



# A Draft Global Strategy for Tuberculosis Research and Innovation

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## SUMMARY

1. Tuberculosis (TB) is the leading cause of death from a single infectious agent, and one of the leading causes of death from antimicrobial resistance. The Sustainable Development Goal (SDG) target for TB, to end the epidemic by 2030, builds on the historic gains made under the Millennium Development Goals. More specific targets for 2030, set out in the WHO Global strategy and targets for tuberculosis prevention, care and control after 2015 (WHO End TB Strategy) (1), include ensuring that no family is burdened with catastrophic expenses as a result of TB, and achieving a 90% reduction in TB deaths and an 80% reduction in TB incidence compared with rates in 2015, with targets for further reductions in deaths and incidence (95% and 90%, respectively) by 2035. An enormous gap persists, however, between current reality and the SDG vision.
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 (including the complex challenges created by the rise of drug-resistant forms of TB). The End TB Strategy stipulates that major technological breakthroughs are needed by 2025 to enable a rapid acceleration in the rate of TB incidence reduction. Delivering on these targets means prioritizing a multisectoral approach to developing and equitably disseminating the most appropriate medical and programmatic innovations. There are, however, numerous challenges and gaps to be overcome with regard to research in, innovation for, and access to TB vaccines, medicines, technologies and services.
3. The political declaration of the 2018 High-Level Meeting of the General Assembly on the fight against tuberculosis (2), which followed the WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era, held in Moscow in 2017, was a renewed expression of Member States' commitment to strengthening national and global efforts in the fight against TB. This strategy aims to provide countries with a framework to facilitate implementation of the commitments on research and innovation articulated in those declarations.
4. The Global Strategy for Tuberculosis Research and Innovation will support the efforts of governments and other stakeholders to accelerate TB research and innovation, and improve equitable access to the benefits of research. It will do so through clear objectives and recommendations, as set out below:
  - (a) Create an enabling environment for high-quality TB research and innovation to increase capacity to conduct research and use its 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 the expectations, needs, interests and values of civil society into the research and development (R&D) process.

- (b) 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 setting a target contribution for the conduct of essential social, health system and operational/implementation research to support the effective scale-up of innovative strategies and tools.
  - (c) Promote and improve approaches to data sharing to advance scientific discovery, reduce duplication of effort, and facilitate the translation of evidence into national and global policies on TB prevention, diagnosis, treatment and care.
  - (d) Promote equitable access to the benefits of research and innovation by strengthening global and national access to TB vaccines, medicines and diagnostics, and through 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, thereby ensuring access for all to essential quality TB health products and services without 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, Member States will be able to accelerate progress towards the milestones and targets of the End TB Strategy. They may consider developing a comprehensive national strategy or roadmap for TB research and innovation to coordinate implementation of this global strategy at the national level.
6. In the spirit of fast-tracking efforts to end TB, all stakeholders must make concerted efforts and collaborate. This document therefore 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 committing to the investments or partnerships (or both) needed to accelerate innovation.

## 1 INTRODUCTION

7. 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 (3, 4). Despite this enormous toll on health and well-being, the response to TB has been slow and underfunded, particularly in the area of research (5).
8. At the Sixty-seventh World Health Assembly, WHO Member States adopted the End TB Strategy. In so doing, they set ambitious targets to end the TB epidemic by eliminating the catastrophic expenses caused by TB and to achieve a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015, in line with the SDGs. Targets were set for further reductions in deaths and incidence (95% and 90%, respectively) by 2035 (1, 6).
9. The 2015 Millennium Development Goal target to halt and reverse TB incidence has already been achieved at the global level. Effective diagnosis and treatment of TB saved an estimated 58 million lives between 2000 and 2018 (3).
10. Although progress has been significant, it remains insufficient. In 2018, an estimated 10 million people around the world developed active TB disease (5.7 million men, 3.2 million women and 1.1 million children), 8.6% of whom were individuals living with HIV. About half a million people develop drug-resistant TB (DR-TB) each year, challenging countries' diagnostic, preventive and treatment capabilities (3).
11. The third pillar of the End TB Strategy – research and innovation – recognizes that to substantially reduce TB incidence and mortality will require developing and introducing new tools and strategies, as well as promoting universal access to, and better use of, existing technologies. New tools and strategies include: rapid point-of-care tests for diagnosing TB infection and TB disease and for detecting drug resistance; shorter, safer regimens for treating TB infection and drug-sensitive TB (DS-TB); shorter, safer and more effective treatment for DR-TB; a TB vaccine that is effective before and after exposure and across a range of age groups and geographical settings; and innovative strategies to address the social and environmental drivers of TB.
12. The current pipelines of new diagnostics, medicines and vaccines do not meet the needs identified above. There is a growing understanding among stakeholders that the pharmaceutical industry alone cannot be responsible for the majority of drug discovery and development in disease areas characterized by complex pathologies, high resource needs and limited investment. A collaborative approach is therefore vital to move TB research forward, sharing resources, benefits and risks across the value chain of product development. Public–private partnerships are the most prominent example of such an approach. These enable governments,

academia, patient organizations and the private sector to create an environment for open sharing of science and resources.

13. Basic biomedical research and disease biology are needed to give new insights into the molecular and biochemical basis of diseases. Such insights would foster a high degree of innovation in TB prevention, diagnosis, treatment and care, as well as 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. Such strategies will allow the rapid and equitable introduction and optimization of new products and approaches, tailored to countries' specific needs.
15. To increase the scope and quality of TB research activities, mechanisms are needed to facilitate collaboration between researchers working on needs-driven topics in different countries, and to promote multidisciplinary research and capacity-building at multiple sites through existing or new national or international TB research networks and consortia that combine discovery and implementation research (preclinical, clinical, operational, implementation and health system research, economic evaluation and social science). WHO or an institution working on its behalf could convene workshops or meetings for such networks to share information and increase the extent and quality of TB research activities (7).
16. TB has several socioeconomic and environmental drivers, as a result of which, effective measures for prevention, diagnosis, treatment and care require partnerships and collaboration between various stakeholder groups (government, academia, civil society and industry) and sectors (health, science, social, environment and finance). Such partnerships and collaboration can improve the effectiveness and impact of new and existing interventions.
17. Progress in addressing TB will bolster efforts to achieve several SDG targets (and vice versa), particularly those on eradicating poverty in all its forms, ending the AIDS epidemic, reducing premature mortality among women and children, strengthening health systems, and supporting research and development in vaccines and medicines for diseases predominantly affecting less economically developed countries. The Copenhagen Consensus Center has identified spending on TB as a “best buy”, based on the calculation that reducing deaths from TB would save US\$ 43 for every dollar spent (8).
18. At the Seventy-first World Health Assembly, Member States requested the WHO Director-General to develop a global strategy for TB research and innovation, recognizing that enhanced and sustained support for complex research endeavours requires strong international cooperation (9).

19. The need for enhanced TB research has been acknowledged at the highest political levels, as demonstrated, for example, in the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis (2); the first WHO Global Ministerial Conference on Ending TB in the Sustainable Development Era: a Multisectoral Response, held in Moscow in 2017; and recent communiqués from Brazil, the Russian Federation, India, China and South Africa (BRICS) and the Group of Twenty (G20) (10-12).
20. Over the past decade, WHO has reviewed innovation trends and drivers for TB prevention, diagnosis, treatment and care, and has held multiple consultations. The aim has been to identify steps that governments and other stakeholders can take, and principles that can be used to formulate policy priorities at the national and global levels, to create research-enabling environments that will help meet the goals and targets of the WHO End TB Strategy (1).
21. Building on this work, and with a concerted effort to implement this 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 (12) and the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis (2) into concrete actions.

POLITICAL DECLARATION ON THE FIGHT AGAINST TUBERCULOSIS

*"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"*

## 2 SCOPE

22. National TB programmes are struggling with challenges new and old: failing to detect people with TB; the HIV/AIDS pandemic and other comorbidities; and the spread of drug resistance. While the use of existing tools could be improved, pipelines for new TB diagnostics, drugs and vaccines offer further opportunities to meet many of these challenges. Accelerating progress will require a substantial increase in (followed by maintenance of) funding for TB research along its full continuum, from basic science and new product development to operational, implementation and health system research. Appropriate policy frameworks allowing for accelerated development and evaluation of research and innovation, and equitable distribution of and access to the accompanying benefits, are also needed.
23. To reach the milestones of the End TB Strategy, rapid progress must be made towards universal access to existing TB tools and services in the context of universal health coverage and socioeconomic development. At the same time, new technologies must be developed and introduced to make meaningful progress.
24. Innovation policies should respond to the needs of patients and health care systems, to ensure that innovations address both health and non-health determinants of TB, are affordable and accessible, and can be made available sustainably. The latter is particularly important, since most people with TB disease are in low- and middle-income countries, or are among vulnerable and hard-to-reach risk groups in both low and high TB 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 in 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 of TB (3, 13, 14).



26. This strategy describes the key challenges and opportunities in TB research and innovation, and then outlines four objectives of equal priority that can help to overcome these challenges, discussing their potential impact on the TB epidemic:
- Objective 1: Create an enabling environment for TB research<sup>1</sup> and innovation.<sup>2</sup>
  - Objective 2: Increase financial investments in TB research and innovation.
  - Objective 3: Promote and improve approaches to data sharing.
  - Objective 4: Promote equitable access to the benefits of research.
27. The strategy also offers recommendations intended to support and strengthen coherence in existing national priorities and plans for health research, 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; 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 terms.
29. The successful implementation of this strategy will depend on 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, regular monitoring will be needed to ensure that progress at both the national and global levels is on track to achieve the stipulated targets.

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<sup>1</sup> 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 (15).

<sup>2</sup> For the purpose of this strategy, “innovation” is the process of translating knowledge (generated through research) into a good or service that creates value.

### 3 CHALLENGES

30. Linking research to innovation is demanding and costly, and the road from discovery to the intended beneficiaries needs to include several support points to expedite the availability of life-saving innovations.
31. Great efforts have been made to replenish the research and development pipeline for TB over the past decade (16). If promising tools are to progress through the pipeline and bring public health benefits, however, increased and sustained funding will be needed, particularly during the later stages of product development (including product registration, market authorization and manufacturing), to optimize their dissemination and to support operational, implementation, health system and social science research.
32. A significant proportion of basic research is aimed at health priorities in developed markets; key elements of basic science in TB biology, vaccines, diagnostics and drug discovery will remain lacking unless specific, dedicated funding for basic TB research is increased.
33. Developing country markets are not sufficiently attractive to the private sector to incentivize the full development of promising diagnostics, treatment and vaccine candidates. New partnerships, investment and incentive models are needed to bridge this gap.
34. Most national TB programmes have weak links to public research institutes and universities, and lack incentives and resources for innovation. This, along with weak research infrastructure, low numbers of academic researchers, and a heavy reliance on foreign funding for research in many high TB burden countries, has slowed the pace of local innovation.
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 annually on TB research and development 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 (3, 18). Currently, however, less than half of 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 research and development spending in any given year (5).
36. The complex regulatory environment in some countries also affects TB research. Policies that encourage research and innovation while also ensuring safety and objectivity are critical to help transfer new ideas to the market, and to attract and sustain private sector engagement. Such policies could include an expedited ethics review process and have predictable and expedited product evaluation and registration processes that do not compromise national, regional and global respect for ethical boundaries or intellectual property rights. Regulatory policies that guide data and material sharing, including the transfer of research reagents and clinical specimens, are also essential to facilitate research.

37. Every year, around a quarter of a million people die 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 intervention, TB is projected to be one of the three biggest drivers of the economic toll of antimicrobial resistance, alongside malaria and *Escherichia coli* (19), with an estimated 2.5–3.0% loss to global gross domestic product (GDP) that will reach US\$ 100 trillion by 2050. The complexity and high cost of managing DR-TB means that a disproportionately high share of national TB budgets is already being allocated to DR-TB treatment. Improvements in the treatment of DR-TB will therefore increase the budget available for scaling up services for other aspects of TB prevention, diagnosis, treatment and care.
38. There is a lack of equitable access to TB medicines and technologies, and low availability or use of services by the populations that need them most. 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 DR-TB); inadequate health care budgets; failure of manufacturers to register 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 limit access to overall care; inadequate financing for health care and medicines; local costs that drive up medicine prices (e.g. taxes and tariffs on health products); gaps in procurement and supply chain frameworks; and a lack of awareness of care opportunities.
39. Robust health care systems are essential to achieving the goals and targets of the End TB Strategy. Health care systems with misaligned capabilities in key areas (health workforce, drug supply, health financing and information systems), will be unable to respond adequately to TB. A strong body of knowledge is needed, including from affected communities, on effective strategies for strengthening health and social care systems, so that use of available technologies in TB can be optimized to deliver maximum impact.
40. Although there is a great deal of useful data on TB detection, pharmacovigilance, clinical testing and surveillance, this needs to be shared in a timely manner with policy-makers and researchers, to guide policy, clinical practice and future research. Given the extent of the public health crisis of DR-TB, Better practices must be adopted for sharing data on surveillance and pharmacovigilance between countries.
41. Specific needs with regard to the development of TB diagnostics, treatments and vaccines are summarized below. These include basic science and research into health and social policy and systems.

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### 3.1 Developing new TB diagnostics: needs, challenges and opportunities

42. Rapid and accurate diagnosis is critical for finding all patients with TB, and for ensuring that TB treatment starts quickly and that treatment outcomes are good, thereby preventing transmission. Yet current diagnostics have many limitations (e.g. poor sensitivity or high complexity and cost), and access to and use of good TB diagnostics remains a persistent challenge. As a result, in 2018, close to one third of the estimated 10 million people with TB disease had either not been diagnosed or had not been formally reported to health care systems (3). It is likely that some of these “missing 3 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. Yet there is still a lack of 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 (triage tests) (20). Meeting these needs will require a sustained increase in funding for TB research and development, to accelerate the development, evaluation and deployment of improved tests.
44. If successful, the most promising TB diagnostics in the current pipeline will primarily meet diagnostic needs at the upper levels of the health care system: 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 (including self-testing) to detect (or at least rule out) TB, including extrapulmonary TB, in all populations. There is also a lack of rapid tests for those who are difficult to diagnose with the tools currently available. Most TB tests require a sputum specimen, which some patients (such as children and people living with HIV) have difficulty producing. Tests that use more easily accessible samples (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 primary care clinics where most patients first present, or at the household level where community health workers conduct TB screening.

46. From a scientific perspective, major limitations include the low level of accuracy of some current tests, either owing to low sensitivity (high risk of false-negative results) or low specificity (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 vital for intensifying TB prevention (21), and thus realizing the ambition of providing preventive therapy to 30 million people by 2022. Increased investment in basic science is necessary to support the discovery, validation and translation of biomarkers (including 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 in guiding the development of a rapid, easy-to-use and affordable test that can be used at point of care and in low-resource settings both for diagnosis and monitoring treatment response. Such innovations are particularly important in countries aiming to eliminate TB.

47. The highest priorities in TB diagnostics development, as agreed by WHO and other TB stakeholders, include (20):

- a biomarker test: a point-of-care, non-invasive and non-sputum-based high accuracy test that can detect all forms of TB (TB infection, DS-TB and DR-TB) in all age groups and subpopulations by identifying characteristic biomarkers or biosignatures, and which can identify people more likely to develop TB disease after infection;
- a triage test: a point-of-care, simple, low-cost test that can be used by first-contact health care providers to identify those who need further testing;
- a smear replacement test: a more accurate (high sensitivity and specificity) point-of-care diagnostic test to replace smear microscopy for detecting pulmonary TB and to monitor treatment response for all subpopulations and age groups; and
- a rapid drug susceptibility test: a test that can be used at the microscopy centre level of the health care system to select appropriate first line regimen-based therapy.

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

- develop a portfolio of more accurate TB diagnostic tools integrated into multiplex diagnostic platforms for the identification of respiratory pathogens, 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.

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### 3.2 Developing new TB treatments: needs, challenges and opportunities

49. Current treatment regimens for TB disease require combinations of multiple drugs over several months, resulting in a global cure rate of 85% for DS-TB and 34–55% for DR-TB. The main challenges 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, and by 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 non-toxic, and that allow for a shorter duration of treatment, in particular, to treat the more than half a million DR-TB infections that arise every year.
50. The advent of new TB drugs in recent years has increased 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 2018, the pipeline included at least 29 compounds, from early stage research to late stage product development. Over the past five years, three new drugs (bedaquiline, delamanid and pretomanid) have been approved in some regions to treat DR-TB or treatment-intolerant/non-responsive DR-TB, as part of combination regimens. At least 10 compounds, including some that have been repurposed from other disease indications, are in late stages of clinical development. The high attrition rate in drug development, coupled with the requirement to evaluate and treat TB using multidrug regimens, means, however, that a greater number of novel experimental compounds will be needed if progress is to be made. More information on the current status and specific needs for all age groups and subpopulations is provided below (22).

- TB preventive treatment research: More effective and shorter treatment options for preventing TB disease are needed, including formulations that safely improve adherence, increase acceptability and feasibility, and improve the cost-effectiveness of TB preventive treatment.
- DS-TB treatment research: Researchers are using a number of novel approaches to improve DS-TB treatment but reducing the duration of therapy while keeping efficacy high remains the overriding focus.
- DR-TB treatment research: Several 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 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 testing these medicines in high TB burden countries;
- developing shorter regimens for TB infection and for drug-sensitive and drug-resistant forms of active TB disease, which are safer and more effective, including regimens that are appropriate for the treatment of children, pregnant women, people living with HIV and people who inject drugs; and
- adopting new TB regimens widely and equitably, together with improved surveillance of drug resistance at the country level.

52. The establishment of new platforms for coordination and collaboration between drug developers is another significant achievement and opportunity. Early-stage development activities have benefited from the “TB Drug Accelerator”, which brings together academic institutions, pharmaceutical companies, the TB Alliance and other researchers to share the results of early-stage discovery programmes, and advance the development of drugs that demonstrate high potential. A global antimicrobial resistance research and development hub, an initiative of G20 leaders, has been set up to advance antimicrobial research, in collaboration with existing and new initiatives in antimicrobial basic and clinical research, and in product development. How the 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, rifampicin-resistant TB and pan-TB treatment (23). In 2018, WHO released a report from a technical consultation on advances in clinical trial design for the development of new TB

treatments, with the aim of supporting developers by highlighting clinical trial characteristics that could help advance innovative new therapies (25).

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### 3.3 Developing new TB vaccines: needs, challenges and opportunities

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 it does not protect adolescents and adults, who account for the majority of TB transmission. Sustaining and improving on this progress requires sufficient production capacity; it also requires countries to have better strategies for forecasting demand and for procurement.
55. Currently, at least 14 vaccine candidates are under active clinical development, with several more at the preclinical stage. Despite significant progress in reinvigorating the TB vaccine pipeline since 2000, the current candidates display little antigenic and immunological diversity. This should be rectified to stimulate the development of vaccines that work in multiple ways: 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 after treatment completion.
56. An effective vaccine may also play an important role in tackling DR-TB. By preventing disease, a vaccine would reduce the need for antibiotics, an essential step for curbing antimicrobial resistance. A therapeutic vaccine, used in combination with drugs, could also reduce treatment duration and the risk of recurrence, thus reducing the development and spread of antimicrobial resistance (19). Recently, a Phase IIb trial conducted in Kenya, South Africa and Zambia found an experimental TB vaccine candidate (M72/AS01<sub>E</sub>) to be significantly protective against TB disease in individuals with evidence of TB infection (26). 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 (27). Further development and validation of the candidate vaccine will depend on collaboration between people with TB, research funders, governments, public–private partnerships, product development partnerships, affected communities and the pharmaceutical industry.



57. There are several challenges to developing new TB vaccines. From a scientific perspective, these 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 or as correlates of protection, and an incomplete understanding of the nature of protective immunity to TB.
58. From a developer perspective, vaccine research and development 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 which disproportionately affects the poor. Mechanisms for reducing risk in the early stages of development (such as grant funding) or for initiatives that lower commercial uncertainty (advanced market commitments) can incentivize stronger engagement from industry, biotechnology firms and other developers (see Table 5.1 for examples of other incentives).
59. Several health economic evaluations have shown that new TB vaccines will be cost-effective and will offer substantial cost savings to health care systems and society (28). Furthermore, new vaccines that prevent TB disease will reduce or eliminate the often catastrophic costs of TB, currently shouldered by patients and their families. A constrained funding environment has, however, slowed progress. The Global Plan to End TB calls for about US\$ 250 million per year to advance TB vaccine research and development, but from 2005 to 2017 average annual investment was only US\$ 95 million (5, 17).
60. WHO, with stakeholders, has developed preferred product characteristics for new TB vaccines, intended to guide scientists, funding agencies and industry groups developing TB vaccine candidates for WHO prequalification and policy recommendations (27).
61. Public and philanthropic sources of funding are essential; the pharmaceutical industry will likely remain cautious about investing in TB vaccine research and development until early scientific hurdles have been overcome. Public and philanthropic support should be directed at improving the full continuum of vaccine research and development, 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.

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### 3.4 Operational, implementation, health system and social science research in TB: needs, challenges and opportunities

62. TB is not only a biomedical and public health crisis; it is 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, ineffective implementation and use of existing interventions due to socioeconomic barriers (stigma, poverty, poor housing conditions and malnutrition, for example), weak health care system infrastructure, inadequate implementation of infection prevention and control measures, and insufficient human resource capacity in health care systems.
63. Low-resource countries 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 (including addressing patient needs and costs); it envisions universal access to high-quality TB services and 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 to enable countries to effectively adapt and implement global recommendations on TB prevention, diagnosis, treatment and care, and to optimize the necessary links with other health services and sectors, including through digital health technologies.
66. Analysis of the TB continuum of care from diagnosis to cure confirms the importance of collaboration with other health and social services, and of prevention and infection control measures, to maximize TB elimination efforts (with special attention to the needs of vulnerable populations<sup>1</sup>) to deliver affordable, quality health services. Examples of other health services include services for smokers, people with HIV, diabetes, chronic lung disease or cancer, and people with alcohol or substance abuse issues, as well as prison health care systems, immigration services and mental health services. Analysis of the TB care continuum also

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<sup>1</sup> “Vulnerable populations” are those whose situations or contexts make them especially at risk, or who experience inequality, prejudice, marginalization, and limits on their social, economic, cultural and other rights (29).

highlights the need for engagement and collaboration with affected communities, civil society and private care providers.

67. Lessons learned from scaling up TB services will help to strengthen efforts to achieve universal health coverage in all countries; barriers to equitable access to health and community services for vulnerable populations are similar everywhere, irrespective of TB incidence rates.
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 system and social science research agenda based on epidemiological findings; it also requires studies of applicable health economics modelling.
69. A primary goal of an agenda for operational, implementation, health systems and social science research would be to identify multisectoral ways to close programme performance gaps (differences between what is recommended and what is actually delivered in practice) in context specific ways, 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 system research 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 (16).
71. Allocating targeted funding for operational, implementation, social science, health system, economics and policy research is key to ensuring that future health care system innovations continue to be needs driven, affordable and socially acceptable, with a strong degree of social ownership, for sustainable health and social care.
72. Innovative digital technologies (such as electronic reporting and adherence support) offer opportunities to improve the efficiency or the effectiveness of TB care (30). Implementation research could enhance the scale-up of evidence-informed products in contexts other than those in which they were studied.

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### 3.5 Advancing basic science research

73. Basic research<sup>1</sup> is vital for improving our understanding of host and bacterial factors (and their interplay), to broaden knowledge and make new discoveries that could ultimately result in the development of new and more effective diagnostics, medicines and vaccines.
74. Although numerous studies have been conducted in humans and various animal models, 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) infection with *M. tuberculosis* and TB 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 and optimize 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, mobilization of which calls for concerted efforts. Establishing biorepositories is a cost-effective way to facilitate the next generation of translational research and precision medicine for patients.
77. Enhanced investment in basic science is essential to further increase the flow of new ideas, products and technologies into the product pipeline. Basic research, which is mainly conducted by academic institutions and public-private partnerships, also contributes to a trained workforce and to the infrastructure that enables advanced discovery.

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<sup>1</sup> 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 (31).

## 4 THE WAY FORWARD

78. A range of incentives, financial and nonfinancial, must be introduced, and existing initiatives strengthened to stimulate innovation at all levels from discovery to diffusion of technologies. Policies that encourage and support new collaborative models for research, sharing data and intellectual property, specimen sharing and public–private partnerships are key to leveraging the comparative advantages of various actors to foster research and development, and to facilitating equitable, affordable and sustainable access to medicines and technologies.
79. Financial investment is crucial to overcoming challenges with regard to TB research. Member States (particularly those with a high TB burden) with strong financial and research capacities have a responsibility to establish new TB research initiatives under robust government leadership and with global collaboration, to address unmet innovation needs in the TB cascade of care. The establishment of the BRICS TB research network is an excellent example of such an initiative.
80. Large donors act as a “pull” mechanism to incentivize innovation and increase access to essential medicines and technologies by guaranteeing innovators a final market for their product. More targeted pull mechanisms, such as milestone prizes awarded against set criteria (e.g. the Life Prize) (32), 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. Pull and push incentive mechanisms should be needs driven, evidence based and guided by the principles of affordability, effectiveness, efficiency and equity.
81. Nonfinancial incentives can 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. Open research databases, for example, 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 encourage timely data sharing from publicly funded research through open access platforms to expedite discovery, improve care and prevent duplication of effort. Open access approaches to data also support the overarching goal of ensuring that the public can benefit from public investments in science. Member States should thus explore how researchers, including those working in public institutions, can share data on open research platforms without having to navigate significant administrative or regulatory barriers.

82. Ensuring that everyone with TB or at risk of TB can benefit from advances in TB research requires new models of innovation and delivery that are needs driven and evidence based, and which are guided by the core principles of affordability, efficiency, equity and collaboration.
83. Thanks to a revitalization of TB research over the past two decades, the TB field is well positioned to play a leading role in the response to antimicrobial resistance. TB research efforts to date have provided significant benefits to the global campaign against antimicrobial resistance by enriching the global pipeline of new antibiotics with new mechanisms of action and helping to reduce overall morbidity and mortality from drug resistance. Furthermore, TB research offers examples of successful initiatives and strategies in combating drug resistance, including the coordination of public–private partnership and product development partnership models, basic science insights into host–pathogen interactions and mechanisms of drug resistance, the development of new tools to prevent, diagnose and treat DR-TB, the refinement of public health strategies for surveillance, the promotion of medication adherence, and infection control in clinics and communities (supported by digital technologies). In the age of an antibiotic resistance crisis, investments in TB research will continue to produce broad benefits for health and medicine, extending well beyond the fight against TB.
84. In September 2018, the United Nations held the first High-level Meeting of the General Assembly on the fight against tuberculosis, which culminated in the adoption of a political declaration outlining strong intentions and actions to address challenges in TB research (2). These intentions included commitments to increase public spending on TB research, share the benefits of TB research so that no one is left behind, and create policy and regulatory frameworks favourable to advancing the partnerships and collaborations needed to expedite research. Through the declaration, governments committed to contribute their “fair share” to the funding needs for TB research and development. The concept of this commitment needs to be developed further, and alignment sought from countries.

## 5 STRATEGIC OBJECTIVES

### Objective 1: Create an enabling environment for high-quality TB research and innovation

85. The political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis calls on governments to increase resources, enhance equitable access to medicines and technologies, and improve regulatory environments to advance TB research and innovation, the achievement of which depends on the concerted efforts of national, regional and global actors (2). An enabling environment for research at country level has a significant bearing on the effectiveness of efforts to provide 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. Intellectual property is an important driver of innovation. Over the past 50 years, the intellectual property and patent systems have not provided sufficient incentives for innovation with regard to TB. Licensing patented technologies on terms oriented towards public health is one way in which intellectual property can be used to promote innovation and facilitate equitable access. Research and development into TB treatment needs to deliver new regimens rather than just individual drugs; if intellectual property is not made appropriately available during the research and development process, innovation can be limited and delayed.
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, this approach should provide researchers, public research institutes and higher education institutions with incentives and opportunities to collaborate, both among themselves and with industry, to expedite discovery and enhance capacity-building.
89. Public–private partnerships, including product development partnerships, are good examples of collaborative research initiatives that bridge the public and private sectors to broaden access to new skills, sources of finance, specialized research and development infrastructure and product pipelines. They will help ensure that the next decade delivers the tools needed to end TB, as stated in the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis(2). 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 between 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 and Developing Countries Clinical Trials Partnership and the Tuberculosis Trials Consortium (33) are examples of important collaborations to advance clinical research in TB, through knowledge generation or research capacity strengthening (or both). Such programmes should be enhanced and expanded to allow for effective and accelerated TB research and innovation.

91. In countries with limited capacity to conduct timely and adequate reviews of new studies or products, researchers and sponsors of clinical trials often face complex and lengthy regulatory and ethics approval processes. These challenges highlight the importance of combining financial commitments and regulatory actions to create research-enabling environments.

92. Strategic, nationally-owned health research capacity-building is critical for the sustainable advancement of health research, which in turn is critical for generating the innovations and evidence needed to protect and promote public health. Building 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 the critical mass of health researchers needed to reach a point of take-off in TB innovation.

93. Capacity-building initiatives should be expanded 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 guiding

POLITICAL DECLARATION ON THE FIGHT AGAINST TUBERCULOSIS

*“Commit to foster cooperation between public and private sector entities in furthering the development of newly approved medicines for multidrug-resistant and extensively drug-resistant tuberculosis and for additional new drugs in the future, as part of Member States’ efforts to contribute appropriately to research and development”*

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”*



local and global decision-makers in clinical practice and policy. Careful analysis and dissemination of high quality programmatic data are also needed to guide national research agendas.

94. TB innovation must also involve the adoption, absorption and adaptation of new knowledge and technologies developed elsewhere, when feasible for the health system. National research and innovation policies should enable effective and swift absorptive capacity at all levels of the national health care system, and in other sectors as applicable, so that patients can benefit fully and equitably from innovation. This requires the availability of frameworks at the country level, that can help to align national policies and regulatory mechanisms with the needs of patients and health care systems. 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 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. Examples of enabling environments for TB research and innovation**

| Category | Key enabling features  | Enabling actions by governments |  |
|----------|--|---------------------------------|--|
| Fiscal   | <p>Financing national TB research strategies and agendas</p> <p>Investing in global, regional and national research networks, and their joint activities</p> <p>Policy frameworks incentivizing public–private partnerships, product development partnerships, pharmaceutical companies, biotech firms and other developers operating in TB research</p> <p>Investing in physical infrastructure (such as research institutes and learning centres) as well as human resources capacity-building</p> | Grant funding                   | Upfront financing awarded through competitive, peer-reviewed processes. This is particularly important during the early, high-risk stages of research. Grant funding is a type of “push funding”.  |
|          |  | Tax levies                      | Taxes on particular products, services or activities instituted with the goal of generating resources for health research and development. Other possibilities include taxes on types of financial transactions, carbon emission taxes or the proposed Solidarity Tobacco Contribution.                            |
|          |  | Biomedical research bonds       | Bonds issued by federal, state or local governments to finance research.   |
|          |  | Research innovation trusts      | Trusts established to facilitate public–private partnerships in return for tax credits issued to private sector companies. Trusts could also allow for investment by individual investors or by public retirement programmes.  |
|          |  | Tax check-off programmes        | Tax payment systems that allow individuals to specify a portion of their tax payment to be directed to medical research.   |
|          |  | Budgetary set-asides            | A proportion of budget envelopes set aside or earmarked for research into a particular disease.  |
|          |  | Prize funds                     | Funds awarded through competition. 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. |

| Category              | Key enabling features   | Enabling actions by governments  |  |
|-----------------------|---|--|--|
|                       |   | Separating price from volume of sales  | Voluntary initiatives and incentive mechanisms that separate the cost of investment in research and development from the price and volume of sales.  |
|                       |   | Advance market commitment  | 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.                         |
| Political and legal   | <p>A research governance system that encompasses the principles of accountability, transparency, equity and responsiveness</p> <p>Public policies that harmonize the interplay between trade, development, intellectual property and health, with the goal of protecting and promoting human health</p> <p>Transparent and favourable policies on investments in health research, education, human capital and information technology</p> <p>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</p> | <p>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.</p> <p>Enabling sharing of research data from publicly funded research.</p> <p>Encouraging the publication of research results and setting up ethical standards for conducting research and disseminating research results.</p> <p>Devolving resources to address TB research needs, including for assuring capacity-building in health research.</p> <p>Supporting civil society engagement in health research.</p> <p>Building cross-sectoral partnerships and improving coordination across agencies and sectors to create innovative, patient-centred care.</p> <p>Supporting policy coherence between trade, intellectual property and health to enable medical innovation that can be accessed by all who need it.</p> <p>Establishing monitoring and evaluation systems.</p> |  |
| Regulatory incentives | Setting policies and strategies that incentivize bilateral and multilateral   | Research decisions   | Decisions that make research as relevant and responsive as possible to the needs of end users, and that provide sufficient incentives to guide research towards global and national health priorities. |

| Category | Key enabling features  | Enabling actions by governments                                   |   |
|----------|--|---|---|
|          | <p>cooperation in research, including through multisectoral collaboration</p> <p>Reducing barriers that unnecessarily slow the conduct of research or use of research outcomes</p> <p>Empowering regulatory authorities to expedite registration of generic products</p> | Expedited and predictable process for TB research protocol review | Regulatory frameworks that allow for expedited and predictable timelines for research protocol review processes (including for clinical trials), considering the urgency of the end TB response. Delayed or unpredictable research protocol review processes significantly reduce the incentives for research.  |
|          |  | Orphan product legislation  | Incentives, or adjustments to registration requirements, to attract developers to enter an otherwise unattractive market. Incentives may include waived registration fees, additional periods of exclusive marketing rights, development grants, priority review eligibility or tax credits.  |
|          |  | Breakthrough therapy designation                                  | A 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. |
|          |  | Fast-track designation  | Similar to breakthrough therapy designation but granted at earlier stages of development with nonclinical or clinical demonstration of potential to address unmet needs.  |
|          |  | Compassionate use   | A way of making available a promising medicine that has not yet been otherwise authorized (licensed) for that specific condition, to help patients with life-threatening, long-lasting or seriously disabling illnesses.  |

| Category      | Key enabling features  | Enabling actions by governments   |
|---------------|--|---|
| Sociocultural | <p>Community engagement</p> <p>Norms of inclusiveness, equity and fairness</p> | <p>Supporting civil society engagement in research advocacy, policy dialogue and implementation, particularly for innovations to address issues of stigma in TB.</p> <p>Ensuring that the benefits of research are shared equitably among all people, including girls and women, and marginalized and disadvantaged societal groups.</p> <p>Supporting innovative initiatives that facilitate access to new products. For example, patent pools are a way of encouraging open, collaborative development through pooling of intellectual property and promoting 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 for HIV and hepatitis C.</p> |

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## Objective 2: Increase financial investments in TB research and innovation

96. In the 2011–2015 Global Plan to Stop TB (34), 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 ambitious targets of the SDGs and End TB Strategy (about US\$ 2 billion per year). Actual expenditure over the past 5 years has, however, consistently fallen short of these targets in every category (16, 34).
97. Present spending on research and development is neither adequate nor commensurate with the global burden of TB. The disease is responsible for nearly 2% of disability-adjusted life-years (DALYs) yet receives only 0.25% of the estimated US\$ 265 billion spent on medical research annually (16). Considering that drug-resistant forms of TB account for a quarter of annual antimicrobial resistance-related deaths, TB is expected to be one of the three biggest drivers of the economic toll of antimicrobial resistance (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 funders from a few countries, highlighting the need to build a wider, more diverse funding base, including through non-traditional partnerships (5).
99. Between 2009 and 2015, total industry expenditure on TB research and innovation amounted to less than 0.25% of overall research and development spending by pharmaceutical companies over that period. Spending by private sector companies has declined gradually over recent years (5). This can be attributed to several major pharmaceutical companies closing their TB drug discovery programmes in an industry-wide shift away from research into anti-infective agents (35). During this period, Pfizer and AstraZeneca ended their programmes on anti-infective agents, and Novartis significantly scaled back its TB drug research and development activities (36–38). These closures reflect the lack of a strong market incentive to attract and keep industry involved in TB research and development in particular, and antibiotic development more generally.

### POLITICAL DECLARATION ON THE FIGHT AGAINST TUBERCULOSIS

*“Commit to mobilize sufficient and sustainable financing, with the aim of increasing overall global investments to 2 billion dollars, in order to close the estimated 1.3 billion dollar gap in funding annually for tuberculosis research, ensuring that all countries contribute appropriately to research and development, to support quality research and development of new and the effective implementation of recently approved health technologies, and to strengthen the academic, scientific, public health and laboratory capacity needed to support research and development for prevention, diagnosis, treatment and care, inter alia through the engagement of national, international and innovative financing mechanisms”*

100. Modest increases in TB research and development spending from existing large funders, and declining investments by industry 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, biotechnology firms and other developers to engage in TB research (5).
101. The political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis describes TB research and development 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” (2).
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 funders’ contributions complement one another and align with affordability, access and health research needs in high and low incidence countries alike. Meaningful engagement of civil society, indigenous peoples and affected communities is also important for 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 burden in terms of both TB incidence and TB deaths, and about 52% of the burden of DR-TB. Increased financial investment, coupled with greater use of institutions by the BRICS countries and a more integrated approach to working collaboratively, would help to transform TB research and development by bringing in new resources and innovation.

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### Objective 3: Promote and improve approaches to data sharing

105. Sharing high-quality data (programmatic, clinical trial, epidemiological and genomic data) fosters scientific progress, promotes discovery (through the testing of new hypotheses), improves future data collection methods (through standardization) and allows for the analysis of similar data from multiple sources, which can subsequently inform national and global policy-making in a cost-effective and timely manner. At both the national and subnational levels, there is a need to use epidemiological and programmatic data to improve both 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 the 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 (regulatory, policy and procedural frameworks) to maximize scientific and social returns on investment. Several voluntary international data-sharing platforms, such as the Global Initiative on Sharing All Influenza Data, have also been successful in leveraging multicountry data to advance global health (39).
107. Examples of global scientific TB databases that are rapidly becoming a crucial part of the infrastructure of the global science system are TB-ReFLECT (40) and TB-PACTS (41) (both of which are collaborative, standardized, patient-level data-sharing platforms from Phase III TB treatment trials), and the TB portals (42) (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 (43). The aim of this platform is to support national and global 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 (44, 45).
108. At country level, there is a need to make adequate and timely contribution to national and global data needs for policy-making and discovery; to make efficient use of resources in TB research; and to effectively put new knowledge to use, without compromising national intellectual property law and the protection of privacy and confidentiality.



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#### Objective 4: Promote equitable access to the benefits of research and innovation

109. The End TB Strategy stipulates that to curb the epidemic, 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.
110. In many parts of the world, patients either go without the necessary treatment or receive low quality services and treatments owing to poor access to and use of new technologies and medicines. Reasons for this include financial cost, risk factors associated with voluntary and involuntary displacement, limited or unpredictable availability of medicines from 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 for tuberculosis care (46).
111. Some medicines are not used to their full potential owing to national regulatory frameworks limiting off-label use, or clinician preferences, or resistance to changing practices. Furthermore, availability can be constrained by high prices and by delays in registration in some countries. Initiatives and incentive mechanisms separating the cost of investment in research and development from the price and volume of sales may therefore be useful in the development of new TB treatments. Considering that the use of new TB medicines is often limited to the most drug-resistant forms of TB (in an effort to prevent the emergence of resistance to these new products), returns on investment that are not contingent on sales volume may be beneficial.
112. The high price of medicines caused by lack of robust competition for certain treatments is a particular challenge for DR-TB care. Public health-oriented voluntary licences, such as those negotiated by the Medicines Patent Pool, can accelerate availability of quality-assured generics for use in low- and middle-income countries. This would bring prices down and facilitate the scaling up of treatment. Governments should reduce barriers to the entry of generics to create a pro-competitive environment for marketing medicines. Governments should also promote affordable access to medicines and technologies, particularly where the public sector contributes substantially to their development.
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. WHO also 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 are crucial in supporting access to life-saving technologies and medicines in high TB burden countries.
115. The Global Drug Facility, 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 private sector actors that are not receiving support from the mechanisms mentioned above. Support for national regulatory channels is therefore needed in respect of the procurement of high-quality biomedical interventions.
117. Civil society and affected communities can play a valuable role in providing a public interest perspective on equitable access and affordability. Meaningful engagement strategies and platforms will, however, be needed if this knowledge base is to be included in discussions about access policy. At the same time, 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 towards communities most at risk. This goes hand in hand with making TB prevention, treatment and care universally accessible and affordable.
118. WHO's Roadmap for access to medicines and vaccines 2019–2023 (47) 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 research and development to quality assurance, regulatory approvals and market authorization, and to supply chain management, prescribing, dispensing and use.
119. As well as ensuring access to life-saving technologies and medicines, Member States 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. The collective contribution of all countries is needed for sustainable gains to be made in monitoring the safety and increasing the public health impact of medical innovations.

## 6 RECOMMENDATIONS

### **Objective 1: Create an enabling environment for high-quality TB research and innovation**

**Potential indicators of effectiveness:** Extent of government engagement in research networks and public–private partnerships for TB research and innovation; and time required to process regulatory approvals for clinical trials and product evaluations

#### **Member State actions**

120. Member States can contribute to meeting this objective by:
- a. streamlining<sup>1</sup> and harmonizing regulatory processes for the review of clinical trials and other research activities to expedite TB research, and strengthening capacity to evaluate products studied elsewhere to allow effective products to be imported for the benefit of patients;
  - b. developing country-specific TB research agendas and strategic plans in line 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, Member States could set 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 bring together stakeholders to develop country-specific research plans;
  - c. strengthening existing public–private partnerships and product development partnerships nationally and globally (and, where necessary, creates new partnerships), and incentivizing further engagement of pharmaceutical companies, biotechnology firms and other developers in research and development of vaccines, medicines, diagnostics and other health technologies, to improve TB prevention and care;
  - d. increasing the number and profile of local researchers engaged in TB research, and the necessary incentives to retain researchers in employment, and developing the required higher-

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<sup>1</sup> 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. If such logistical considerations are lacking, the cost and complexity of clinical trials may increase, resulting in delays.

- level and specialized trainings for new researchers, research infrastructure and incentives to stimulate innovation and increase the capacity to make use of innovations;
- e. participating in and funding 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 High-level Meeting of the General Assembly on the fight against TB; and
  - f. engaging 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 research and development process.

### **Secretariat actions<sup>1</sup>**

#### **121. Actions to be taken by the Secretariat:**

- a. initiating a process for relevant stakeholders to consider the global landscape of TB prevention, diagnosis, treatment and care, to identify areas that will most benefit from enhanced research and data generation, which in turn will stimulate the development of evidence for policy around critical knowledge gaps for countries and communities;
- b. providing technical assistance to 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; and
- c. promoting collaboration between TB researchers in different countries around common research goals, and promoting multisite and multidisciplinary research. This will rely on existing or new international TB research networks and consortia that are dedicated to discovery, preclinical, clinical, operational/implementation, health system and social science research.

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<sup>1</sup> Secretarial functions are coordinated by the WHO Global Tuberculosis Programme.

### **Actions by international and national partners**

122. National and international stakeholders in TB research and development, including academia, public–private partnerships and product development partnerships, should encourage and support Member States in establishing in-country research infrastructure. Such infrastructure provides the foundation for the building national, regional and global TB research networks to advance the implementation of high-quality science in line with national TB research priorities.
123. Research funders and sponsors should commit to strengthening community engagement in TB clinical research.
124. Civil society and affected communities should advocate for and support the development and implementation of health research policies that advance person-centred health and social care, and are inclusive of vulnerable groups and marginalized communities.
125. The pharmaceutical industry should cooperate with public–private partnerships and public development partnerships, and increase industry’s meaningful contributions to their activities.
126. Professional medical associations, funders and relevant foundations, and non-State actors 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 indicator of effectiveness:** At the country level, proportion of gross domestic expenditure on research and development that is allocated to TB research

### **Member State actions**

127. Member States can contribute to meeting this objective by:
- a. gradually increasing funding for TB research and development in relation to GDP and gross domestic expenditure on research and development on health research and development to address unmet needs in TB research;
  - b. implementing the commitments on TB research financing made in the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis, together with incentives that separate the cost of investment in research and development from the price and volume of sales; and
  - c. setting a target contribution for TB research funding that includes both domestic funding and funding for international collaboration. For the latter, the funding model should be streamlined with others to allow for meaningful and effective collaborative financing, taking into account the research needs of high TB burden countries.

### **Secretariat actions**

128. Actions to be taken by the Secretariat include:
- a. monitoring financial flows to the various disciplines of TB research and the state of the research and development pipeline under the auspices of the WHO Global Observatory on Health research and development and relevant advisory mechanisms, to allow for an assessment of the TB research and development landscape; and
  - b. consulting with Member States, philanthropic organizations and the pharmaceutical industry on innovative financing mechanisms to expedite the development and diffusion of more affordable and effective vaccines, diagnostics, medicines and technologies.

### **Actions by international and national partners**

129. Research funders in the public and private sectors (including the pharmaceutical industry) should invest in the development of effective and low-cost tools, for preventing, diagnosing and treating TB infection and TB disease for different subpopulations (including children, pregnant women, people living with HIV and people with other comorbidities). They should also increase the funding allocated to

operational, implementation, health care system and social science research, including for effective delivery models that are programme and patient friendly.

130. International funding agencies and development assistance organizations should consider providing greater and longer-term funding for TB research, to foster capacity-building and allow discoveries to mature.
131. International funders and foundations should better align and harmonize their funding programmes to national and global TB research agendas, and adopt flexible spending mechanisms to allow for the development of responsive science and technology initiatives.
132. Bilateral and multilateral donor agencies, especially those already involved in the large-scale funding of TB care programmes, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, should consider allocating a dedicated budget for operational, implementation, social, economic and health system research.
133. International funders and donor agencies involved in research on antimicrobial resistance should address the challenges presented by DR-TB as a key component of the global antimicrobial resistance response.

### Objective 3: Promote and improve approaches to data sharing

**Potential indicators of effectiveness:** extent of government efforts to establish or strengthen a well-resourced national open data initiative for TB research, from a variety of 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 actions

134. Member States can contribute to meeting this objective by:
- a. establishing or strengthening 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), thereby enabling detection and monitoring of subnational, national, regional and global trends to inform decision-making;
  - b. developing or enhancing a policy of open data for and access to publicly funded scientific research (both nationally and globally), to reduce duplication of effort, expedite research and facilitate the translation of evidence into national and global policies on TB prevention, diagnosis, treatment and care, while maintaining patient privacy and confidentiality and protecting intellectual property; and
  - c. fostering voluntary technology transfer policies for the development and diffusion of knowledge and the wider transfer of evidence to policy and practice. Initiatives (such as the World Intellectual Property Organization's Re:Search) and patent licensing mechanisms (the Medicines Patent Pool) can complement TB research and development efforts by facilitating partnerships and the licensing of intellectual property among organizations. Publicly searchable patent databases also promote the diffusion of knowledge by facilitating access to the information disclosed in a patent.

#### Secretariat actions

135. Actions to be taken by the Secretariat include:
- a. supporting Member States by facilitating protected data sharing to produce global and regional TB epidemic trends and review the effectiveness, safety and applicability of medical interventions, for policy guidance;
  - b. establishing, with the support of partners and Member States, 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 the global and national levels. This platform should complement existing



platforms for sharing and storing data, while maintaining patient privacy and confidentiality;  
and

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

### **Actions by international and national partners**

- 136. International funders, partners, professional associations and aid and technical agencies should support low- and middle-income countries in improving data quality and accessibility through targeted capacity-building initiatives.
- 137. International funders of TB research should promote 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 indicators 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 percentage of TB-affected households that experience catastrophic costs as a result of TB

### Member State actions

138. Member States can contribute to meeting this objective by:

- a. ensuring the availability of the most recent guidelines on the prevention, diagnosis and treatment of TB, together with the necessary human, infrastructure and material resources (such as adequate availability of medicines and technologies) at all levels of the health care system, including those catering to key TB populations (such as prisoners and migrants);
- b. including TB technologies and medicines in the national essential medicine and technology list, and ensuring effective supply-chain management to facilitate the procurement and use of high-quality medicines and technologies. To facilitate this, funding should be allocated to support operational, implementation, social, economic and health system research to optimize effective and efficient delivery of research benefits, particularly for vulnerable groups in high and low TB incidence countries alike;
- c. developing policies on trade, health and intellectual property through multisectoral collaborative frameworks to address access and innovation simultaneously, to meet the needs of people with TB, as highlighted in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (48);
- d. developing regulatory frameworks and fostering partnerships across sectors to reduce trade and distribution mark-ups 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
- e. supporting replenishment of global financing mechanisms such as Unitaid and the Global Fund to Fight AIDS, Tuberculosis and Malaria, which are helping to ensure that the most vulnerable populations can access essential medicines and innovations.

### Secretariat actions

139. Actions to be taken by the Secretariat include:

- a. providing technical assistance under World Health Assembly resolution WHA72.8 on improving the transparency of markets for medicines, vaccines and other health products, and the WHO Roadmap on access to medicines and vaccines 2019–2023 (47), which is being developed to help Member States improve access to medicines, vaccines and technologies;

- b. collaborating with other relevant international and regional organizations (including the World Trade Organization, World Intellectual Property Organization, United Nations Development Programme, and United Nations Conference on Trade and Development) to provide, on request, technical support to Member States on aspects of intellectual property and trade policies; and
- c. setting norms and standards, developing guidelines and advising Member States on issues related to quality assurance of medicines in national and international markets, and assisting Member States in building national capacity for regulating public health through networking, training and information sharing.

### **Actions by international and national partners**

- 140. Pharmaceutical companies should enable affordable and sustainable access to essential TB medicines, vaccines and technologies in countries with high numbers of patients living in poverty, or where public health programmes are chronically underfunded and do not have access to generic, more affordable equivalents.
- 141. Pharmaceutical companies should consider adopting patent and enforcement policies that facilitate the greater access to the 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, to facilitate greater access to safe, effective and high-quality products. These licences should be accompanied by data exclusivity waivers and technology-transfer activities.
- 142. Non-State actors and partners, including global mechanisms such as the Global Drug Facility, Unitaid and the Global Fund to Fight AIDS, Tuberculosis and Malaria, should support Member States in the strengthening and implementation of national regulatory practices for efficient stewardship and access to TB vaccines, medicines and innovations.
- 143. 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.
- 144. 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

145. The proposed strategy is expected to help Member States accelerate implementation of the political declaration of the High-level Meeting of the General Assembly on the fight against tuberculosis (2) and the Moscow Declaration to End TB (12). Governments have a key role in facilitating the strengthening of policies related to the four main objectives stated in this strategy. Their approaches to doing so will vary, however, owing to differences in their economic, institutional, regulatory and human resource capacity, and differences in their approaches to policy (regarding the role of public versus private sectors in research and innovation). Translating this strategy into effective and appropriate actions at both the local and national levels may mean developing a national strategy or roadmap for TB research based on country needs and context.
146. Systematic monitoring and evaluation of efforts by Member States, mindful of each country's context, is needed to ensure that the necessary policy changes are being made and implemented, and to track their impact with regard 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 an opportunity to monitor such progress. Such a framework would allow policy-makers to learn from ongoing efforts, and from sharing experiences and good practices between countries (49).
147. WHO will support Member States in implementing the global strategy and monitoring progress, including by fostering mutual learning, identifying good policy practices and fostering international cooperation.
148. Funders, researchers, the private sector, civil society, indigenous peoples, affected communities and other relevant research actors must 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.

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