversity of potentially protective immune responses	Explore candidates that generate non-conventional cellular immunity, protective antibody responses and trained innate immunity.	
	Study mucosal immune responses	Understand the determinants of protective immune responses in the lung parenchyma and mucosa, and how these can be inferred by systemic responses.	
	Discover antigens that are protective in humans	Identify Mtb expressed proteins, peptides and non-protein antigens that can be recognized by the human host immune system, applying IFN-γ as well as non-IFN-γ based screening approaches, including by genome-wide strategies.	
Develop and apply improvedvaccine formulations and delivery platforms	Study the effects on vaccination outcomes of adjuvants, vaccine platforms and lineage of the Mtb challenge strain	Amongst others through experimental medicine studies.	200
	Explore new routes of vaccine administration	Including aerosol and intravenous approaches, amongst others through experimental medicine studies.	
	Study how vaccines can direct immune responses to the lungs	Evaluate the capacity of different formulations and delivery platforms to induce mucosal immune responses.	

Establish a Controlled human infection model	Develop a controlled human infection model for immunobiology studies	To inform basic knowledge gaps, as well as for proof-of-principle studies to inform down- selection of candidates, platforms and routes of administration. Participant safety, sensitivity and ethical issues will be critical to address.	50
Advance promising vaccine candidates from early preclinical to clinical development	Conduct the necessary studies for IND or equivalent regulatory submission	To provide development partners, funders and regulators with sufficient evidence of safety (including necessary toxicology studies) and intended biological activity (e.g., immunogenicity; protection in pre-clinical challenge models) to support and enable advancement into phase 1 clinical studies.	550

Table 2a. Priorities and actions to accelerate clinical development of new TB vaccines: animal models

Objective 2: Optimize and standardize animal models for understanding TB mechanisms of protection and accelerating vaccine development			
R&D priority	**Key actions**	**Comments**	
Optimized animal models	Develop *fit for purpose* animal models	Back-translate into immunogenicity, infection and disease animal models the results/findings from adolescent/adult and paediatric trials, ideally using the exact same product as in humans, and from clinical studies of disease progression and subclinical disease.	735
	Develop animal models to provide insight into the relation between prevention of Mtb infection (POI) and prevention of TB disease (POD)	Leverage results from human trials with PoI and, ideally, both PoI and PoD endpoints, as well as from clinical studies of clearance and disease progression to optimize animal models.	

	Develop immune compromised animal models that can predict/replicate findings in specific human target populations	Back-translate into disease animal models the results that will emerge from clinical trials including those in all age groups and immune compromised humans.	
Comparison of vaccine candidates within and across animal models	Standardize and harmonize animal models	Including harmonization and standardization of challenge strain selection; definition of protection outcomes, including the use of imaging and scoring gross pathology specimens. Identify priorities for future experimental directions, e.g., assessing aerosolized delivery of vaccines.	
	Perform head-to-head testing of candidate vaccines	In independent laboratories using the standardized models that best predict protection in humans.	

Table 2b: Priorities and actions to accelerate clinical development of new tuberculosis vaccines: clinical trials

Priority 3: Advance candidates through clinical trials			
R&D priority	**Key actions**	**Comments**	**Total $ incomplete costing**
Conduct clinical trials utilizing portfolio management and common stage-gating criteria	Implement Phase 3 trials of vaccine candidates that meet criteria to advance to licensure. and policy recommendations		6500
	Continue to support vaccine candidates through the clinical pipeline and initiate new Phase I/IIa/IIb trials using PoI, PoR, and POD endpoints	Bias toward selection of PoD endpoint in adolescent /adult population considering likely disproportionate effect on reducing spread of Mtb (as compared to PoI or PoR approaches or studies in infants and young children)	
	Include safety trials or safety assessments for people living with HIV in clinical trial		

	planning and implementation		
Ensure adequate Clinical Trial site capacity in high TB burden regions to conduct global regulatory standard human trials of novel vaccines	Make inventory of clinical trial site capacity	Identify potential sites beyond the existing ones; assess quality and suitability in terms of existing technical and laboratory infrastructure.	
	Collect epidemiological data in sites considered for phase II/III trials	In various parts of the world, as a continuous process: age-stratified data on TB incidence; age- stratified incidence/prevalence of latent TB infection; Mtb lineage distribution; data on special populations such as people living with HIV and other populations considered for vaccine trials.	
	Develop vaccine trial sites, including sustainable human capacity	Develop infrastructure and human capacity, including mentorship and support of junior investigators, in diverse geographic locations to take account of potential variation in efficacy and safety due to heterogeneity in host and bacteriological genetic background.	
	Study potential barriers to trial acceptance	Social science research of barriers to participating in TB vaccine trials and completing follow-up, including TB-associated stigma, other stigma, and social barriers; compile best practices from successful vaccine trial sites.	
	Promote community engagement in TB vaccine trials	Integrate Community engagement into all phase II or phase III studies sponsors and developers should start developing plans for community engagement before phase I studies start.	
Trial endpoints	Define standardized PoD trial endpoints that better capture the various TB disease states in	Standardize definition of laboratory-confirmed pulmonary TB; develop clinical endpoints representative of subclinical TB if established as a substantial contributor to TB transmission;	8

	diverse target populations	improve bacteriological confirmation of TB disease in neonates and infants and people living with HIV; improve bacteriological confirmation of extrapulmonary disease.	
	Define and develop better PoI trial endpoints	Define an endpoint for Mtb infection for establishing PoI; this endpoint should differentiate Mtb infection from vaccine-induced immune response.	
	Quantify the clinical translation of PoI into PoD	Analyse existing and new observational data; include secondary PoI endpoints in phase III PoD trials, considering that this quantification may be different for different types of vaccines.	
Correlates of protection (CoPs)	Collect biospecimens for identifying CoPs	In planned and ongoing phase IIb and phase III trials.	800
	Identify CoPs for TB disease	From phase IIb and phase III trials that have shown protection: analyse data and putative CoP values from individual trials and, if possible, from meta-analyses of several trials.	
	Validate CoPs for TB disease	Validate putative CoP identified by back-translation of trial results in terms of vaccine-induced response and clinical protection in immunogenicity studies, new trials with a clinical PoD endpoint and potentially controlled human infection models. Validate identified COP in PWHIV to enable immuno-bridging studies	
Trial harmonization and design	Harmonize clinical trial protocols	Define an agnostic trial “shell” of standardized outcomes, inclusion criteria and measurements for clinical trials for different vaccine types. This would also address secondary endpoints; inclusion criteria for people living with HIV infection or diabetes; and standardized measurements over time.	7
	Evaluate and develop new models for TB vaccine clinical trials with	Phase I: explore innovative trial designs that provide information on the local human immune response. Phase IIb/III: efficacy trials within contact investigations, active case	

	increased time-and cost-efficiency	finding programs and high-risk populations; adaptive trial designs for evaluating the safety, immunogenicity and efficacy of different vaccine types.	
Improve preclinical and clinical readouts	Standardize reagents, harmonize assays and benchmark relevant signals by forward as well as back-translation/ verification between preclinic and clinic	Gather stakeholder input and come to consensus on path forward; continue to expand on programs to provide reagents to laboratories and research facilities; develop necessary assays based on stakeholder consensus	150

Table 3a. Priorities and actions to ensure public health impact: epidemiology and modelling

R&D priority	Key actions	Comments
Country-specific data and projections	Conduct in-depth country-specific value proposition analyses	Assess value drivers for new TB vaccines across different countries and stakeholders considering preferred delivery strategies; efficacy relative to safety; manufacturing, strain standardization and price; willingness to pay; and cost of delivery.
	Collect epidemiological data at country and subnational level	To inform economic and impact modelling related to country decisions on introduction of new TB vaccines and market volumes: (sub)national TB disease and infection prevalence including in specific risk groups (people living with HIV, elderly); identify potential target groups for vaccination based on contribution to transmission; map *M. tuberculosis* genotypic variation.
	Modelling to define vaccine development investment cases and country-specific vaccine use cases	Modelling of implementation scenarios, the epidemiological impact, cost-effectiveness and budget impact in consultation with countries for vaccines that are close to market introduction, using transmission and economic modelling as well as other quantitative approaches.
Post-licensure studies	Develop valid approaches for real-life vaccine scale-up studies	Develop designs and validated tools for establishing real-world effectiveness, safety and public health impact following introduction; establish and/or support post-licensure registries making use of existing expertise from introduction of other

		vaccines; strengthen surveillance systems for collection of baseline epidemiologic data.
	Conduct post-licensure evaluations of vaccine effectiveness, impact and safety	Real-world post-licensure studies and surveillance to establish effectiveness across various subpopulations (e.g., people living with HIV) and Mtb lineages; effectiveness and safety when given concurrently with other vaccines; safety in subpopulations (e.g., pregnant women); impact on TB disease incidence; non-specific health effects for vaccines replacing BCG.

Abbreviations: BCG - Bacille Calmette-Guérin, Mtb - *Mycobacterium tuberculosis,* R&D - research and development, TB - tuberculosis.

Table 3b. Priorities and actions to ensure public health impact: research to ensure optimal implementation

R&D priority	Key actions	Comments
Health system conditions for vaccine introduction	Define the generic public health system requirements to deliver a new TB vaccine	For a vaccine for adolescents and adults: determine in different countries the feasibility of various strategies including vaccination campaigns; conditions for immunization programs to implement these strategies; requirements for optimizing access for different population groups; integration of TB vaccination within and beyond national TB programmes; and approaches to measuring vaccine uptake in adolescents/adults. For a vaccine for neonates and infants: determine the fit in the Expanded Programme on Immunization and required timing with regard to other vaccinations.
	Conduct pre- and post-introduction assessments of country immunization programmes	Assess the pre-introduction country-specific readiness of immunization programmes and health systems to handle, store and administer the new TB vaccine (considering its characteristics, particularly for delivery to adolescents and adults), to monitor vaccine coverage and adverse events, and to communicate adverse events.
Barriers and enablers of vaccine uptake	Assess drivers of acceptability and uptake of new TB vaccines in various settings	Social and behavioural research to determine across countries and settings decision makers' and public and health workers' perceptions around new vaccines, related to dosing, safety concerns, religious concerns, gender, use with other vaccines versus specialized

		programmes, and for immunotherapeutic vaccines, integration with TB treatment.

Abbreviations: R&D - research and development, TB - tuberculosis.

Table 4: Priorities and actions with regard to enabling conditions for tuberculosis vaccine development

Enabling priority	Actions
Funding	
Attract new investments in TB vaccine R&D	Develop a comprehensive global value proposition for TB vaccines that encompasses vaccine characteristics, use case, societal value, business case, investment case, and health and micro/macro-economic impact assessment.
	Broaden the funding base with governments, charitable funders and donors. Mobilize domestic R&D funding from large countries' governments; get specific donors involved that could contribute to funding downstream aspects of TB vaccine R&D; engage with the HIV and antimicrobial resistance communities.
	Attract new entrants in TB vaccine R&D. Involve actors, technologies, models and knowledge from outside the TB vaccine research field; funders should promote such involvement in their funding programmes, e.g., in the specification of calls and eligibility criteria.
Innovate financing for TB vaccine R&D	Create collaborations or partnerships for joint funding of trials with mechanisms for pooling resources between R&D funders, governments and industry with selection procedures that are product and country agnostic, and strict norms for what the funding will be used for and under which conditions.
	Customize calls to the clinical development pathway through options for their flexibility long term funding (e.g., ten years, with intermediate go/no-go decisions) allowing consortia to adopt a long-term R&D perspective for a specific candidate or approach.
Create mechanisms that attract investment in early stages of development	Reduce commercial uncertainty by providing incentives for stronger engagement from industry and other vaccine developers through grant funding and advance market commitments with a clearly defined path to commercialization, including production of a successful candidate.
	Ensure that intellectual property can be used efficiently, openly, and equitably to facilitate TB vaccine R&D in ways that promote collaboration among universities, biotech and pharmaceutical companies, and government funders.
Open science	

Promote timely and open access of data, specimens and results	Funders and product development partnerships should require registration of all animal and human studies, open access publication of both positive and negative results, data-sharing and posting in open access databases as condition for funding and/or consortium membership.
	Biospecimens collected in clinical studies should be made available based on peer review, overseen by an access committee. Access to biospecimens should not be granted on first-come first-serve basis but to researchers with the most innovative ideas and approaches.
	Establish publicly searchable patent databases for TB vaccine research (as exist for drug development) to promote the diffusion of knowledge by facilitating access to the information disclosed in a patent, including antigens, adjuvants, platforms, and processes.
Create a mechanism for coordinating open science in TB	Establish a platform for data sharing, starting with data from clinical studies, including generic protocols for contextual data (e.g., for what purpose was the data collected); proper use (e.g., ethical rules, privacy regulations) and acknowledgement of original collectors/contributors of the data in secondary use and publications.
	Develop and coordinate systems and procedures needed for efficient data and specimen sharing across the field of TB research and across TB research funders.
Stakeholder engagement	
Create a supportive environment for TB vaccines	Raise political commitment for new TB vaccines to ensure new political commitment at country level and continue high level commitments making sure that existing commitments and defined targets are met, based on clear communication about the need, efficacy and safety for new TB vaccines towards policy makers, including the risk-benefit and cost-benefit analysis of a new TB vaccine.

2714
2715
2716

	Advocate for development and uptake of new TB vaccines with vaccine developers and the public through positive messaging about opportunities and actions in vaccine development.
	Harmonize and fast-track regulatory review and local approval of vaccine trial protocols based on the example of AVAREF; establish NITAGs in countries that do not have them and strengthen their capacity; fast-track regulatory approval of TB vaccines.
	Create innovative incentives by forecasting demands from countries and engaging multilateral funders, including GAVI, GFATM, Unitaid and CEPI in offering novel financing mechanisms.
Overcome barriers to delivery and uptake	Engage with end-user communities to address stigma, vaccine hesitancy and adherence; provide and communicate a convincing rationale for (high-risk) target groups to be vaccinated; involve end-user communities in the research process; build resilient information systems to counter vaccine related misinformation and disinformation.

	Develop approaches to community-level delivery (e.g., through community health workers) to address gaps in access to vaccination; educate healthcare networks, the medical community and the general public about TB vaccine introduction through targeted, country-specific approaches.
Promote TB vaccine and research literacy	Create a global program for community engagement and training for new TB vaccines; develop mechanisms for engaging community representatives in TB vaccine development; engage and educate community representatives who can speak to policy makers to invest in the development and introduction of new vaccines; support community engagement in TB vaccine clinical trials.
	Foster strategic and reciprocal partnerships between vaccine scientists/sponsors and representatives of civil society and TB affected communities to support the involvement of all parties in advocacy for new TB vaccines.

2717
2718

2719
2720

Meeting the unique needs of children and adolescents

Research efforts directed towards TB in children and adolescents have focused mostly on finding out how to better apply existing tools. However, children and adolescents have needs that differ from those of adults. For example, children have a hard time producing sputum, making them poor candidates for diagnosis using tests that require sputum collection (e.g., the rapid diagnostic test Xpert MTB/RIF).

Treatment Action Group and the Stop TB Partnership Child & Adolescent TB Working Group and Treatment Action Group have laid out a detailed agenda for child and adolescent TB R&D. Priorities include:

Prevention: Identify new, shorter, and simpler preventive regimens; develop a new vaccine for infants, children and adolescents that improves on the current BCG vaccine.

Diagnosis: Develop novel tests that are not invasive, do not rely on sputum, and can be used at the point of care.

Treatment: Evaluate the safety and efficacy of new TB medicines in children and adolescents to determine optimal dosing; identify treatment regimens that are shorter and simpler than those currently available; and ensure that TB treatment regimens are available in child- friendly formulations.

Basic science research: Research is needed to better understand how TB affects infants, children, and adolescents, including the immune response to infection and associated biomarkers that can inform the development of new tools.

Invest at least US$800 million in basic science research.

Scientists still do not fully understand how *M. tuberculosis* causes infection. The world would especially benefit from understanding more about how the TB bacillus interacts with the body, and how the body mobilizes a protective immune response. Gaining this understanding would help drive innovation and enhance the ability to develop new tools to prevent, diagnose and treat TB.

Basic science research is typically conducted by academic institutions, industry and public–private partnerships, which rely in a large part on public funding. At least US$ 400 million is needed annually to advance TB basic science research. This funding should be used to address priorities such as:

- Undertaking research to understand:
  - how TB infection progresses to disease
  - how to predict the risk and stages of disease progression based on biomarkers
  - how to more easily and reliably know when a person has been cured through treatment
- R&D infrastructure, including biorepositories (i.e., facilities for collecting, storing, processing and distributing specimens used for scientific research)
- Developing and sustaining a larger field of TB researchers
- Improving collaboration between researchers and research centers

Expand the use of operational research

Operational research involves a wide range of research activities used to investigate strategies, interventions, tools and knowledge that can improve the performance of health systems and programmes. Despite improvements in recent years, large implementation gaps still exist in the delivery of TB care that is quality-assured and people-centred. Scaling up country-level capacity for operational research is essential to close those gaps and to reach universal access to TB prevention, diagnosis and treatment. Operational research is also necessary to understand how best to introduce and scale up new tools within various populations, and how best to combine medical care with social-service support in order to achieve the best treatment outcomes and better address the underlying factors that put people and communities at risk of TB.

Research funders should allocate specific funding for operational research, directing it as a priority towards initiatives that will build the evidence base for informing decisions that can close implementation gaps in LMICs.

To be sustainable, operational research capacity needs to be more routinely embedded within NTPs, with dedicated operational research professionals and resources allocated through annual budgets.

Key priorities for operational research:

1. understand how TB tools are used in local contexts, informing early-stage planning for the introduction of new tools in order to reduce delays between licensure and effective use

2. understand how to most efficiently and effectively conduct active case finding, an approach by which health systems proactively reach out to people at risk of TB and see that people receive screening, diagnosis and appropriate care and support

3. improve access to treatment, care and psychosocial support, including assessing, monitoring and overcoming social, legal, political and economic barriers to access, for both DS- and DR-TB

4. improve access and equity for hard-to-reach populations in LMICs, which is critical to achieving UHC

5. understand how public and private sectors can coordinate and collaborate to improve all aspects of accessing and delivering TB care and support

6. optimize TB infection control in order to reduce transmission

7. improve methods for conducting disease surveillance, monitoring and evaluation of TB programmes

8. understand the role that TB affected communities and TB survivors can play throughout and beyond the TB cascade of care, including in TB service delivery

Box: SORT-IT

TDR—a joint effort by UNICEF, UNDP, the World Bank and WHO—provides a model for supporting the training of TB researchers who are working to improve TB care at the health systems level in LMICs. Through the Structured Operational Research and Training IniTiative (SORT IT)—a global operational research partnership led by TDR in and implemented with over 60 partners—researchers are trained to conduct operational research according to country priorities, build sustainable operational research capacity, and make evidence-informed decisions for improving TB programme performance. Participants perform classroom work, develop a research protocol and application for ethics review, receive training in data management and analysis, design a data analysis plan, write and submit a paper to a peer-reviewed journal, and acquire the skills and tools for improved communication of research findings (for research uptake) for policymakers and stakeholders.

Develop and implement digital tools.

Digital health refers to using a mix of digital technologies and software applications to transform health services. They can be applied to a wide range of healthcare issues, processes and functions in order to improve physical and mental well-being at the individual and population levels (Table TK).

Scale up the use of digital health tools

Scaling up digital health has many potential benefits:

- Makes health services more efficient
- Reduces capacity constraints in the health workforce
- Reduces costs for health systems and for people
- Improves people's access to the health system
- Reduces health inequities
- Improves health outcomes and well-being

Scaling up digital health in low and middle-income countries (LMICs), especially, would help address staffing and resource constraints that have historically made it difficult both to deliver and to access TB care. Though access to the Internet, smartphones, and other forms of technology is still relatively limited in LMICs, mobile "feature" phones (i.e., phones that lack the advanced functionality of smartphones but can make calls, send text messages, and access some simple Internet features through a text-based interface) are extremely common. These phones can be used for digital health.

Box: Common types of digital health tools

- **Electronic Health Records (EHR), also known as Electronic Patient Records (EPR).** These are software solutions that replace paper records with digital records. They can also facilitate digital transactions.

- **Telecare, also known as telehealth.** This refers to the delivery of healthcare (e.g., consultation, treatment monitoring and support) remotely using telecommunications technology.
- **Digital medical electronics.** These include a wide range of devices that can be used both inside or outside of a person's body. Common applications include medical imaging (e.g., digital chest x-rays) and electronic sensors (including sensors that can be ingested or implanted to monitor bodily functions).
- **Mobile devices, services and apps.** These are solutions that monitor and share health information using mobile technology. Devices are wearable. Apps appear on mobile phones.
- **Health analytics and bioinformatics.** These use powerful computing technology to analyse large amounts of data. Health analytics tends to focus on helping health program managers understand trends in real time, which helps them make better decisions that improve health care delivery and better manage disease in a population. Bioinformatics uses technology to collect and analyse large quantities of biological data, such as genomic information.
- **Digital adherence tools.** These are digital tools that support people with TB to complete a full course of appropriate treatment in a people-centred way. They can use video chat where video communication technology is available and can be appropriately organized and operated by health care providers and people receiving care. Mobile technology can also be used, including text messages or telephone calls, to provide ongoing treatment adherence support.

If scaled up, the digital health tools that would be especially helpful for ending TB include:

- Computer-aided detection (CAD): CAD is an image-based diagnostic tool. CAD is powered by software that uses artificial intelligence (AI) to read chest x-rays for signs of TB and provide an output that can be used for screening and triage.
- Diagnostics connectivity solutions: Diagnostic connectivity provides the ability for diagnostic instruments to remotely share data, allowing for instant reporting of results to clinicians and databases, routine epidemiological surveillance, and real-time monitoring of diagnostic supplies.
- Telemedicine that connects TB specialists with people who need care for remote consultations and treatment monitoring and support.
- Remote adherence technologies that support people with TB to complete treatment.

Table XXTK. Applications of digital health solutions at different levels of the health system.

Health system level	Applications		
Population health	Disease surveillance and forecasting Population health risk management Intervention selection and targeting Communicating health information to the public or key populations Incentivizing people to seek health services		
Individual health	*Diagnosis*	*Treatment*	*Prevention*

	Image-based diagnosis Whole genome sequencing Screening and triage, including self-screening Monitoring health or diagnostics data, including self-monitoring	Digital adherence support Drug 3D printing Personalized treatment Telehealth	Identifying vaccine candidates Predicting risk of disease progression
	Managing referrals between points of service Providing health-education content to patients and families		
Health system	Real-world, real-time data collection Transmitting data/medical information to healthcare providers Detecting drug resistance Providing training content to healthcare providers Capacity planning and management Quality assurance Delivering supplies by drone		
Pharmaceutical and insurance industries	Drug discovery Supply chain management Monitoring inventories Real-world evidence collection and analysis Adaptive trial design Remotely monitoring clinical trials		

Provide guidance for scaling up implementation of digital health tools

TB programs need to know what tools to procure and implement, where, and how. They need to know how to prioritize, how to operationalize, and how to optimize solutions. This is a complex undertaking that poses numerous challenges.

Governments and technical agencies need to provide clear, up-to-date guidance for innovators, implementers and policymakers to aid them in developing, operationalizing and providing an enabling environment for digital health.

As applications for digital health tools continue to expand, as access to information and communications technologies continue to grow in LMICs, and as AI becomes more capable, operational research will continue to be essential in order to understand how best to apply digital tools to support people with TB and improve the quality of care. Concerns remain that digital technology has the potential to replace human contact, or even be misappropriated for uses that overstep the purposes of improving support and quality of care by violating people's rights to privacy and autonomy. Therefore, it will remain essential to seek input from people with TB and survivors in designing digital health applications. Adhering to ethical standards will also remain critical in navigating issues of privacy, oversight, accountability, public trust, data governance and management in the application of digital health tools.

Develop strategies for integrating digital health tools into national TB programs

With effective guidance, national TB programs would be better positioned to develop strategies for integrating digital health in their TB elimination efforts. These strategies are essential for prioritizing which tools to invest in and where, and for coordinating governments, innovators, implementers and end users in the integration process.

Countries will have more technical resources that can be used for strategy development as WHO works to strengthen the evidence base for digital health in the fight against TB, evolves its guidance in line with advancements in digital health tools, provides technical assistance to countries, and supports digital health policy development.

Create a research-enabling environment

Accelerating TB R&D requires changes in the surrounding research environment that can enable major leaps in innovation. Enabling TB R&D requires improving:

- support and incentive structures for researchers, including in LMICs
- data-, information-, and sample/material-sharing practices
- support for research centers and research collaborations
- capacity to conduct clinical trials, especially in LMICs
- regulations and policies that underpin R&D and product approval
- strengthening advocacy for TB innovation

Develop and sustain a talented field of TB researchers

Ensuring long-term success in TB R&D will require nurturing and incentivizing researchers to focus their efforts on TB innovation, from basic science through translational research and clinical trials.

Training the next generation of scientific investigators is a priority traditionally supported by mechanisms such as Wellcome Trust fellowships, National Institutes of Health (NIH) support at the pre- and post-doctoral levels, and European Union funding. These initiatives are critical but insufficient to fill the void.

Both governmental and nongovernmental funders must recognize the urgent need to train and sustain the next generation of researchers, and special efforts should be made to support and strengthen the capacity of researchers in high TB burden LMICs. Support should include financial investment, proactive career support and career development activities, as well as additional opportunities for training, networking and presenting research in local, regional and global forums. These efforts should be particularly aimed at graduate, post-graduate (doctoral), and junior faculty early-career researchers. Two model initiatives are SORT-IT for operational research and ADVANCE for HIV research (see Box below).

The COVID-19 pandemic has had multiple impacts on this collective investment in early career TB researchers. Firstly, resources in the form of grants and early research opportunities, which previously focused on TB and other infectious diseases have been diverted to prioritize COVID-19 research. Many TB scientists were diverted to assist with COVID-19 solutions using TB research infrastructure, including access to human cohorts and nonhuman primates, clinical operations, supply chain for lab reagents, and biosafety level 3 facilities. Furthermore, students considering careers in infectious disease research have

been attracted to study COVID-19 by its higher profile and the enormous resources devoted to it, which makes it more difficult to recruit early trainees to study TB.

The lockdowns and travel restrictions imposed by COVID-19 and inequitable global vaccine access have also dramatically decreased access to conferences and networking opportunities for early career investigators, impacting their ability to showcase their work to other investigators in the field, which would previously have led to collaborations and opportunities for employment and career advancement. The focus now should shift toward repurposing the expanded COVID-19 research infrastructure to other infectious diseases, particularly a high-priority respiratory disease such as TB.

Box: ADVANCE

Supported by USAID, ADVANCE (Accelerating the Development of Vaccines and New Technologies to Combat the AIDS Epidemic) is a multi-partner research initiative that increases the involvement of African and Indian researchers in all stages of HIV vaccine R&D. New initiatives along the lines of SORT IT and ADVANCE, applied to TB basic science research and clinical research, would help to ensure the long-term capacity for innovation in all areas of TB research.

Support Open Science and Information Sharing

The Roadmap for TB Vaccine Research and Development and the WHO Global Strategy for Research & Innovation identify the importance of open science and information to the R&D process. The WHO Global Strategy notes that "Sharing high-quality data…fosters scientific progress, promotes discovery…, improves future data collection methods… and allows for the analysis of similar data from multiple sources, which can subsequently inform national and global policy-making in a cost-effective and timely manner." Key actions to promote open science identified in the Roadmap are outlined in Table X.

Table XXTK. Key Actions to Promote Open Science, Roadmap for Research & Development of New TB Vaccines

Promote timely and open access of data, specimens and results	Funders and product development partnerships should require registration of all animal and human studies, open access publication of both positive and negative results, data-sharing and posting in open access databases as condition for funding and/or consortium membership.
	Biospecimens collected in clinical studies should be made available based on peer review, overseen by an access committee. Access to biospecimens should not be granted on first-come first-serve basis but to researchers with the most innovative ideas and approaches.
	Establish publicly searchable patent databases for TB vaccine research (as exist for drug development) to promote the diffusion of knowledge by facilitating access to the information disclosed in a patent, including antigens, adjuvants, platforms, and processes.
	Establish a platform for data sharing, starting with data from clinical studies, including generic protocols for contextual data (e.g., for what purpose was

Create a mechanism for coordinating open science in TB	the data collected); proper use (e.g., ethical rules, privacy regulations) and acknowledgement of original collectors/contributors of the data in secondary use and publications.
	Develop and coordinate systems and procedures needed for efficient data and specimen sharing across the field of TB research and across TB research funders.

Increase support for research institutions, partnerships and collaborations

Research institutions urgently need more support to advance TB innovation. Below are examples of institutions, partnerships and collaborations that are key to accelerating the R&D of new TB tools. Each entity carries out its work through multisectoral collaboration.

Product development partnerships (PDPs) remain critical to advancing R&D for new TB tools. PDPs, a type of public–private partnership, are not-for-profit organizations that work through collaborations with private-sector manufacturers, governments, NGOs and academia, and typically pool resources and technical expertise to develop and commercialize new tools. PDPs are especially important for developing new TB tools because traditional market incentives are not powerful enough to drive innovation for TB.

Table XXTK Key TB R&D entities

Entity	Model	Focus
TB Alliance	PDP	medicines/treatment regimens R&D
Foundation for Innovative New Diagnostics (FIND)	PDP	diagnostics R&D
International AIDS Vaccine Initiative (IAVI)	PDP	vaccines R&D
TB Vaccines Initiative (TBVI)	PDP	vaccines

TB Trials Consortium	government consortium	clinical, laboratory, epidemiological research
AIDS Clinical Trials Group (ACTG)	network	TB-HIV clinical trials
Medicines Patent Pool	UN-associated organization	licensing
BRICS TB Research Network	government network	basic research, R&D, clinical trials, operational research
European and Developing Countries Clinical Trials Partnership (EDCTP)	partnership between non-profit, government and private sectors	R&D
UNITE4TB	government-sponsored consortium	treatment regimens Phase 2 clinical research
European Regimen Accelerator for TB (ERA4TB)	public-private partnership	medicines/treatment regimens R&D
Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PANAcea)	government and EDCTP-sponsored consortium	treatment regimens clinical research
PAN-TB	philanthropic-nonprofit-private-sector consortium	medicines/treatment regimens R&D
EU-PEARL	public-private partnership	clinical research platforms

Increase site capacity for conducting clinical trials in LMICs

The most promising new tools for ending TB will be those that have been demonstrated to work well in countries and settings with the highest burden of TB. This requires testing new tools in the environments where they will be most widely used and will have the greatest impact. As new diagnostics, medicines, and vaccines enter late-stage trials, investment in the development of trial site and laboratory capacity is becoming increasingly urgent. This includes investing in physical infrastructure to ensure appropriate laboratory capacity is available for large-scale trials, and in human capacity and training to ensure that trials are conducted in accordance with Good Clinical Practice, Good Participatory Practice and Good Laboratory Practice standards.

Clinical trial capacity must be developed and enhanced in multiple regions, as the efficacy of any new tool might vary in different populations and regions. A new tool's licensure and acceptance for use can also be affected by where it was tested.

Existing clinical trial sites should be used for TB research wherever possible. Sites should be developed with an aim toward sustaining their capacity over the long term, providing continued opportunities for trained staff, and utilizing the developed infrastructure for other disease areas.

Barriers to conducting trials in LMICs include:

- a lack of financial and human resources
- ethical and regulatory system obstacles
- lack of physical research infrastructure
- operational barriers
- competing demands.

Addressing these challenges requires steps to be taken together:

- LMIC governments should invest in strengthening domestic research capacities.
- All partners should work together to strengthen international collaboration with the aim to improve or create new systems for conducting clinical trials in LMICs.
- Research funders should promote investigator-driven research by local researchers in LMICs.
- Research organizations should strengthen their engagement of affected communities in trial design and execution as laid out in the Good Participatory Practice Guidelines for TB Drug Trials and the Good Participatory Practice Guidelines for TB Vaccine Research 2017.

Ensure an efficient and predictable regulatory and policy environment

A frequent obstacle to accessing new tools is the lack of transparency in the national registration process. When registering medicines, for example, there is often no forum for interaction between the drug sponsor applicant, regulatory authorities, and communities. The present lack of regulatory

harmonization has resulted in staggered, country-by-country approval procedures for new tools, resulting in deadly delays.

Country governments should build their capacity to evaluate new tools that have already been tested in other countries, allowing those that are shown to be safe and effective to be imported for use. WHO-issued guidance can support and expedite country policy-setting and adoption of new tools, particularly in countries without rapid regulatory processes. One other potential solution is to help expedite TB research by streamlining and harmonizing regulatory processes from clinical development to regulatory submission and regional approval.

Apply access principles in rolling out and optimizing the use of new tools

Any time lost between the licensure of a new tool and people in need being able to use it leads to unnecessary suffering and loss of life. With proper planning and a strategic, evidence-based approach to access and optimization of use, people can get the most value and benefit from new tools. The following section lays out activities that national governments should undertake to scale up access and understand the most effective ways of deploying new tools within the health system.

The Universal Declaration of Human Rights, the International Covenant on Economic, Social and Cultural Rights, and the Declaration of the Rights of People Affected by Tuberculosis uphold the rights of people to enjoy the benefits of scientific progress and its applications. In keeping with these rights, the accessibility of new TB tools needs to be considered from the outset of the R&D process.

The accessibility of new tools is intimately tied to how R&D is financed and conducted, including incentive strategies, policies of research funders, governance of research institutions, and the values, norms and standards that guide R&D. As the UN Political Declaration on TB states, TB R&D should be "needs-driven, evidence-based, and guided by the principles of affordability, effectiveness, efficiency and equity". These principles should guide R&D from the earliest point in the R&D process.

While there are important areas of progress, TB R&D has long been underfunded. Given TB's public health significance as an airborne communicable disease that is responsible for more deaths than any other single infectious agent, where discrimination is both a cause and a consequence of the disease, and where large numbers of people in poor and marginalized populations are chiefly affected, states have an obligation to promote the development of new diagnostics, treatment regimens and vaccines, including through robust international cooperation, and to ensure access for all.

The UN Committee on Economic, Social and Cultural Rights has defined the right to health to include the availability, accessibility, acceptability and quality of health-related goods and services, where:

- availability requires making health goods and services available in sufficient quantity;

- accessibility involves four elements, all of which require attention be paid to how they impact key populations: non-discrimination, physical accessibility, affordability and access to information;

- acceptability requires all health facilities, goods and services to be respectful of medical ethics and culturally appropriate, sensitive to sex and life-cycle requirements, as well as designed to respect confidentiality while improving the health status of people;

- quality requires goods and services to be scientifically and medically appropriate and of good quality.

It is essential that all stakeholders involved in promoting and carrying out TB R&D design and implement their activities in ways that respect, protect and ensure these rights-based principles at every stage in the R&D process, including the delivery of new tools.

Apply best practices in community engagement throughout the R&D process

Researchers and research institutions must embrace the involvement of communities as a standard part of the R&D process. Best practices should be followed for engaging TB-affected communities within all research activities and within decision-making bodies and fora. The International Ethical Guidelines for Health-related Research Involving Humans establishes universal principles for engaging communities in research activities, advising that:

"Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results."

Specifically related to TB, research institutions should consult the Good Participatory Practice Guidelines for TB Vaccine Research and Good Participatory Practice Guidelines for TB Drug Trials, which help to facilitate effective engagement with affected communities and stakeholders at all stages of the research process.

Engaging communities in research also fulfills a key guideline in WHO's Ethics Guidance for the Implementation of the End TB Strategy: "Community members should have the opportunity to participate in research beyond their role as potential trial participants. This participation should extend throughout each stage of the research process, from the design and conduct of studies to the dissemination of results."

Community participants should be from the geographic area where the research is being conducted. They can be a subpopulation among the participants recruited and can include groups within the broader society who have a stake in the outcomes of the research. Key populations are discussed in Chapter 7.

These groups must be engaged and their capacity strengthened as a priority in all aspects of research activities. Community engagement must be human-rights-based, gender-sensitive and people-centred.

Communities should be consulted early in the research process, before a study is even initiated, to inform the research design. Community engagement should then remain ongoing through established modes of communication between researchers and community members.

Engaging with communities in all aspects of R&D also creates new groups of informed people who can advocate for TB R&D. People affected by TB, particularly TB survivors, must be engaged as experts in this space.

TB-affected communities can play a key role in monitoring the outputs of research, helping to ensure that the benefits of scientific progress are accessible to all people, free from stigma and discrimination, irrespective of how they individually identify or where they live. TB-affected communities can also champion enhanced research on the successes and benefits of TB community-based service delivery, advocacy, and monitoring for social accountability.

Community advocates play a critical role in research. They are uniquely placed to document, monitor and analyse the intersectionality between social determinants of health and effective TB responses. Their increased engagement stems from community demands for self-determination and meaningful participation in the TB response.

Box: Models of community engagement in research

Community Advisory Boards (CABs): Research entities can establish CABs to ensure that community voices, needs and priorities are reflected at each stage of the research process, from designing studies and conducting trials to disseminating results and working to translate results into policy change.

Community-based participatory research (CBPR): In the CBPR model, community members and researchers collaborate on all aspects of a research project, and community members work with scientists as equal partners. The CBPR model is grounded in principles of collaborative and equitable community engagement in research and shared ownership of research issues, processes and products.

Strengthen advocacy for TB innovation

Implementing the priority actions above will only be possible with powerful advocacy. Informed by the Global Plan and the WHO Global Strategy for TB Research and Innovation, TB researchers, civil society, affected communities and survivors must work together to advocate for R&D funding, for the actions that contribute to a research-enabling environment, and for equitable access to the products and benefits created through innovation.

Priorities for strengthening advocacy for TB R&D include improving research literacy among the advocacy community, building advocacy skills among TB researchers, and strengthening collaboration between researchers and advocates.

Improving research literacy among the advocacy community

Research literacy means understanding and being able to effectively communicate key concepts, processes and goals being pursued in TB R&D. Wherever research literacy is lacking, TB advocates will be limited in their capacity to affect change.

Better research literacy training opportunities and supporting tools need to be developed and made accessible for advocates across civil society. They should support advocates in three areas:

- Developing an understanding of key concepts in TB R&D, so they can effectively track developments in TB R&D
- Developing skills to communicate about TB R&D issues, so they can translate R&D priorities into effective messages
- Understanding the landscape of TB R&D community (i.e., research institutions, policymaking processes, regulatory bodies), so they can identify and pursue effective advocacy strategies

Deepen the research community's involvement in advocacy

Likewise, advocacy funders and research institutions should support initiatives that support researchers to become more effective advocates for the TB R&D agenda. Scientists can speak credibly not only about new research findings, but also have important insights about barriers and opportunities in TB innovation. There are challenges, however, that need to be overcome to involve researchers in advocacy, particularly when it comes to communications habits and ability to navigate the advocacy landscape. Priorities for deepening the research community's involvement in advocacy include:

- providing more advocacy and strategic communication training opportunities for TB researchers
- strengthening relationships with TB advocates and coalitions
- elevating the visibility of TB research

Scientific researchers are typically trained to communicate with other scientists, creating challenges when it comes to communicating with advocates, policymakers, the news media and other stakeholders who are not scientists. This communications gap can create a significant barrier for advocacy, undermining progress in TB R&D.

Research scientists have also typically not been trained in advocacy strategy and tactics and lack familiarity with the advocacy landscape. It can be difficult to know where or how to become involved in advocacy, even when members of the research community want to.

However, with larger cadres of advocacy-savvy TB researchers, advocacy organizations can find more opportunities to enroll researchers in advocacy campaigns and policymaker outreach. Research studies and key insights from the research community can be routinely shared with advocates who can help translate findings and recommendations into advocacy messages to share important studies with decision-makers and key influencers such as the news media.

Better advocacy training opportunities and supporting tools need to be developed and made accessible for members of the R&D community. They should support researchers in four areas:

- Developing knowledge of common advocacy strategies and tactics
- Building strategic communications skills, such as media training, Op-Ed writing and public speaking
- Translating research findings and insights into action and impact
- Building collaborative relationships with professional TB advocates and advocacy coalitions

See Chapter 9 for further discussion of TB advocacy priorities.