A Draft Global Strategy for TB Research and Innovation

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<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
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<tr>
<td>BCG</td>
<td>bacille Calmette–Guérin</td>
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<tr>
<td>BRICS</td>
<td>Brazil, Russian Federation, India, China and South Africa</td>
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<td>CEWG</td>
<td>WHO Consultative Expert Working Group on Research and Development: Financing and Coordination</td>
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<td>DALY</td>
<td>disability-adjusted life-year</td>
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<td>DR-TB</td>
<td>drug-resistant TB</td>
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<td>DS-TB</td>
<td>drug-sensitive TB</td>
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<td>EU</td>
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<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
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<td>G7</td>
<td>Group of Seven</td>
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<td>G20</td>
<td>Group of Twenty</td>
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<td>Gates Foundation</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<td>GDF</td>
<td>Global Drug Facility</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
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<td>GERD</td>
<td>gross domestic expenditure on research and development</td>
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<td>Global Fund</td>
<td>Global Fund to Fight AIDS, Tuberculosis and Malaria</td>
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<td>HIV</td>
<td>human immunodeficiency virus</td>
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<td>IP</td>
<td>intellectual property</td>
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<td>MDR-TB</td>
<td>multidrug-resistant TB</td>
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<td>MTB</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>NGO</td>
<td>nongovernmental organization</td>
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<td>PDP</td>
<td>product development partnership</td>
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<td>PPP</td>
<td>public–private partnership</td>
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<td>RR-TB</td>
<td>rifampicin-resistant TB</td>
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<td>R&amp;D</td>
<td>research and development</td>
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<td>SDG</td>
<td>Sustainable Development Goal</td>
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<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>The Union</td>
<td>International Union Against TB and Lung Disease</td>
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<tr>
<td>UHC</td>
<td>universal health coverage</td>
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<tr>
<td>UNGA-HLM</td>
<td>United Nations General Assembly High-Level Meeting on TB</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>XDR-TB</td>
<td>extensively drug-resistant TB</td>
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SUMMARY

1. Tuberculosis (TB) is the leading cause of death from a single infectious agent globally, and is one of the leading causes of death from antimicrobial resistance. The Sustainable Development Goals (SDGs) target for TB builds on historic gains made under the Millennium Development Goals to “end the epidemic” by 2030; more specific targets for 2030, set in the World Health Organization’s (WHO’s) End TB Strategy, include ensuring that no family is burdened with catastrophic expenses due to TB, and achieving a 90% reduction in TB deaths and an 80% reduction in TB incidence compared with 2015 levels, with targets for further reductions (95% and 90%, respectively) by 2035. However, there is still an enormous gap between current reality and the vision of the SDGs.

2. Robust efforts are needed to sustain and improve on the gains made to date, and to address persistent challenges that have led to uneven progress in the fight against TB. The End TB Strategy stipulates that major technological breakthroughs are needed by 2025, so that the rate at which TB incidence falls can be accelerated dramatically compared with historic levels. Delivering on these targets requires a multisectoral approach to developing and equitably diffusing the right medical innovations and strategies as a top priority. However, there are multiple challenges and gaps to be addressed in research, innovation and access to TB vaccines, medicines, technologies and services.

3. The United Nations General Assembly High-Level Meeting on TB, held in September 2018, and the WHO Global Ministerial Conference on Ending TB, held in Moscow in 2017, renewed the commitment of Member States to strengthen national and global efforts in the fight against TB. This document aims to provide countries with a framework to facilitate the implementation of the commitments on research and innovation articulated in those declarations.

4. The Global Strategy for TB Research and Innovation will support efforts by governments and other partners to accelerate TB research and innovation, and to improve equitable access to the benefits of research, by setting clear objectives and recommendations, as highlighted below:

4.1 Create an enabling environment for TB research and innovation to increase the capacity for conducting and using research outcomes equitably in a sustained and effective manner, by strengthening public–private partnerships; streamlining and harmonizing regulatory processes for the review of research protocols and products; and integrating civil society’s expectations, needs, interests and values into the research and development (R&D) process.
4.2 Increase financial investments in TB research and innovation, by setting a target contribution for TB research funding; developing innovative and collaborative financing mechanisms to facilitate the timely development and diffusion of appropriate and affordable biomedical tools and technologies; and a target contribution for the conduct of the social, health system and operational/implementation research that is vital to support effective scale-up of innovative strategies and tools.

4.3 Promote and improve approaches to data sharing to advance scientific discovery; reduce duplication of effort; and facilitate the translation of evidence to national and global polices on TB prevention, diagnosis, treatment and care.

4.4 Promote equitable access to the benefits of research and innovation by strengthening global and national access initiatives for TB vaccines, medicines and diagnostics, and by providing appropriate governance structures that foster research and innovation as a shared responsibility that is needs driven, evidence based and guided by the core principles of affordability, effectiveness, efficiency and equity, with a view to enabling everyone to access essential quality TB health products and services without facing financial hardship.

5. This document is aimed primarily at Member States, particularly ministries of health, science and technology, finance and education. By aligning their national health research and innovation strategies and actions (and related investments) to the framework presented in this strategy, all countries can accelerate progress towards the milestones and targets of the End TB Strategy. In this regard, Member States may consider developing a comprehensive national strategy or roadmap for TB research and innovation, to coordinate the implementation of the Global Strategy at a national level.

6. In the spirit of fast-tracking efforts to end TB, a prerequisite for success is that all stakeholders make concerted efforts and collaborate. Hence, this document also makes the case for a unified and aligned response in which key relevant national and international partners and affected communities support Member States by undertaking the investments or partnerships (or both) necessary for accelerating innovation.
1. INTRODUCTION

7. Tuberculosis (TB) ranks as the leading cause of death among infectious diseases in human history, claiming over a billion lives in the past two centuries alone (1, 2). Despite this enormous toll on health and well-being, the response to TB has been slow and underfunded, particularly in the area of research (3).

8. Member States adopted the End TB Strategy during the 67th session of the World Health Assembly, with its high-reaching targets of ending the TB epidemic by eliminating catastrophic expenses due to TB and achieving a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030 compared with 2015, in line with the Sustainable Development Goals (SDGs), with targets for further reductions (95% and 90%, respectively) by 2035 (4, 5).

9. The 2015 Millennium Development Goal target to halt and reverse TB incidence has already been achieved on a worldwide basis. Overall, effective diagnosis and treatment of TB saved an estimated 54 million lives between 2000 and 2017 (1).

10. Although progress has been significant, it is still insufficient. In 2017, an estimated 10 million people developed TB disease (5.8 million men, 3.2 million women and 1 million children), 9% of whom were individuals living with HIV. About half a million people develop rifampicin-resistant TB (RR-TB) each year, challenging the diagnostic, preventive and treatment capacities of the countries in which those infections occur (1).

11. The third pillar of the End TB Strategy – research and innovation – recognizes that achieving substantial reductions in TB incidence and mortality will require the development and introduction of new tools and strategies, in addition to promoting universal access to existing technologies and the better use of those technologies. Such tools and strategies include a rapid point-of-care test for diagnosing TB infection and TB disease, and for detecting drug resistance; safer, shorter regimens for treating TB infection and drug-sensitive TB (DS-TB); shorter, safer and more effective treatment for drug-resistant TB (DR-TB); a new TB vaccine that is effective both before and after exposure, and across a range of age groups and geographic settings; and innovative strategies to address the social and environmental drivers of TB.

12. The current pipelines of new diagnostics, medicines and vaccines are inadequate to meet the needs identified above. There is a growing understanding among stakeholders that the pharmaceutical industry cannot be solely responsible for most of the drug discovery and development in disease areas characterized by complex pathologies, high resource needs and limited investment. A collaborative approach is thus vital to move the field of TB research forward by sharing resources, benefits and risks throughout the value chain of product development. Public–private partnerships (PPPs) are the most prominent example of such an
approach, through which governments, academia, patient organisations and the private sector can create an environment of open science and resource sharing.

13. A strong emphasis on reinvigorating basic biomedical research and disease biology is needed to reveal new insights into the molecular and biochemical underpinnings of diseases that will deliver a high degree of innovation in TB prevention, diagnosis, treatment and care, and clinical research to translate these discoveries into affordable clinical tools.

14. Achieving universal access will require social science research, as well as operational/implementation and health system research, to support the development of cost-effective and high-impact service delivery strategies that allow the quick and equitable introduction and optimization of new products and approaches tailored to country-specific needs.

15. To increase the extent and quality of TB research activities, there is a need for mechanisms to facilitate collaborations between researchers in different countries around needs-driven research topics, and to promote multidisciplinary research at multiple sites through existing or new national or international TB research networks and consortia that combine discovery and implementation research (e.g. preclinical, clinical, operational/implementation, health system, economic evaluation and social science). As outlined in the World Health Organization (WHO) Global Action Framework, these networks could be coordinated from a hub located in an institution with expertise in the relevant focus area, in alignment with ministries of health (6).

16. TB has multiple socioeconomic and environmental drivers; therefore, effective measures for prevention, diagnosis, treatment and care require partnership and collaboration among various stakeholder groups (e.g. government, academia, civil society and industry) and sectors (e.g. health, science, environment and finance) to improve the effectiveness and impact of new and existing interventions.

17. Progress against TB will bolster efforts to achieve a number of SDG targets and vice versa, particularly the targets focused on eradicating poverty in all its forms, ending the AIDS epidemic, reducing premature mortality among women and children, strengthening health systems, and supporting the research and development (R&D) of vaccines and medicines for diseases that primarily affect less economically developed countries. The Copenhagen Consensus has identified spending on TB as a “best buy”, based on the calculation that reducing deaths from TB would be worth US$ 43 for every dollar spent (7).
18. During the 71st session of the World Health Assembly, Member States requested the Director-General of the WHO to develop a global strategy for TB research and innovation, recognizing that enhanced and sustained support for complex research endeavours requires strong international cooperation (8).

19. The need for enhanced TB research has received additional recognition at the highest political levels, as demonstrated, for example, by the 2018 political declaration of the United Nations General Assembly High-Level Meeting (UNGA-HLM) on the fight against TB (9); the first WHO Global Ministerial Conference on Ending TB, held in Moscow in 2017; and by recent communiqués from Brazil, Russian Federation, India, China and South Africa (BRICS) and the Group of Twenty (G20) (10-12).

20. WHO has reviewed trends and drivers in innovation processes in TB prevention, diagnosis, treatment and care in the past decade, and has convened multiple consultations. The aim has been to identify steps that governments and other stakeholders can undertake, and principles that can be used to formulate policy priorities at the national and global levels, to create research-enabling environments that will help to achieve the goals and targets of the End TB Strategy (13).

21. Building on this work, and through a concerted effort of implementing a strategy on TB research and innovation, governments will be able to translate political commitments on research and innovation under the Moscow Declaration to End TB and the UNGA-HLM political declaration on the fight against TB into concrete actions.

*Commit to advancing research for basic science, public health research and the development of innovative products and approaches, which may include evidence-based, regulated medicines, including traditional medicines as adjuvant therapies, including in cooperation with the private sector and academia, without which ending the tuberculosis epidemic will be impossible, including towards delivering, as soon as possible, new, safe, effective, equitable, affordable, available vaccines, point-of-care and child-friendly diagnostics, drug susceptibility tests and safer and more effective drugs and shorter treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection, as well as innovation to strengthen health systems such as information and communication tools and delivery systems for new and existing technologies, to enable integrated people-centred prevention, diagnosis, treatment and care of tuberculosis*

*Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis [73/3]. New York: United Nations General Assembly; 2018*
2. SCOPE

22. Left to rely primarily on imperfect approaches and tools, national TB programmes are struggling with challenges both new (e.g. missing people with TB) and old (e.g. the HIV/AIDS pandemic and other comorbidities, and the spread of drug resistance). The current pipelines for new TB diagnostics, drugs and vaccines can meet some – but not all – of these challenges. Achieving progress will require a substantial increase in (and then maintenance of) funding for TB research along its full continuum, from basic science and new product development to operational/implementation and health system research. Also needed are appropriate policy frameworks that will allow for accelerated development, evaluation and equitable distribution of and access to the benefits from research and innovation.

23. To reach the End TB Strategy milestones, rapid progress towards universal access to existing TB tools and services in the context of universal health coverage (UHC) and socioeconomic development is needed. At the same time, the development and introduction of new technologies is required to make meaningful progress.

24. Policies for health innovation should align with the demands of health care systems, to ensure that innovation is affordable and accessible, and can be made available sustainably, considering that most people with TB disease are in low- and middle-income countries, or are among vulnerable and hard-to-reach risk groups of low incidence countries. In promoting health system research, there is a need for mechanisms that steer innovation towards sustainable, ethically acceptable and socially desirable interventions (communicated effectively in the affected community’s local language).

25. Investment in TB research and innovation and the necessary policies that enable research and innovation to thrive, will bring significant societal and economic returns when measured against the anticipated morbidity and mortality and associated economic tolls from TB (1, 14, 15).

26. This strategy first describes the key challenges and opportunities in TB research and innovation, then outlines the four strategic objectives that can help to tackle these challenges, discussing their potential impact on the TB epidemic (the objectives are not in order of priority):

➢ Objective 1: Create an enabling environment for TB research and innovation.¹

¹ For the purpose of this strategy “innovation” is the process of translating knowledge (generated through research) into a good or service that creates value.
➢ Objective 2: Increase financial investments in TB research\(^1\) and innovation.
➢ Objective 3: Promote and improve approaches to data sharing.
➢ Objective 4: Promote equitable access to the benefits of research.

27. This strategy also provides recommendations that are intended to support and strengthen coherence in existing national priorities and plans for health research, in order to produce research evidence and innovations for improving health and well-being in people with TB.

28. Long-term sustainability is an important element in research; hence, the strategy aims to serve as a reference for research policy-makers, funders, civil society and other relevant actors on the urgent priorities of TB research and innovation in the short and long term.

29. The successful implementation of this strategy will require cooperation between national, regional and global actors; various ministries (health, science and technology, finance, trade, social affairs, labour and international relations); and people affected by TB. Moreover, actions will need to be monitored regularly, so that national and global progress will achieve the stipulated targets.

3. THE CHALLENGES

30. **Linking research to innovation is demanding and costly**, and the road from discovery to the market or the intended beneficiary needs to include several support points, to expedite the availability of life-saving innovations.

31. Great efforts have been made to replenish the R&D pipeline for TB in the past decade (13). However, if promising tools are to progress through the pipeline and generate public health benefits, **increased and sustained funding will be needed**, particularly during the later stages of product development (including product registration, market authorization and manufacturing), as well as for operational/implementation, health system and social science research, to optimize their dissemination.

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\(^1\) For the purposes of this strategy, “research” is defined as the development of knowledge with the aim of understanding health challenges and mounting an improved response to them. This definition covers the full spectrum of research, which spans five generic areas of activity: measuring the problem; understanding its cause(s); elaborating solutions; translating the solutions or evidence into policy, practice and products; and evaluating the effectiveness of solutions (16).
32. A large share of basic research is directed towards health priorities in developed markets; thus, key elements of basic science in TB biology, vaccines, diagnostic and drug discovery will continue to be lacking unless specific dedicated funding for basic TB research is increased by funders of public health research.

33. For the private sector, developing country markets are not sufficiently attractive to incentivize the full development of promising diagnostics, treatment and vaccine candidates. New models of partnerships, investment and incentives are needed to bridge this gap.

34. Most national TB programmes have weak links to public research institutes and universities, and few incentives and resources for innovation. Coupled with weak research infrastructure, few academic researchers, and a heavy reliance on foreign funding for research in many high TB burden countries, this has slowed the pace of local innovations.

35. The Stop TB Partnership’s Global Plan to End TB, 2016–2020: the paradigm shift estimates that the world needs to spend about US$ 2 billion on TB R&D annually to deliver the necessary innovations required to end TB (17). This is a fraction of the global annual cost of the TB epidemic: US$ 20 billion per year in diagnosis, treatment and lost productivity (1, 18). However, currently, only one third of the required financial investment needs are being met. Moreover, funding is highly concentrated: 30 institutions from a handful of countries account for more than 90% of TB R&D expenditures in any given year (3).

36. TB research also suffers from complex regulatory environment in some countries. Policies that encourage research and innovation – for example, through an expedited ethics review process, and predictable and expedited product evaluation and registration processes (that do not compromise national, regional and global respect for ethical boundaries) – are critical to help transfer new ideas to the market, and to attract and sustain private sector engagement. Aligned to this need, to facilitate research, it is essential to have regulatory policies that guide data and material sharing, including the transfer of research reagents and clinical specimens.

37. About a quarter of a million people die annually from drug-resistant forms of TB. The spread of DR-TB is a major public health concern that threatens to make TB an untreatable and highly fatal disease, particularly in low-resource settings. Without an intervention, TB is projected to be one of the three biggest drivers of the economic toll of antimicrobial resistance (AMR), alongside malaria and Escherichia coli (19), with an estimated 2.5–3.0% loss to global gross domestic product (GDP) that will be worth US$ 100 trillion by 2050. Already, a disproportionatenly high share of national TB budgets is allocated to DR-TB treatment, owing to the complexity and high cost involved with the management of DR-TB. Improvements in the treatment of DR-TB will therefore increase the availability of the budget for scaling up services in other aspects of TB prevention, diagnosis, treatment and care.
38. The TB field still suffers from a lack of equitable access to medicines and technologies, and low availability/use of services by the populations that need them most. The challenges include complex legal and regulatory mechanisms for introducing new medicines and technologies, high prices of medicines due to a lack of robust competition for certain treatments (particularly for MDR-TB), manufacturers not registering products in high TB burden countries or not seeking TB indications for medicines, weak health care system infrastructure and social care, stigma and discrimination that limits access to overall care, inadequate financing for health care and medicines, local costs that drive up the price of medicines (e.g. taxes and tariffs on health products), gaps in procurement and supply chain frameworks, and a lack of awareness of opportunities to obtain care.

39. Strong health care systems are a prerequisite to achieving the goals and targets of the End TB Strategy. If health care systems have misaligned capabilities in key areas (e.g. the health workforce, drug supply, health financing and information systems), it will not be possible to respond adequately to TB. There is a need for a strong body of knowledge, including from affected communities, on effective strategies for strengthening health and social care systems so that available technologies in TB deliver the maximum impact.

40. Although there is a great deal of useful data on TB detection, pharmacovigilance, clinical testing and surveillance, a major hurdle is the timely sharing of high-quality data with policymakers and researchers, to guide policy, clinical practice and future research. Considering the serious problem of drug resistance in TB, it is particularly important for countries to adopt better practices for sharing data related to both surveillance and pharmacovigilance.

41. Specific needs in the development of TB vaccines, diagnostics and treatment – including basic science and research into health and social policy and systems – are summarized below.
3.1 Developing new TB diagnostics: needs, challenges and opportunities

42. Rapid and accurate diagnosis is critical for finding all patients with TB, starting TB treatment quickly and ensuring good treatment outcomes, thereby preventing transmission of TB to others. Yet current diagnostics have many limitations (e.g. poor sensitivity or high complexity and cost), and access to good TB diagnostics or their use remains a persistent challenge for many people. As a result, up to 36% of the estimated 10 million people with TB disease in 2017 were either not diagnosed or not formally notified to health care systems (1). Probably, some of these “missing 4 million” were people with TB who were treated late, treated with suboptimal regimens or not treated at all, resulting in continued TB transmission.

43. The past decade has seen major advances in the development of new diagnostic technologies for TB. However, the TB field still lacks adequate tests for the simple, rapid and accurate detection of TB and drug resistance, as well as better tests to either rule out TB or identify those who require confirmatory testing (i.e. a triage test) (20). Meeting these needs will require a sustained increase in funding for TB R&D, to accelerate the development, evaluation and deployment of improved tests.

44. The most promising of TB diagnostics in the current pipeline will, if successful, primarily meet diagnostic needs at the upper levels of the health care system; that is, well-equipped reference laboratories, and secondary or tertiary care centres. There are few technologies under development at the low-complexity end of the pipeline that could lead to an inexpensive and rapid diagnostic tool for use in primary care centres, which is where most people with TB first seek care.

45. From a patient perspective, a major limitation is the lack of a rapid test to detect (or at least rule out) TB, including extrapulmonary TB, in all populations, including self-testing; in addition, there is a lack of rapid tests for those who are difficult to diagnose with currently available tools. Most TB tests require a sputum specimen, which some patients (e.g. children and people living with HIV) have difficulty producing. Tests using more easily accessible samples (e.g. urine, blood, stool or breath) are urgently needed. Moreover, there is no point-of-care test that can be used at the most peripheral levels of the health care system, such as the primary care clinics where most patients first present for care, or at the household level where community health workers do TB screening.

46. From a scientific perspective, major limitations include the low accuracy of some of the current tests, either as a result of low sensitivity (i.e. high risk of false-negative results) or low specificity (i.e. high risk of false-positive results). There are no known, validated biomarkers
that can reliably predict or serve as surrogate markers of immunity to TB, disease progression or cure. Predictive biomarkers that indicate risk of progression from infection to active TB disease are key for intensifying TB prevention efforts (21), and thus for realizing the ambition of providing preventive therapy to a cumulative 30 million people by 2022. Increased investment in basic science is necessary to support the discovery, validation and translation of biomarkers (e.g. those that can identify individuals who are most likely to progress to active TB disease) into affordable clinical tools. The improved application of traditional biomarkers and the discovery of additional markers will be critical to guide the development of a rapid, easy to use and affordable diagnostic tool that can be used at point of care in low-resource settings. Such innovations are particularly important in countries aiming to eliminate TB.

47. According to WHO and a consensus of TB stakeholders, the highest priorities in TB diagnostics development include (20):

➢ a point-of-care, non-invasive and non-sputum-based test of high accuracy that is capable of detecting all forms of TB by identifying characteristic biomarkers or biosignatures (known as a biomarker test), with the capacity to identify people more likely to develop TB disease after being infected;
➢ a point-of-care triage test, which should be a simple, low-cost test that can be used by first-contact health care providers to identify those who need further testing (the triage test);
➢ a more accurate (high sensitivity and specificity) point-of-care sputum-based test to replace smear microscopy for detecting pulmonary TB (the smear-replacement test) and tests to monitor treatment response; and
➢ a rapid drug-susceptibility test that can be used at the microscopy-centre level of the health care system to select first-line regimen-based therapy (the rapid test for drug susceptibility).

48. In line with these priorities, key stakeholders in the TB diagnostics field set the following objectives for the next 5 years of TB diagnostics research (17):

➢ develop a portfolio of more accurate diagnostic tools with accompanying solutions and the necessary capacity-building in countries to ensure that results translate into patient treatment;

➢ evaluate the portfolio of new diagnostic tools and solutions – including new and cost-effective screening strategies for all forms of TB, approaches for optimized use and innovative delivery mechanisms – to demonstrate patient benefits and predict the likely impact of new tests within the health care system; and
➢ support the wide availability and appropriate use of new diagnostic tools and solutions in countries where TB is endemic, and support continuous research to further improve and build on next-generation tools.
3.2 Developing new TB treatments: needs, challenges and opportunities

49. Current treatment regimens for TB disease require combinations of multiple drugs for several months, resulting in a global cure rate of 85% for DS-TB, 55% for multidrug-resistant TB (MDR-TB) and 34% for extensively drug-resistant TB (XDR-TB). The main challenges in treatment of TB disease are the duration and complexity of treatment regimens, difficulties in adherence, toxic side-effects, drug resistance and the absence or limited availability of paediatric drug formulations for second-line treatment. TB treatment in HIV-coinfected individuals is further complicated by drug–drug interactions between anti-TB and antiretroviral therapies, as well as cumulative drug toxicities that amplify the risk of immune reconstitution inflammatory syndrome. There is a pressing need for regimens that are more effective, more affordable and nontoxic, and that allow for a shorter duration of treatment – in particular, to treat the more than half a million RR-TB infections that arise every year.

50. The advent of new TB drugs in recent years has raised the prospect of a more effective, better tolerated and possibly shorter treatment. In 2000, there were almost no new drug candidates in the TB pipeline. By 2017, the pipeline included more than 30 compounds, from early-stage research to late-stage product development. In the past 5 years, two new drugs (bedaquiline and delamanid) have been approved to treat DR-TB in some regions, as additions to existing regimens. Six compounds, including some that have been repurposed from other disease indications, are in late phases of clinical development. However, the high attrition rate in drug development – and the requirement to evaluate and treat TB using multidrug regimens – means that a greater number of novel experimental compounds are needed to make progress. More information on the current status and specific needs is provided below (22):

- **TB preventive treatment** – Long-acting drug formulations for preventing TB disease need to be developed to improve adherence and safety, increase acceptability and feasibility, and improve the cost-effectiveness of TB preventive treatment.

- **DS-TB treatment research** – Researchers are following a number of novel approaches to improve DS-TB treatment, but the overriding focus is still on reducing the duration of therapy while keeping efficacy high.

- **DR-TB treatment research** – Multiple groups are testing novel approaches that could lead to an all-oral, short-term treatment for DR-TB. Breakthroughs in treatment regimens, and drugs with high activity and novel mechanisms of action against DR-TB, would also be likely to play an important role in improved treatments for DS-TB.
51. Together, these activities will require (17, 23):

➢ sustaining the pipeline through the basic discovery of TB drugs and increased clinical trial site capacity for the testing of these medicines in high burden countries;
➢ developing shorter regimens for both TB infection, and drug-sensitive and drug-resistant forms of active TB disease, that are safer and more effective, including regimens that are appropriate for the treatment of children, pregnant women, people with HIV and people who inject drugs; and
➢ adoption, both widely and equitably, of new TB regimens together with improved drug-resistance surveillance at the country level.

52. The formation of new platforms for coordination and collaboration across drug developers is another significant achievement and opportunity. Early-stage development activities have benefited from the “TB Drug Accelerator”, which is supported by the Bill & Melinda Gates Foundation (Gates Foundation). The accelerator brings together academic institutions, pharmaceutical companies, the TB Alliance and other researchers to share the results of early-stage discovery programmes, and to advance the development of drugs that demonstrate high potential. A global AMR R&D hub, an initiative of G20 leaders, has been established to advance antimicrobial research, in collaboration with existing and new initiatives in antimicrobial basic and clinical research, and in product development (how this R&D hub will support TB research is yet to be defined) (24).

53. The field has also benefited from a greater degree of global coordination and consultation. For example, in 2016, WHO published the target regimen profiles for TB treatment, to help drug developers identify important features of new regimens for rifampicin-susceptible TB, RR-TB and pan-TB treatment (23). In 2018, WHO released a report on a technical consultation on advances in clinical trial design for the development of new TB treatments, to support developers by highlighting clinical trial characteristics that can help to advance innovative new therapies (25).
54. Vaccines are one of the most successful and effective public health interventions to reduce and even eradicate life-threatening infectious diseases. However, the only licensed TB vaccine, bacille Calmette–Guérin (BCG), has been inadequate in halting the global TB epidemic, despite its almost global administration. BCG provides moderate to good protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually), but does not protect adolescents and adults, who account for the majority of TB transmission; sustaining and improving on this progress requires sufficient production capacity, and requires countries to have better demand forecast and procurement strategies.

55. Currently, at least 12 vaccine candidates are under active clinical development, and several more are in preclinical development. Despite significant progress in rejuvenating the TB vaccine pipeline since 2000, the current candidates display little antigenic and immunological diversity. This must be corrected to stimulate the development of vaccines that work in multiple ways; for example, by preventing establishment of an initial infection (pre-exposure) or by preventing progression to disease (post-exposure). A vaccine might also serve as an immunotherapeutic agent by shortening TB treatment or reducing the risk of recurrence following treatment completion.

56. An effective vaccine may also play an important role in tackling DR-TB. By preventing disease, vaccines would reduce the need for antibiotics, an essential step for curbing AMR. Therapeutic vaccines, used in combination with drugs, could also reduce treatment duration and the risk of recurrence, thus reducing the development and spread of AMR. Recently, an experimental TB vaccine candidate (M72/AS01E) was found to be significantly protective against TB disease in a Phase IIb trial conducted in Kenya, South Africa and Zambia, in individuals with evidence of TB infection. Moreover, the study showed that a proof-of-concept human trial on the prevention of pulmonary TB in adults – the most relevant clinical outcome when considering public health need – is possible. Further development and validation of the candidate vaccine is conditional on collaboration between people with TB, research funders, governments, PPPs, PDPs, affected communities and the pharmaceutical industry.

57. There are several challenges to developing new TB vaccines. From a scientific perspective, significant challenges include a lack of validated, predictive animal models of TB infection and disease, a lack of biomarkers that can act as prospective signatures of the risk of developing TB.
TB or as correlates of protection, and an incomplete understanding of the nature of protective immunity to TB.

58. From a developer perspective, vaccine R&D is an expensive process with lengthy timelines. Industry engagement in TB vaccine development is low, owing to the lack of market incentives to invest in a disease that is concentrated in low- and middle-income countries, and that disproportionately affects the poor. Mechanisms for reducing the risk in early stages of development such as grant funding, or for initiatives that lower commercial uncertainty such as advanced market commitments, can incentivize stronger engagement from industry, biotech firms and other developers (see Table 5.1 for examples of other incentives) (28).

59. Multiple health economic evaluations have shown that new TB vaccines will be highly cost-effective and will offer substantial cost savings to health care systems and society (29). In addition, new vaccines that are effective in preventing TB disease will reduce or eliminate the often catastrophic costs of TB shouldered by patients and their families. However, a constrained funding environment has slowed progress. The Global Plan to End TB calls for about US$ 250 million per year to advance TB vaccine R&D, but the average annual investment was only US$ 95 million (3, 17).

60. WHO, together with stakeholders, has developed preferred product characteristics for new TB vaccines, to guide scientists, funding agencies and industry groups developing TB vaccine candidates intended for WHO prequalification and policy recommendations (27).

61. Public and philanthropic sources of funding are essential because the pharmaceutical industry will probably remain cautious with investments in TB vaccine R&D until early scientific hurdles are overcome. Public and philanthropic support should be directed at improving the full continuum of vaccine R&D – from early-stage research to translational science and clinical trials – this should be considered when setting the price of any vaccine that results from a collective development effort.
3.4 Operational/implementation, health system and social science research: needs, challenges and opportunities in TB

62. TB is not only a biomedical and public health crisis, but also a disease associated with several adverse social factors. Many people get ill and die from TB, owing to underlying socioeconomic determinants of transmission; occupational health risks; and ineffective implementation and use of existing interventions that result from socioeconomic barriers (including stigma, poverty, poor housing conditions and malnutrition), weak health care system infrastructure, inadequate implementation of infection prevention and control measures, and insufficient human resource capacity in health care systems.

63. Countries in low-resource settings also face challenges from weak laboratory environments that are caused by suboptimal infrastructure, and a lack of human capacity, laboratory policies and strategic plans.

64. The End TB Strategy acknowledges the need for a holistic mix of health and social interventions (e.g. addressing patient costs); it envisions universal access to high-quality TB services, as well as psychosocial support, through multisectoral action to enable patients to complete care without the risk of financial ruin or impoverishment.

65. Achieving this goal requires evidence-based approaches that would enable countries to effectively adapt and adopt global recommendations on TB prevention, diagnosis, treatment and care, and to optimize the necessary linkages and integrations with other health services and sectors, including through digital health technologies.

66. Analysis of the TB care continuum between diagnosis and cure confirms the need for collaboration with other health and social services, and with prevention and infection control measures, to maximize TB elimination efforts (with special attention to the needs of vulnerable populations\(^1\)) to deliver affordable, quality health services. Examples of other health services are those for people who smoke; people with HIV, diabetes, chronic lung disease, cancer and alcohol-use disorder; prison health care systems; and immigration, mental health and substance

\(^1\) “Vulnerable populations” are those whose situations or contexts make them especially vulnerable, or who experience inequality, prejudice, marginalization, and limits on their social, economic, cultural and other rights (30).
abuse services. Analysis of the TB care continuum also highlights the need for engagement and collaboration with affected communities, civil society and private care providers.

67. Lessons learned from scale-up efforts of TB services will help to strengthen UHC efforts in both high and low TB incidence countries, because both types of country are confronting similar barriers to improving equitable access through strengthened health and community services for vulnerable populations.

68. Developing the evidence base to better understand and address the structural, social and cultural barriers to TB prevention, diagnosis, treatment and care requires a health systems and social science research agenda that is resourced by epidemiological findings; it also requires studies of applicable health economics modelling.

69. A primary goal of an agenda for operational/implementation and health systems and social science research would be to identify multisectoral approaches to close programme performance gaps (i.e. the difference between what is recommended and what is actually delivered in routine practice) in ways that are context specific, to improve the health and well-being of patients and their families.

70. By assessing the feasibility, acceptability, effectiveness and impact of new strategies or interventions on health outcomes – and on broader benefits to communities, health care systems and economies – operational/implementation research, health systems and social science research also guide the translation of efficacy (documented by research) into effectiveness in the community. However, insufficient investment continues to be a challenge; for example, only 13% of all TB research publications in the past decade were related to operational/implementation health research (13).

71. Allocating specific funding for operational/implementation, social science, health systems, economics and policy research is key to ensuring that future health care system innovations remain needs driven, affordable and socially acceptable, with a strong degree of social ownership, for sustainable health and social care.

72. Innovative digital technologies (e.g. electronic reporting and adherence support) offer opportunities to improve the efficiency or the effectiveness of TB care (31). Implementation research could enhance the scale-up of evidence-informed products in contexts that differ substantially from the ones where they were studied.
3.5 Advancing basic science research

73. Basic research\(^1\) is vital for improving our understanding of host and bacterial factors (and their interplay), to improve knowledge and lead to new discoveries that could ultimately result in the development of new and more effective diagnostics, medicines and vaccines.

74. Although many studies have been conducted in humans and various animal models, our understanding of the natural history and pathological mechanisms of TB in humans remains incomplete. Engineering new technologies to identify, treat and prevent TB disease requires additional knowledge about the pathogen that causes TB (*Mycobacterium tuberculosis*), and a good understanding of the immune mechanisms responsible for limiting (or failing to limit) *M. tuberculosis* infection and disease in humans.

75. Possibly the most important consequence of advances in basic research is the opportunity to understand the mechanism of disease development and the associated host or pathogen predictive biomarkers or surrogate end-points associated with disease progression and cure. Such an understanding could be used to develop or to more accurately determine optimal medical interventions.

76. It is vital to establish biorepositories for the collection, processing, storage and distribution of biospecimens from the various populations affected (including women and children) to support current and future scientific investigation. Establishing and governing a repository requires considerable resources, and concerted efforts are needed to mobilize those resources. Biorepositories will enable the next generation of translational research and precision medicine for patients, in a cost-effective way.

77. Enhanced investment in basic science is essential to further increase the flow of new ideas, products and technologies into the product pipeline. The field of basic research, which is mainly conducted by academic institutions and PPPs, also contributes to a trained workforce and to the infrastructure that enables advanced discovery.

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\(^1\) Basic research is experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundation of phenomena and observable facts, without any particular application or use in view (32).
4. THE WAY FORWARD

78. A range of incentives – both financial and nonfinancial – must be initiated, and existing initiatives must be strengthened to stimulate innovation at all levels, from discovery to diffusion of technologies. Policies that encourage and support new collaborative models for research, data and IP sharing, and public–private partnerships (PPPs) are key to leveraging the comparative advantages of various actors to foster R&D, and to facilitating equitable, affordable and sustainable access to medicines and technologies.

79. Financial investment is the most important intervention in addressing challenges in TB research. Member States, particularly high TB burden countries with strong financial and research capacity, have a responsibility to establish new TB research initiatives under strong government leadership and with global collaboration, to address unmet innovation needs in the TB cascade of care, as illustrated most notably through the establishment of the BRICS TB research network.

80. Large donors, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and Unitaid, act as a “pull” mechanism to incentivize innovation and increase access to essential medicines and technologies, by providing certainty to innovators that there will be a final market for their product. However, more targeted pull mechanisms – for example, milestone prizes awarded against set criteria (e.g. the Life Prize) (33), and volume guarantees or advanced market commitments – would provide an important additional incentive. “Push” mechanisms are key to stimulating discovery by providing upfront financing – examples include direct funding to researchers by governments in the forms of grants and tax credits. Both push and pull incentive mechanisms should be needs driven, evidence based and guided by the principles of affordability, effectiveness, efficiency and equity. The medical products and technologies resulting from publicly funded incentives should be considered as public goods, ensuring public return on investment through affordability and accessibility for all.

81. Nonfinancial incentives indirectly encourage innovation at various stages of product development and delivery. They typically identify and address specific obstacles to research, product development and market access. For example, open research databases host a wealth of information and can assist in the early stages of drug discovery; they also expedite the translation of research results into national and global policy guidance. Member States should proactively ensure that data arising from publicly funded research are made available through open access platforms in a timely manner, to expedite discovery, improve care and prevent
duplication of efforts. Open access approaches to data also support the overarching goal of ensuring that the public can benefit from public investments in science. To this extent, Member States should explore how researchers, including those working in public institutions, can share their data on open research platforms without having to navigate significant administrative or regulatory barriers.

82. Ensuring that all people with TB or at risk of TB can benefit from advancement in TB research requires new models of innovation and delivery that are needs driven and evidence based, and are guided by the core principles of affordability, efficiency, equity and collaboration.

83. Thanks to the revitalization of TB research over the past 2 decades, the TB field is well positioned to play a leading role in the AMR response. TB research has much to offer the global campaign against AMR, from the coordination of PPP and product development partnership (PDP) models, to basic science insights into host–pathogen interactions and mechanisms of drug resistance, to the development of new tools to prevent, diagnose and treat DR-TB, to the refinement of public health strategies for promoting medication adherence and infection control in clinics and communities (e.g. supported by digital technologies). In an age of antibiotic resistance, investments in TB research will continue to produce broad benefits to health and medicine that extend well beyond the fight against TB.

84. In September 2018, the first-ever UNGA-HLM on TB resulted in the adoption of a political declaration outlining strong intentions and actions to address challenges in TB research (9). These intentions included commitments to increasing public spending on TB research, sharing the benefits of TB research so that no one is left behind, and creating policy and regulatory frameworks favourable to advancing the partnerships and collaborations needed to expedite research. This declaration committed all countries to contribute their “fair share” to the funding needs for TB R&D. This concept needs to be developed further and alignment sought from countries.
5. STRATEGIC OBJECTIVES

Objective 1: Create an enabling environment for TB innovation

85. The political declaration on the fight against TB calls on governments to increase resources, enhance equitable access to medicines and technologies, and improve regulatory environments to advance TB research and innovation, whose achievement depends on the concerted efforts of national, regional and global actors (9). A research-enabling environment at country level strongly influences the effectiveness of those actors’ efforts in providing innovative solutions to end TB. Here, an enabling environment is defined as a set of legal, fiscal, political and sociocultural factors that promote the capacity of conducting and using research outcomes equitably in a sustained and effective manner (Table 5.1).

86. The intellectual property (IP) and patent systems play an inadequate role in incentivizing innovation in the TB field, and as policy tools to facilitate access to essential medicines and technologies, including those that were developed with public and philanthropic funding, and through a collective effort. Poorly structured IP systems, can hamper the ability of governments to safeguard the health of their populations. Licensing patented technologies on terms oriented towards public health is one way through which IP can be used to promote innovation and facilitate equitable access. For example, TB treatment R&D needs to deliver new treatment regimens, and not just individual drugs: if IP is not made appropriately available during the R&D process, it can limit and delay innovation.

87. Many countries have a strategic approach that considers the full spectrum of policies to create, diffuse and apply knowledge, to improve efficiency in the ways that research and its benefits are regulated, managed, designed, conducted, disseminated and reported.

88. Ideally, the strategic approach should provide researchers, public research institutes and higher education institutions with incentives and opportunities to collaborate, both among themselves and with industry, in order to expedite discovery and enhance capacity-building.

89. PPPs, including PDPs, are good examples of collaborative research initiatives, which bridge public and private sectors to broaden access to new skills, sources of finance, specialized R&D infrastructure and product pipelines, so that the next decade delivers the tools needed to end TB, as stated in the UNGA-HLM political declaration on the fight against TB. Maximizing these contributions depends on governments creating appropriate incentives, and access safeguards guided by the principles of affordability, effectiveness, efficiency and equity.
90. Effective bilateral and multilateral North–South and South–South collaborations among researchers and research institutions in high-income and in low- and middle-income countries are also critical for expediting demand-driven research and cross-fertilizing research capacity-building. The contributions of the European & Developing Countries Clinical Trials Partnership and the Tuberculosis Trials Consortium (34) are examples of important collaborations to advance clinical research in TB, through knowledge generation and/or research capacity strengthening. Such programmes should be strengthened and expanded to allow for impactful and accelerated TB research, and for innovation.

91. Researchers and sponsors of clinical trials often face complex and lengthy regulatory and ethics approval processes in countries that have limited capacity to conduct timely and adequate reviews of new studies or products. These challenges highlight the importance of countries using a mixture of financial commitments and regulatory actions to create research-enabling environments.

92. Strategic and nationally owned health research capacity-building is critical for enabling sustainable advancement of health research, which in turn is critical for generating the innovations and evidence needed to protect and promote public health. Building the capacity for health research requires complementarity between national health priorities, health research policies, broader science and technology strategies, and capacity-building strategies through the education sector and professional organizations, to train and retain a critical mass of health researchers that would allow a country to reach a point of take-off in TB innovation.

93. Capacity-building initiatives should expand to include enhancing knowledge and capacity in the management of national TB programmatic data (including surveillance data). Such data provide the evidence base for understanding the impact of health interventions, and for guiding local and global decision-makers in clinical practice and policy. The careful analysis and dissemination of high-quality programmatic data is also necessary in guiding national research agendas.

POLITICAL DECLARATION ON THE FIGHT AGAINST TUBERCULOSIS

“Commit to create an environment conducive to research and development of new tools for tuberculosis, and to enable timely and effective innovation and affordable and available access to existing and new tools and delivery strategies and promote their proper use, by promoting competition and collaboration, removing barriers to innovation, and working towards improving regulatory processes and capabilities”
94. Another fundamental consideration is that the field of TB innovations needs to involve the adoption, absorption and adaptation of new knowledge and technologies developed elsewhere. Thus, national research and innovation policies should enable effective and speedy absorptive capacity at all levels of the national health care system, and in other sectors as applicable, so that patients can fully and equitably benefit from innovation. Such absorptive capacity requires the availability of frameworks based on epidemiological, clinical and economic assessments, policies and regulatory mechanisms; it also requires the infrastructure to provide patients with rapid access to life-saving technologies.

95. Civil society, indigenous peoples and affected communities can usefully support governments in the implementation of these actions by contributing to social innovations, improving patient and community engagement in research, supporting resource mobilization, improving public acceptance of innovation, and supporting innovative approaches to scientific research into eliminating the stigma and discrimination associated with TB.
**Table 5.1. Illustrative examples of enabling environment for TB research and innovation**

<table>
<thead>
<tr>
<th>Category</th>
<th>Key enabling features</th>
<th>Illustrative government-enabling actions</th>
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<tr>
<td>Fiscal</td>
<td>– Financing national TB research strategies and agendas</td>
<td>Grant funding: Upfront financing awarded through competitive, peer-reviewed processes – particularly important during the early, high-risk stages of research. Grant funding is a type of “push funding”.</td>
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<td>– Investing in global, regional and national research networks, and their joint activities</td>
<td>Tax levies: Taxes on particular products, services or activities instituted with the goal of generating resources for health R&amp;D. The international solidarity levy on airline tickets that supports Unitaid is one prominent example. Other possibilities include taxes on types of financial transactions, carbon emission taxes or the proposed Solidarity Tobacco Contribution.</td>
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<td>– Policy frameworks incentivizing PPPs, PDPs, pharmaceutical companies, biotech firms and other developers operating in TB research</td>
<td>Biomedical research bonds: Bonds issued by federal, state or local governments to finance research.</td>
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<td>– Investing in physical infrastructure (e.g. research institutes and learning centres) as well as capacity-building of human resources</td>
<td>Research innovation trusts: Trusts established to facilitate PPPs in return for tax credits issued to private sector companies. Trusts could also allow for investment by individual investors or by public retirement programmes.</td>
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<td>Tax check-off programmes: Tax payment systems that allow individuals to specify a portion of their tax payment to be directed to medical research.</td>
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<td>Budgetary set-asides: A proportion of budget envelopes set aside or earmarked for research into a particular disease.</td>
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<td>Prize funds: Milestone prizes can be awarded to compounds or technologies that meet certain criteria when they advance from one stage of research to the next. End prizes can also be issued for products that receive regulatory approval. Prize funds are an example of “pull” mechanisms.</td>
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<tr>
<td>Political and legal</td>
<td>Separating price from volume of sales</td>
<td>Voluntary initiatives and incentive mechanisms that separate the cost of investment in R&amp;D from the price and volume of sales.</td>
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<td>Advance market commitment</td>
<td>A binding contract, typically offered by a government or other financial entity, that can be used to guarantee a viable market for a product once it is successfully developed.</td>
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<td>– A research governance system that encompasses the principles of accountability, transparency, equity and responsiveness</td>
<td>– Working with all relevant stakeholders, developing and implementing a sound, fully budgeted national TB strategic plan that aligns with overall national health and science sector plans, and contains clear objectives and responsibilities for relevant stakeholders.</td>
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<td>– Public policies that harmonize the interplay between trade, development, IP and health, with the goal of protecting and promoting human health</td>
<td>– Enabling sharing of research data from publicly funded research.</td>
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<td>– Transparent and favourable policies on investments in health research, education, human capital and information technology</td>
<td>– Encouraging the publication of research results, and setting up ethical standards for the conduct and dissemination of research results.</td>
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<tr>
<td>– A research governance system that supports the meaningful engagement of civil society, indigenous peoples and affected communities in research, and that incentivizes cross-sectional partnerships and coordination across national and international agencies</td>
<td>– Devolving resources to address TB research needs, including for assuring capacity-building in the conduct of health research.</td>
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<tr>
<td>– Setting policies and strategies that incentivize bilateral and multilateral cooperation in research, including through multisectoral collaboration</td>
<td>– Supporting civil society engagement in health research.</td>
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<tr>
<td>Regulatory incentives</td>
<td>Research decisions</td>
<td>Decisions that make research, as far as possible, relevant and responsive to the needs of end users, and that provide sufficient incentives to guide research towards global and national health priorities.</td>
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<td>– Expedited and predictable</td>
<td>Expedited and predictable</td>
<td>Regulatory frameworks that allow for expedited and predictable timelines for research protocol review processes (including for clinical trials), considering the urgency of the</td>
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<td>Sociocultural</td>
<td>Community engagement</td>
<td>– Supporting civil society engagement in research advocacy, policy dialogue and implementation, particularly for innovations to address issues of stigma in TB.</td>
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<td>– Norms of inclusiveness, equity and fairness</td>
<td>– Ensuring that the benefits of research are shared equitably among all people, including girls and women, and marginalized and disadvantaged societal groups.</td>
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<td>– Reducing barriers that unnecessarily slow the conduct or use of research outcomes</td>
<td>Empowering regulatory authorities to expedite registration of generic products</td>
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<td>process for TB research protocol review</td>
<td>end TB response. Delayed or unpredictable research protocol review processes significantly reduce the incentives for research.</td>
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<td>Orphan product legislation</td>
<td>Incentives, or adjustments to registration requirements, to attract developers to enter an otherwise unattractive market. Incentives can include waived registration fees, development grants, priority review eligibility or tax credits.</td>
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<tr>
<td>Breakthrough therapy designation</td>
<td>Regulatory incentive intended to expedite development programmes for breakthrough therapies that show preliminary clinical evidence of improvement over existing therapies. Breakthrough therapy designation could entail expedited or rolling review in advance of full submission, or the opportunity to receive frequent guidance from regulators.</td>
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<tr>
<td>Fast-track designation</td>
<td>Similar to breakthrough therapy designation, but granted at earlier stages of development with nonclinical or clinical demonstration of potential to address unmet needs.</td>
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<td>Compassionate use</td>
<td>A way of making available a promising medicine that has not yet been otherwise authorised (licensed) for that specific condition, to help patients with life-threatening, long-lasting or seriously disabling illnesses.</td>
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<td>Patent pools</td>
<td>A way of encouraging open, collaborative development through pooling of IP and facilitating access to new medicines through market competition. The Medicines Patent Pool is an example of a patent pooling mechanism that has played a pivotal role in facilitating access to new medicines in HIV and hepatitis C.</td>
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HIV: human immunodeficiency virus; IP: intellectual property; PDP: product development partnership; PPP: public–private partnership; R&D: research and development; TB: tuberculosis.
Objective 2: Increase financial investments in TB research and innovation

96. In the 2011–2015 Global Plan to Stop TB, the New Tools Working Groups of the Stop TB Partnership estimated the amount of funding required in each research area to enable scientific progress to meet the ambitions of the SDGs and End TB Strategy (about US$ 2 billion per year). However, actual expenditures during the past 5 years consistently fell short of these targets in every category (13, 36).

97. The present level of R&D expenditure is both inadequate and not commensurate with the global burden of TB. The disease is responsible for nearly 2% of disability-adjusted life-years (DALYs) but receives only 0.25% of the estimated US$ 265 billion spent on medical research annually (13). Considering that drug-resistant forms of TB account for a quarter of annual deaths due to AMR, TB is expected to be one of the three biggest drivers of the economic toll of AMR (19).

98. Funding for TB research and innovation is heavily reliant on public sector institutions (66% in 2017). Across sectors and research areas, funding is highly concentrated in a handful of institutions from a few countries, highlighting the need to build a wider, more diverse funding base.

A 2018 report found that Australia, Canada, European Union, Germany, India, Netherlands, South Africa, South Korea, the United Kingdom and the United States accounted for at least 60% of global TB R&D funding (3).

99. Between 2009 and 2015, total industry expenditures on TB research and innovation amounted to less than 0.25% of overall R&D spending by pharmaceutical companies over that period. Spending by private sector companies has also been progressively declining over recent years (3). This can be attributed to several major pharmaceutical companies closing their TB drug discovery programmes, as part of an industry-wide shift away from research into anti-infective agents (37). Pfizer and AstraZeneca ended their programmes on anti-infective agents, and Novartis significantly scaled back its TB drug R&D activities during this period (38-40). These
closures reflect the lack of a strong market incentive to attract and keep industry involved in TB R&D in particular, and in antibiotic development more generally.

100. Declining investments by industry and flat expenditures from existing major funders point to the need to bring new resources and funding models into the TB research field, and for innovative incentives tailored to encourage pharmaceutical companies, biotech firms and other developers to engage in TB research.

101. The political declaration of the UNGA-HLM on the fight against TB describes TB R&D as a “shared responsibility”; it articulates a commitment to ensuring that “all countries contribute appropriately to research and development”, including through “global collaboration to ensure accelerated development of accessible and affordable diagnostic tools, and shorter and more effective oral regimens, including those that meet the unique needs of children; and through an urgent response to multidrug-resistant tuberculosis and the scale and severity of local and national epidemics of the disease” (9).

102. Collaborative financing is an important way to “do more” with existing resources, by joining forces to conduct high-impact multisite and multidisciplinary studies. In particular, collaborative funding for large, late-stage clinical trials is urgently needed, to create pull and push incentives, and to reduce the lag time in bringing promising breakthroughs to the approvals stage.

103. Collaborative financing is most effective when the various contributions of funders are complementary to one another and align with affordability, access and health research needs in both high incidence and low incidence countries. In addition, meaningful engagement of civil society, indigenous peoples and affected communities has an important role in guiding the efficient use of resources, by helping to ensure that research reflects patient and community needs.

104. With growing scientific and economic capacity in low- and middle-income countries, high TB burden countries have a responsibility to increase health research financing for TB. This is particularly so for the BRICS countries, which account for more than 40% of the global TB disease burden in terms of both TB incidence and TB deaths, and about 50% of the burden of DR-TB. Increased financial investment, coupled with greater use of institutions by the BRICS countries and a more integrated way of working collaboratively, can help to transform the TB R&D field by bringing in new resources and innovation.
Objective 3: Promote and improve approaches to data sharing

105. Sharing of different types of high-quality data (e.g. programmatic, clinical trial, epidemiological and genomic data) fosters scientific progress, promotes discovery through the testing of new hypotheses, improves future data collection methods (standardization) and allows for the analysis of similar data from multiple sources, to inform national and global policy-making in a cost-effective and timely manner. At both the national and sub-national levels, there is a need to use epidemiological and programmatic data to improve the impact and reach of TB prevention and care efforts.

106. Sharing and providing open access to research data in a responsible and timely manner (including release of preliminary data before publication, when necessary for public health policy decision-making) provides greater returns from public investment in research by maximizing the impact of existing knowledge. Several countries have research data access arrangements (e.g. regulatory, policy and procedural frameworks) to maximize scientific and social returns on investment. Also, several voluntary international data-sharing platforms have been successful in leveraging multicountry data to advance global health; for example, the Global Initiative on Sharing All Influenza Data (41).

107. Some examples of global scientific databases in TB that are rapidly becoming a crucial part of the infrastructure of the global science system are TB-ReFLECT (42) and TB pacts (43) (both collaborative, standardized, patient-level data-sharing platforms from Phase III TB treatment trials), and TB portals (44) (an integrated clinical, medical imaging and bacterial genomic data-sharing platform). Another example is ReSeqTB, a new bioinformatics platform for DR-TB surveillance programmes based on sequencing technologies, which supports the analysis and interpretation of de-identified pathogen genetic information from multicountry surveillance data (45). The aim of this platform is to support national and global level surveillance of drug resistance and to stimulate new research and discovery in prevention, diagnostics and treatment. The WHO Global TB Programme also routinely conducts meta-analysis of independent individual patient data, to support its work in TB treatment policy (46, 47).

108. At country level, there is a need to allocate adequate and timely support to contribute to the national and global data needs for policy-making and discovery; make efficient use of resources in TB research; and effectively put new knowledge to use, without compromising national IP laws and the protection of privacy and confidentiality.
Objective 4: Promote equitable access to the benefits of research

109. The End TB Strategy stipulates that more effective diagnostics, vaccines and treatment options for TB infection, DS-TB and DR-TB should be available, affordable and accessible to all who need them, to curb the epidemic.

110. In many parts of the world, patients go without the necessary treatment or receive poor-quality services and treatments, because of poor access to and use of new technologies and medicines. Reasons for this situation include financial cost, risk factors associated with voluntary and involuntary displacement, limited or unpredictable availability of medicines by manufacturers, regulatory challenges that result in complex and lengthy product evaluation and registration procedures, manufacturers not registering products in countries, weak national procurement processes, inadequate health and social service availability, stigma and discrimination, and slow adoption of or poor adherence to the International Standards of TB Care (48).

111. Some medicines are not used to their full potential because of country regulatory frameworks that limit off-label use, or because of clinician preference or resistance to change practices; also, the availability of some medicines is constrained owing to delays in registration in countries and high prices. Initiatives and incentive mechanisms that separate the cost of investment in R&D from the price and volume of sales, as well as increasing transparency on overall R&D cost (including investments, incentives and subsidies) throughout the value chain, are key to lowering pricing barriers for access to new medicines, vaccines, diagnostics and other health technologies (9, 22, 35).

112. The high price of medicines, due to the lack of robust competition for certain treatments, is a particular challenge for MDR-TB care. Public health–oriented voluntary licenses, such as those negotiated by the Medicines Patent Pool, can accelerate availability of quality-assured generics for use in low- and middle-income countries, which would bring down prices and facilitate the scaling up of treatment. Governments should work to create a procompetitive environment for the marketing of medicines, by reducing barriers to the entry of generics. Moreover, where the public sector contributes substantially to the development of medicines and technologies, affordable access should be assured.

113. WHO’s prequalification programme supports access to safe, effective and quality-assured diagnostics, medicines, vaccines, and equipment and devices related to immunization for high burden diseases of poverty (including TB), by ensuring that they meet global standards of quality, safety and efficacy before they are recommended to countries. In addition, WHO sets norms and standards, develops guidelines and advises Member States on issues related to access and quality assurance of medicines for national and international markets.

114. Global financing mechanisms, such as Unitaid and the Global Fund, are crucial in supporting access to life-saving technologies and medicines in high TB burden countries.
115. The Global Drug Facility (GDF), which was launched in 2001, is negotiating more affordable and consistent prices for quality-assured TB drugs and diagnostics, by consolidating demand from different countries.

116. The global TB market includes many countries and actors in the private sector that are not receiving support from the mechanisms mentioned above. Hence, there is a need for support for national regulatory channels in the procurement of high-quality biomedical interventions.

117. Civil society and affected communities can have a valuable role in providing a public interest perspective on issues of equitable access and affordability, but meaningful engagement strategies and platforms are needed to include this knowledge base in discussions about access policy. In return, evidence-based and culturally appropriate approaches to building awareness and knowledge about TB prevention, treatment and care need to be adequately funded and appropriately targeted to those communities most at risk. This goes hand in hand with making TB prevention, treatment and care universally accessible and affordable.

118. WHO’s access roadmap for medicines, vaccines and other health products 2019–2023 (49) describes how WHO intends to work to improve equitable access to essential medicines, vaccines and other health products during the full cycle of innovation, from R&D to quality assurance, regulatory approvals and market authorization, and to supply chain management, prescribing, dispensing and use.

119. Along with ensuring access to life-saving technologies and medicines, countries should pursue proper drug safety monitoring and management, and should share real-world data and evidence with relevant actors, including regulatory agencies and WHO, to support global policy decision-making. It is through the collective contribution of all countries that sustainable gains can be made in monitoring the safety and increasing the public health impact of medical innovations.
6. RECOMMENDATIONS

Objective 1: Create an enabling environment for TB innovation

Potential measure of effectiveness: Extent of government engagement in research networks and PPPs for TB research and innovation, and extent of time it takes to process regulatory approvals for clinical trials and product evaluations

Member State action

120. Streamlines1 and harmonizes regulatory processes for the review of clinical trials and other research activities in order to expedite TB research; and strengthens capacity to evaluate products studied elsewhere, to allow impactful products to be imported for the benefit of patients.

121. Develops country-specific TB research agendas and strategic plans that are aligned with the national health research strategic plan, to expand and accelerate TB research at the country level through capacity-building and collaboration among other actors in the innovation system (particularly in the national science, technology, education and development sectors). – To evaluate the success of such efforts, sets up systems to observe and report on TB research undertaken at the country level and its impact, in the form of national TB research networks; such networks can also serve as platforms for bringing together stakeholders to develop country-specific research plans.

122. Strengthens existing PPPs and PDPs nationally and globally (and, where necessary, creates new partnerships), and incentivizes further engagement of pharmaceutical companies, biotech firms and other developers in research and development of vaccines, medicines, diagnostics and other health technologies to improve TB prevention and care.

123. Increases the number and profile of local researchers engaged in TB research, and the necessary incentives to retain researchers in employment; also, develops the required higher-level and specialized trainings for new researchers, research infrastructure and incentives to stimulate innovation and increase absorptive capacity to innovation.

124. Participates in and funds international collaborative research initiatives to support the development of new approaches and medical innovations to fight TB through North–South and South–South, bilateral, regional and global collaborations and research networks, in a manner that facilitates equitable and affordable access to the benefits of research, as stated in the political declaration of the UNGA-HLM on the fight against TB.

125. Engages civil society and affected communities to contribute to TB research, with a view to increasing the quality, relevance and acceptability of innovation by integrating civil society’s expectations, needs, interests and values into the R&D process.

1 Streamlining can involve creating a predictable process for ethics and regulatory approvals, and providing a simpler pathway for the transfer of biological samples, study drugs, research reagents and equipment in and out of a country, taking into account protection of privacy and confidentiality. Lack of such logistical considerations can increase the cost and complexity of clinical trials, and result in avoidable delays.
Secretariat action

126. Initiates a process for the relevant stakeholders to agree on consensual global TB research priorities, to stimulate the development of evidence for policy around knowledge gaps that are critical for countries and communities.

127. Coordinates capacity-building efforts for national TB programme staff from low- and middle-income countries, to strengthen their capacity to use national data, conduct research and use research evidence for decision-making, together with the Special Programme for Research and Training in Tropical Diseases.

128. Promotes collaborations between TB researchers in different countries around common research goals, and promotes multisite and multidisciplinary research. This will rely on existing or new international TB research networks and consortia dedicated to discovery, preclinical, clinical, operational/implementation, health system and social science research.

International and national partners’ action

129. National and international stakeholders in TB research – including academia, PPPs and PDPs – should encourage and support Member States in forging in-country research networks, as well as regional and global networks of TB research, to advance the implementation of high-quality research in line with national and global TB research priorities.

130. Research funders and sponsors should commit to strengthening community engagement in TB clinical research.

131. Civil society and affected communities should advocate for and support the development and implementation of health research policies that help to advance person-centred health and social care, and are inclusive of vulnerable groups and marginalized communities.

132. The pharmaceutical industry should cooperate with PPPs and PDPs, and increase industry’s meaningful contributions to their activities.

133. Professional medical associations, funders and relevant foundations, and nongovernmental organizations (NGOs) should support high TB burden countries in strengthening clinical trial capacity and regulatory infrastructure.
**Objective 2: Increase financial investments in TB research and innovation**

**Potential measure of effectiveness:** At the country level, proportion of gross domestic expenditure on research and development (GERD) that is allocated to TB research

**Member State action**

134. Progressively increases TB R&D funding in relation to GDP and gross domestic expenditure on research and development (GERD) on health R&D.

135. Implements the commitments on TB research financing that have been made in the political declaration of the UNGA-HLM on the fight against TB, together with incentives that separate the cost of investment in R&D from the price and volume of sales.

136. Sets a target contribution for TB research funding that includes both domestic funding and funding for international collaboration. For the latter, streamlines its funding model with others, to allow for meaningful and impactful collaborative financing, taking into account the research needs of high TB burden countries.

**Secretariat action**

137. Monitors the financial flows to the various disciplines of TB research and the state of the R&D pipeline under the auspices of the WHO Global Observatory on Health R&D and relevant advisory mechanisms, to allow for the assessment of the TB R&D landscape.

138. Consults with Member States, philanthropic organizations and the pharmaceutical industry on innovative financing mechanisms to expedite the development and diffusion of more affordable and more effective vaccines, diagnostics, medicines and technologies.

**International and national partners’ action**

139. Research funders in both the public and private sectors (including the pharmaceutical industry) should invest in the development of effective and low-cost tools, and of appropriate formulations (including for children) for preventing, diagnosing and treating TB infection and disease in different subpopulations (including pregnant women, people living with HIV and other comorbidities); they should also increase the allocated funding for operational/implementation, health care system and social science research, including for effective delivery models that are programme and patient friendly.

140. International funding agencies and development assistance organizations should commit to larger and longer term funding for TB research, to foster capacity-building and allow discoveries to mature.

141. International funders and foundations should better align and harmonize their funding programmes to country and global TB research agendas and adopt flexible spending mechanisms to allow for the development of responsive science and technology initiatives.

142. Bilateral and multilateral donor agencies, especially those already involved in the large-scale funding of TB care programmes (e.g. Global Fund), should consider allocating a dedicated budget for operational/implementation, social, economic and health system research.

143. International funders and donor agencies involved in AMR research should address the challenges presented by DR-TB as a key component of the global AMR response.
Objective 3: Promote and improve approaches to data sharing

**Potential measure of effectiveness:** Extent of government efforts to establish/strengthen a well-resourced national open data initiative for TB research, from different disciplines and sectors, and government contribution to global data-sharing mechanisms in a timely and consistent manner to guide global policy decision-making processes and development of new tools for TB

**Member State action**

144. Establishes or strengthens national health information and vital registration systems for the collection of high-quality data that allow for reliable tracking of the TB epidemic (in terms of absolute numbers and trends in incidence and deaths), so that national, regional and global trends can be detected and monitored.

145. Develops or strengthens a policy of open access to and open data for the results of scientific research (both nationally and globally) that receives public funds, to reduce duplication of efforts, expedite research and facilitate the translation of evidence to national and global polices on TB prevention, diagnosis, treatment and care, while maintaining patient privacy and confidentiality.

146. Fosters voluntary technology-transfer policies that enable the development and diffusion of knowledge, and the wider transfer of evidence to policy and practice. For example, initiatives such as WIPO Re:Search and patent licensing mechanisms such as the Medicines Patent Pool can complement TB R&D efforts by facilitating partnerships and the licensing of intellectual property among organizations.

**Secretariat action**

147. Supports Member States by facilitating protected data sharing, to produce global and regional trends of the TB epidemic, and to review the effectiveness, safety and applicability of medical interventions, for policy guidance.

148. With support from partners and Member States, establishes a global TB data platform for sharing programmatic, survey or surveillance, clinical trial and genome-sequencing data, as well as de-identified drug safety monitoring data, to support the development of policy guidance at both global and national levels; this platform should complement existing platforms for sharing and storing data, while maintaining patient privacy and confidentiality.

149. Provides technical assistance on the conditions necessary for the promotion of open data principles and implementation at global level, especially in the context of bilateral, multilateral and international collaborative research initiatives and networks.

**International and national partners’ action**

150. International funders, partners, professional associations and aid and technical agencies should support low- and middle-income countries to improve data quality and accessibility, through targeted capacity-building initiatives.

151. International funders of TB research should incentivize open access to research data and intellectual property generated through their funding.
Objective 4: Promote equitable access to the benefits of research and innovation

Potential measure of effectiveness: Proportion of people with TB or at risk of TB with affordable access to the best proven standard of diagnosis, treatment and prevention; and the percentage of TB-affected households that experience catastrophic costs as a result of TB

Member State action

152. Ensures the availability of the most recent guidelines on the prevention, diagnosis and treatment of TB, together with the necessary human, infrastructural and material resources (e.g. adequate availability of medicines and technologies) at all levels of the health care system, including those catering to key TB populations (e.g. prisoners and migrants).

153. Includes TB technologies and medicines in the national essential medicine and technology list, and retains effective supply-chain management, to facilitate the procurement and use of high-quality medicines and technologies. To facilitate this, allocates funding for operational/implemention, social, economic and health system research to optimize effective and efficient delivery of research benefits, particularly for vulnerable groups in both high and low incidence countries.

154. Harmonizes policies on trade, health and IP through multisectoral collaborative frameworks, to address access and innovation simultaneously to meet the needs of people infected with TB, as highlighted in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (50); the UN report on innovation and access to medicines (51); and the World Health Assembly resolution on improving the transparency of markets for medicines, vaccines and other health products (22).

155. Develops regulatory frameworks and fosters partnerships across sectors to reduce trade and distribution markups on the prices of essential TB medicines and technologies, and to support policies that promote transparency in the public disclosure of clinical trial data and R&D costs.

156. Supports replenishment of global financing mechanisms such as Unitaid and the Global Fund, which are enabling access to essential medicines and innovations to the most vulnerable populations.

Secretariat action

157. Provides technical assistance as part of the implementation of the World Health Assembly resolution on improving the transparency of markets for medicines, vaccines and other health products and WHO's access roadmap for medicines, vaccines and other health products 2019–2023 (49), which is being developed to support Member States to improve access to medicines, vaccines and technologies.

158. Collaborates with other relevant international and regional organizations (e.g. the World Trade Organization, World Intellectual Property Organization, the UN Development Program, and the UN Conference on Trade and Development) to provide, upon request, technical support to Member States on public health related aspects of intellectual property and trade policies.

159. Sets norms and standards, develops guidelines and advises Member States on issues related to quality assurance of medicines in national and international markets, and assists Member States in building national regulatory capacity through networking, training and information sharing.

International and national partners’ action

160. Pharmaceutical companies should enable affordable and sustainable access to essential TB medicines, vaccines and technologies in countries where there are high numbers of poor patients, and/or where public health programmes are chronically underfunded and without access to generic, more affordable equivalents.

161. Pharmaceutical companies should be encouraged to adopt patent and enforcement policies that facilitate greater access to TB vaccines, medicines and technologies needed in low- and middle-income countries. Companies are also encouraged to grant non-exclusive voluntary licences in these countries,
where this will facilitate greater access to safe, effective and high-quality products, and to accompany such licences with data exclusivity waivers and technology-transfer activities.

162. **NGOs and partners** – including global mechanisms such as the GDF, Unitaid and the Global Fund – should support Member States in the strengthening and implementation of national regulatory practices for efficient stewardship and access to TB vaccines, medicines and innovations.

163. Countries and pharmaceutical companies (including generic producers) should promote the voluntary transfer of technology and local production of biomedical tools to low- and middle-income countries with manufacturing capacity, where this makes economic sense and promotes the availability, accessibility, and affordability of needed products.

164. Civil society, indigenous peoples and affected communities should support governments and partners in the development, implementation and monitoring of policies and frameworks for access to TB medicines, technologies and services.

**7. IMPLEMENTATION AND MONITORING PROGRESS**

165. It is expected that the proposed strategy will substantially help countries to accelerate the implementation of the UNGA-HLM political declaration on the fight against TB and the Moscow Declaration to End TB. Governments have a key role in facilitating the strengthening of policies related to the four main objectives stated in this strategy. However, governments will vary in the approaches they use, owing to differences in their level of economic, institutional, regulatory and human resource capacity, and differences in their approaches to policy (e.g. regarding the role of public versus private sectors in research and innovation). Translating this strategy into effective and appropriate actions at both local and national levels may require the development of a national strategy or roadmap for TB research that is framed around country needs and context.

166. Systematic monitoring and evaluation of efforts by Member States, appropriate to each country’s context, is needed to ensure that the necessary policy changes are being made and implemented, and to track whether the implemented policies are having an impact that is linked to achieving the goals and targets set in national TB strategic plans and the End TB Strategy. The implementation of a multisectoral accountability framework to accelerate progress to end TB presents one opportunity to monitor such progress, which would allow policy-makers to learn from ongoing efforts, and from the exchange of experiences and good practices across countries (52).

167. WHO will continue to provide a platform for mutual learning; for example, by identifying good policy practices and fostering international cooperation.

168. It is essential that global funders, researchers, the private sector, civil society, indigenous peoples and affected communities, and other relevant research actors support governments in the development, implementation and monitoring of policies and frameworks that will accelerate progress towards eliminating TB as a public health threat by 2030.
REFERENCES


