GLOBAL INVESTMENTS IN TUBERCULOSIS RESEARCH AND DEVELOPMENT
PAST, PRESENT, AND FUTURE

A POLICY PAPER PREPARED FOR THE FIRST WHO GLOBAL MINISTERIAL CONFERENCE ON ENDING TUBERCULOSIS IN THE SUSTAINABLE DEVELOPMENT ERA: A MULTISECTORAL RESPONSE
Global investments in Tuberculosis research and development: past, present and future. A policy paper prepared for the first WHO global ministerial conference on ending tuberculosis in the sustainable development era: a multisectoral response

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A policy paper prepared for the First Global Ministerial Conference on
Ending TB in the Sustainable Development Era
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GLOBAL INVESTMENTS IN TB R&D PAST, PRESENT, AND FUTURE

ABBREVIATIONS

ACTG  AIDS  AMR  BCG  BRDPI  BRICS  CAGR  CDC  CEWG  CHIM  CMV  CPI  DALY  DNA  DOD  DR-TB  DS-TB  EDCTP  EU  FDA  FDC  FIND  Gates  GDP  GERD  Global Fund  HIV  LPA  LTBI  MDR-TB  MTB  NCE  NIH  NTP  OR/IR  PEPFAR  POI  R&D  RCT  SAMRC  SDG  TAG  TB  TBTC  The Union  UN  UNESCO  United Kingdom  US  USAID  USAMRIID  USPHS  WHO  XDR-TB

FOREWORD

Research is the sine qua non to pursue substantial improvements in health outcomes: every diagnosis, intervention and treatment carried out in tuberculosis (TB) programmes has been conceived and developed through scientific research. Simply put, research translates into health benefits every day, with wider (and usually underestimated) positive benefits trickling down to create further social and economic well-being. In the WHO End TB Strategy, we make the case for TB research being central to improving patient health, and positively transforming health-care services with better interventions and products. In doing this, we need to consider three main issues. The first is that an estimated 10 million people contract TB disease every year, most of them in poor, underserved areas, and all of them need to have their safety and well-being protected. Second, only one third of investment needs for TB research and development are currently met – a situation that hampers the development of new and better tools for detecting, treating and preventing TB. Third, what sets 2017–2018 apart is our ability, through two forthcoming unprecedented high-level meetings, to secure commitment from Member States and the research community at large in addressing critical impediments to TB R&D. Hence, now it is a critical time to articulate what we need from TB R&D.

Together with our various partners, academics and civil society groups, we have developed a policy paper on TB R&D for use in the context of the “WHO's First Global Ministerial Conference on Tuberculosis in the Sustainable Development Era – A Multisectoral Response” in Moscow. This document aims to articulate a coherent vision of the research needs to end TB and elaborates on the funding and structural requirements that are necessary to operationalize this vision. It describes how some of the research funded in the past has delivered benefits to patients and influenced policy- and decision-making, but also how little is being invested in TB R&D in comparison with other diseases, such as HIV and malaria, that also affect poor populations. The paper shows that, despite significant progress, previous investments were not sufficient to warrant success in tackling difficult challenges, such as multidrug-resistant TB (MDR-TB), expedited development of new and improved tools, and effective deployment of such tools. To tackle these challenges, the present policy paper recommends the development of a global strategy for TB Research to foster collaboration, improve efficiency and increase R&D financing. The strategy, will serve as a coherent source of direction so the opportunities commencing from the forthcoming meetings are used optimally.

Further findings from this report are expected to inform the debate at both national and global levels on prioritizing the policy approaches that are urgently needed to advance TB R&D in the era of the SDGs.

Since it is our shared responsibility to foster TB R&D at all levels (national, regional and global) and lay the foundations for the speedy development of new tools and strategies, we need to take tangible steps to increase our TB R&D commitments. Such steps include increasing research funding & capacity, reducing regulatory impediments in health research, and encouraging greater public, private and civil society engagement to facilitate equitable and affordable access to new diagnostics, medicines and vaccines.

All relevant stakeholders – including governments, industry, nongovernmental organizations, academics and civil societies at large – should continue to explore ways to support innovations that address the unique set of scientific, economic and regulatory challenges presented by TB, while promoting access to affordable treatment and prevention.

The two forthcoming high-level meetings offer a unique and exciting opportunity for Members States, partners, stakeholders and the overall TB community at large to move forward and foster innovative R&D policies that can promote the rapid achievement of the WHO End TB Strategy targets as well as the relevant SDGs target of ending the TB epidemic.

Through our united efforts, we must echo the pledge of the SDGs to “Leave No One Behind”. This begins with reinvigorated research as the basis for innovation.

Dr Mario Raviglione
Director, Global TB Programme
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EXECUTIVE SUMMARY

Tuberculosis (TB) is the most lethal infectious disease in human history, and it remains the leading cause of death from a single infectious agent globally. Drug-resistant forms of TB are responsible for a quarter of annual deaths due to antimicrobial resistance (AMR) and, if left unchecked, by 2050 it will claim millions of lives and cause the global economy to incur losses worth billions of dollars. The present and future threat that TB poses to human health is mainly a consequence of the enormous neglect the TB research field has experienced over the past several decades. Reversing this neglect and ending the TB epidemic by 2030 – as called for by the United Nations Sustainable Development Goals (SDGs) and WHO End TB Strategy – will require a decisive commitment by all countries and stakeholders to increase their support for TB research and innovation.

A renewed, global commitment to TB research and development should be led by country governments working in concert with the private and philanthropic sectors, civil society and communities affected by TB. Funding for TB R&D must increase substantially over past levels, and regulatory and other institutional barriers to research should be resolved with urgency. The End TB Strategy indicates that new tools must be introduced by 2025 in order to reach the 2030 targets of a 90% reduction in TB deaths and 80% reduction in TB incidence compared with 2015 levels. In particular, the End TB Strategy calls for the introduction of rapid point-of-care tests for diagnosing TB and detecting drug resistance; shorter, safer and more effective regimens for treating TB in all its forms; and a more effective TB vaccine.

The analyses of the past decade of TB research funding presented in this policy paper make clear that past and present expenditures on TB R&D are wholly inadequate when measured against these ambitions. TB accounts for nearly 2% of disability-adjusted life-years (DALYs) and 2% of deaths globally, but receives only 0.25% of the estimated US$ 265 billion spent on medical research annually. TB research receives less support than other global health threats such as HIV and malaria, both in absolute terms and relative to its share of DALYs and premature mortality. Annual funding for TB R&D has not grown appreciably since 2009 and has even lost ground in the face of inflation. Moreover, funding is highly concentrated: 30 institutions from a handful of countries account for over 90% of TB R&D expenditures in any given year. Declining investments by industry over the past 5 years, coupled with flat expenditures from major public and philanthropic funders, mean that there is a need to bring new resources into the TB research field.

Case studies assessing the pipelines for new TB diagnostics, drugs and vaccines show how chronic underfunding has slowed the pace of product development and created challenges in translating advances in basic science into new interventions. When adequately funded, many TB research efforts over the past decade have met with success. However, even then, insufficient investment in operational research has compromised the scale-up of new technologies, limiting their impact on the TB epidemic and keeping millions of people with TB, or at risk of TB, from enjoying the full benefits of scientific progress. An analysis of published TB studies points towards growing
research output by scientists in high TB burden countries – particularly Brazil, Russian Federation, India, China and South Africa – yet much TB research remains dependent on funders located in high-income, low TB burden nations. Limited funding is not the only obstacle; TB researchers often face complex and lengthy regulatory processes in countries that have limited capacity to conduct efficient, adequate reviews of new studies or products. These challenges convey the importance of matching increased funding for TB research with steps to create research-enabling environments at the country level.

Ending the TB epidemic by 2030 and averting the looming crisis of AMR will require breaking out of business-as-usual approaches. States must work together and in partnership with other stakeholders to develop and deploy innovative mechanisms for financing research. To ensure that the next decade of TB R&D delivers the transformative new tools required to end the TB epidemic, governments should commit to pursuing a series of actions at the national and international levels.

At the national level, governments should take steps to create research-enabling environments that nurture and facilitate TB R&D. This will entail:

- developing country-specific TB research agendas and strategic plans to expand TB research at the country level through capacity-building and multisectoral partnerships;
- activating domestic financing mechanisms to increase funding for TB R&D; and
- streamlining regulatory processes for the expedited review of clinical trials and other research activities in order to advance research.

At the international level, governments should work together and in collaboration with WHO and other partners to develop a new Global Strategy for funding and coordinating TB research. This global strategy should have several aims, including:

- enhancing the cooperation and coordination of research to promote efficient use of available resources;
- reinforcing TB research priorities and stimulating actions over a targeted duration of time;
- mobilizing resources for TB research, including through innovative financing mechanisms and incentive strategies, and through developing a more diverse funding base;
- promoting the sharing of data and information under a larger framework for monitoring, evaluation and reporting; and
- facilitating the rapid scale-up of new strategies and tools.
A new global strategy for TB R&D is needed because achieving the advances necessary to end the TB epidemic will require enhanced and sustained support for complex research endeavours that are best pursued through international cooperation.

The increased investment in TB research required to achieve the vision of a TB-free world – estimated by the Stop TB Partnership to be US$ 9 billion between 2016 and 2020 – is modest compared to the costs of inaction. The Stop TB Partnership has warned that a 5-year delay in funding TB R&D at the targeted level of US$ 9 billion could result in an additional 8.4 million TB cases and 1.4 million TB deaths by 2030, equating to over US$ 5 billion in excess treatment costs. As one of the leading drivers of AMR, TB will contribute to even greater economic losses, which could exceed US$ 100 trillion by 2050 in the absence of concerted action today. Thus, complacency comes with a cost and, given the scale of these costs, the least expensive option for governments is to act by supporting TB R&D. TB research is not a luxury, it is a necessity that no government committed to working towards the SDG vision of a healthier, more prosperous and secure world can afford to ignore.
INTRODUCTION
Tuberculosis (TB) is the leading cause of death from a single infectious agent globally, responsible for 1.8 million deaths in 2015 (1). It also ranks as the biggest infectious disease killer in human history, claiming over a billion lives in the past 2 centuries alone (2). Despite this oversized toll on health and well-being, the response to TB is critically underfunded, especially in the realm of research, as the analyses in this policy paper will demonstrate. The research agenda for TB is large, ambitious and in urgent need of increased investment. Funding for TB research and development is insufficient, concentrated in a handful of institutions and showing signs of decline.

In May 2014, the 67th World Health Assembly endorsed the WHO End TB Strategy, which envisions a world without TB (3). In line with the Sustainable Development Goals (SDGs) adopted by United Nations (UN) member states in September 2015, governments called for high-reaching targets for ending the TB epidemic, with a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030 compared with 2015 (4). In addition to being named an explicit component of SDG 3 (good health and well-being) in its own right, TB is emblematic of the interconnectedness of the SDGs. As a disease that disproportionately affects the poor and other vulnerable populations, TB sits at the intersection of health and development. Progress against TB will therefore bolster efforts to achieve a number of SDG targets, particularly those focused on eradicating poverty in all its forms, ending the AIDS epidemic, reducing premature mortality among women and children, strengthening health systems, and supporting the R&D of vaccines and medicines for diseases that primarily affect developing countries.

The inclusion of R&D under SDG 3 is echoed by the End TB Strategy, which situates research at the heart of its framework, alongside patient-centred care and prevention, and bold policies and supportive systems. The third pillar of the strategy – research and innovation – recognizes that achieving substantial reductions in TB incidence and mortality will require the development and introduction of new tools, in addition to ensuring universal access to existing technologies. Potentially game-changing innovations include a rapid point-of-care test for diagnosing TB and detecting drug resistance; safer, shorter regimens for treating drug-sensitive TB (DS-TB) and latent TB infection (LTBI); shorter, safer and more effective treatment for drug-resistant TB (DR-TB); and a new TB vaccine that is effective both before and after exposure. The current pipelines for new TB diagnostics, drugs and vaccines are poised to satisfy some, though not all, of these ambitions. To bring forth the transformative advances called for by the End TB Strategy, funding for TB research must increase substantially over past levels.

Between 2005 and 2015, the world spent US$ 6.3 billion on TB R&D. Annual funding for TB research increased from US$ 358 million in 2005 to US$ 620 million in 2015. However, growth over the period varied considerably, and in several recent years, expenditures on TB R&D fell compared with the year before. Over 60% of TB research expenditures over the period 2005–2015 came from the public sector; also, within each sector, funding is highly concentrated in a handful of institutions. The two largest funders of TB research – the United States (US) National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation (Gates Foundation) –
together contributed 37% of all money spent on TB research since 2005. Annual pharmaceutical industry spending on TB R&D peaked at US$ 145 million in 2011 before falling to nearly US$ 87 million in 2015 following the withdrawal of several companies from the field and the maturation of clinical development programmes for new TB drugs. Thus, funding for TB R&D has not grown appreciably since 2009 and has even lost ground in the face of inflation. Declining investments by industry and flat expenditures from existing major funders point to the need to bring new resources into the TB research field and develop innovative, flexible and collaborative mechanisms for advancing the science needed to end TB. Funding is not the only challenge. Researchers and sponsors of clinical trials often face complex and lengthy regulatory and ethics approval processes in countries that have limited capacity to conduct timely, adequate reviews of new studies or products. Considered together, these challenges convey the importance of using a mixture of financial commitments and regulatory actions to create research-enabling environments in countries.

The present level of R&D expenditure is not only inadequate measured against the ambitions of the SDGs and End TB Strategy, it is also not commensurate with the global burden of TB. Based on analyses presented in this policy paper, TB is responsible for nearly 2% of disability-adjusted life-years (DALYs) and 2% of deaths globally, but receives only 0.25% of the estimated US$ 265 billion spent on medical research annually. In addition, drug-resistant forms of TB account for a quarter of annual deaths due to antimicrobial resistance (AMR), and TB is expected to be one of the three biggest drivers of the economic toll of AMR (5). TB receives less funding for research than other global health pandemics such as HIV and malaria, both in absolute terms and relative to its share of DALYs and premature mortality. An analysis in this paper of new products developed and brought to market for TB, HIV and malaria shows that the TB pipeline has lagged behind those for HIV and malaria, suggesting that limited funding has slowed the pace of research. This has had devastating consequences for people with and at risk of TB, who urgently need better tools for preventing, diagnosing and treating TB in all its forms.

This policy paper shows how countries and stakeholders can take resolute actions to promote the R&D required to successfully reach the SDG target of ending the TB epidemic by 2030. The paper concludes by recommending steps governments and other stakeholders can take at the national and international levels to create research-enabling environments and increase funding for TB research; namely, the creation of a global strategy for TB R&D and the deployment of innovative, collaborative financing mechanisms.
2. HOW RESEARCH CAN SUPPORT THE END TB STRATEGY

Key messages

- TB research has suffered enormous neglect over the past several decades, contributing to the striking fact that TB has regained its position as the world’s leading infectious disease killer.

- A successful global campaign to end TB by 2030 in line with the SDG and WHO End TB Strategy targets will depend on continuous disease-specific research complemented by the investigator-initiated basic science that is needed for the development of future preventive, diagnostic and therapeutic tools. This will require substantially increasing – and then maintaining – funding for TB research along its full continuum, from basic science to new product development to operational research and implementation science.

- The End TB Strategy calls for new tools to be introduced no later than 2025. In particular, it highlights the urgent need for rapid point-of-care tests for diagnosing TB and detecting drug resistance; shorter, safer and more effective regimens for treating all forms of TB; and a more effective TB vaccine.

- Increased investments in TB research are modest compared to the costs of complacency, especially when measured against the anticipated economic toll of drug-resistant-TB and AMR. Governments should see funding for TB R&D not as a cost, but as an investment in lives, livelihoods and national economies.
2.1 PAST CONTRIBUTIONS OF TB RESEARCH TO PUBLIC HEALTH

The fight against TB in the second half of the 20th century demonstrates both the power of research to advance public health and the perils of closing research programmes after early signs of success (6). TB research advanced swiftly throughout the 1940s and 1950s, taking TB treatment from the sanatorium era into the antibiotic era. The introduction of multiple new antibiotic compounds from the 1950s to the 1970s culminated in the short-course combination chemotherapy that is still in use today (7). These developments complemented earlier technologies, including the bacille Calmette–Guérin (BCG) vaccine (introduced in 1921) and diagnosis of TB through acid-fast sputum smear microscopy (developed in the late 19th century) (8).

These early advances against TB represented major progress for medical science at large. For example, the development of BCG was one of the first demonstrations of a powerful new technique for creating vaccines: attenuation via serial passaging (9). In another first, in 1948 the British Medical Research Council conducted the world’s first randomized controlled trial (RCT) in medicine, studying streptomycin, the earliest TB drug (10). Research over the following decade moved TB treatment well beyond streptomycin, and the discovery of other TB drugs with different mechanisms of action in the 1950s gave rise to the combination drug therapy required to guard against antibiotic resistance (11). Paradoxically, TB research fell victim to its early success, and investments in TB R&D evaporated quickly in the 1970s and 1980s. By 1986, two of the groups behind many of the initial victories in TB treatment research – the British Medical Research Council and the US Public Health Service (USPHS) – had disbanded their TB research programmes (12). Funding for TB R&D shrank to a few institutions, each awarding a few million dollars per year (13). As a result, the TB field lost out on a decade of scientific progress, and missed the opportunity to attract and train a new generation of young scientists. Left to rely on tools developed in the 19th and 20th centuries, TB programmes struggled to maintain the achievements of the postwar period in the face of challenges both new (e.g. the rise of HIV) and old (e.g. the spread of drug resistance) (6, 14).

Other contemporary public health campaigns avoided the mistake of winding down research programmes too soon. The successful global campaign to eradicate smallpox, for example, maintained “a vigorous research program ... to ensure that methods that proved ineffective in the field could be replaced with new approaches” (15). Support for basic science – not tied to any particular public health mobilization – has proven instrumental in responding to emerging global health threats. Research conducted in the 1960s and 1970s on retroviruses – at the time not known to be associated with any human disease – led decades later to the development of protease inhibitors to treat HIV, as well as treatments for hepatitis C and adult T-cell leukaemia (16). Unlike TB research, which slowed dramatically after the introduction of early therapeutic agents, HIV research did not halt with the advent of highly active antiretroviral therapy in 1996 (8). The public health responses to smallpox and HIV demonstrate the importance of continuous disease-specific research complemented by the inspired, investigator-initiated basic science that is needed for the development of future preventive, diagnostic and therapeutic tools.
PRESENT CONTRIBUTIONS OF TB RESEARCH TO PUBLIC HEALTH

Research on TB slowed for several decades, but the TB epidemic did not. Present failures to adequately respond to TB are, to a large extent, the result of lost opportunities in research funding over the past few decades (13). An outbreak of DR-TB in New York City in the early 1990s epitomized how a lack of innovation – coupled with the dismantling of TB clinics and public health infrastructure – left public health programmes unprepared to respond to the resurgence of TB in the wake of the HIV epidemic and the rise of DR-TB. The DR-TB outbreak in New York City cost over US$ 1 billion to fully control (equivalent to US$ 1.8 billion in 2015 dollars) (17). Responding to that single outbreak cost more than global expenditures on TB R&D in the past 3 years combined.

The New York City DR-TB outbreak made visible the cost of inaction, and it marked a turning point in TB research. In response to a surge in US Government funding for TB, the US Centers for Disease Control and Prevention (CDC) reconstituted the USPHS TB research unit in 1993 by organizing a network of clinical trial sites that would later become the Tuberculosis Trials Consortium (TBTC) (18). Funding for TB research at the NIH increased from about US$ 3.5 million in 1991 to US$ 35 million in 1997, partly owing to substantial NIH support for research on HIV and its comorbidities (13). Globally, the growing toll of the colliding TB and HIV epidemics drew political and scientific attention to the inadequacy of existing tools, and in 1993 WHO declared TB a public health emergency (19).

Although there are no precise estimates of TB R&D funding from this period, observers point to a significant increase in resources for TB research starting in the early 1990s. Funding for TB R&D increased from less than US$ 20 million in 1991 to over US$ 30 million in 1993, and reached an estimated US$ 100 million by 2000 (20, 21). The entry of the Gates Foundation into the TB research field at the turn of the millennium unlocked substantial philanthropic funding. After this point, TB research entered a period of revitalization that was made possible by an infusion of resources and the formation of new research networks and platforms, including several product-development partnerships based on innovative models of financing and collaboration.

Investments in TB research over the past 15 years have resulted in several significant advances, including:

- the conditional approval by stringent regulators of two new drugs from novel classes to treat TB (bedaquiline and delamanid), the first in over 4 decades;
- the development of a shorter regimen for treating LTBI that is safe and efficacious, including in children and people with HIV (the 3HP regimen, which provides a 12-dose, 3-month combination of rifapentine and isoniazid);
- the development of several new diagnostics, including a rapid and robust alternative to smear microscopy (Xpert MTB/RIF), a simple test that can identify TB in people with HIV with severe immunosuppression via the lipoarabinomannan assay (TB LAM), and several options for detecting first- and second-line drug resistance faster than conventional culture (GenoType MTBDRplus, Nipro Assay and MGIT);
- the creation of a pipeline of candidate TB vaccines and the completion of the world's first efficacy trial of a TB vaccine since the 1960s;
- the organization of national, regional and global platforms to build in-country capacity for operational research to improve TB programmes and patient care – one prominent example being the Structured Operational Research and Training Initiative (SORT IT), a research mentoring and training programme developed by the International Union Against TB and Lung Disease (The Union) and Médecins Sans Frontières, and now coordinated by the WHO Special Programme for Research and Training in Tropical Diseases; and
- the beginnings of a true paradigm shift in fundamental understandings of the biology of Mycobacterium tuberculosis (MTB), the causative agent of TB, and its complex interactions with the human immune system. Indeed, MTB infection and TB disease are now understood to lie along a spectrum of host and pathogen activity rather than exist as binary, mutually exclusive states (22). This important conceptual advance builds on earlier achievements in basic science, such as the sequencing and deciphering of the MTB genome (23), and advances in immunology.
Despite significant achievements, the scientific advances of the past 15 years will not be sufficient to reach the SDG targets. Mathematical modelling indicates that major reductions in TB incidence will require the development and introduction of drastically new technologies (24). To reach the 2025 End TB Strategy milestones of a 75% reduction in TB mortality and 50% reduction in TB incidence, the annual decline in global TB incidence must accelerate from the current 2% decline per year to 10% by 2025 (25). This can be accomplished by making rapid progress towards universal access to existing TB tools and services in the context of universal health coverage and socioeconomic development (see Fig. 1). This projection is based on the historical experience of western Europe and North America, where TB incidence and mortality fell rapidly following the Second World War (14). However, new tools must be introduced by 2025 in order to sustain progress beyond this point. In particular, the End TB Strategy highlights the need for a vaccine that is effective pre- and post-exposure, better diagnostics, and safer and easier treatment for LTBI (25). In the interim, safer, shorter and more effective treatment regimens for both DS-TB and DR-TB would have a large effect on reducing deaths from TB (26). The current pipelines for new TB diagnostics, drugs and vaccines can meet some – but not all – of these needs, so progress in product development will depend on continued and increased support for basic science and discovery. Given the longstanding underfunding of TB research, “greatly enhanced and immediate investments in research and development will be required” to introduce new tools by 2025 (26).

Several modelling studies have explored the potential epidemiological impact of new tools. In a 2009 study, Abu-Raddad et al. (2009) used a mathematical model of TB transmission to estimate the epidemiological benefits of employing more effective TB diagnostics, drugs and vaccines, singly and in various combinations (27). Focusing on the South-East Asia region, the authors found that combinations of interventions – especially those targeting the vast reservoir of LTBI with either mass chemoprophylaxis or pre- and post-exposure vaccines – would avert the most TB cases and deaths between 2015 and 2050. Two combinations of interventions stood out for their potential to prevent 75–80% of incident TB cases and 73–75% of TB-related deaths: a 2-month treatment regimen for DS-TB plus mass LTBI therapy, and a pre-exposure vaccine coupled with a post-exposure vaccine given to people who are at high risk of TB disease.
with LTBI. Without novel interventions, the South-East Asia region would be expected to have over 100 million cases of DS-TB and 18 million deaths over the same period.

More recent work assessing the prospects for TB elimination (defined as less than one TB case per 1 million population) in four countries – China, India, South Africa and the United States – by 2050 reached a similar conclusion regarding the importance of addressing LTBI: “Achieving TB elimination requires a direct attack on the reservoir of latent infection, with a drug or a vaccine (or both) that is effective against established infection” (24). The authors concluded that TB cannot be eliminated with existing technology because “the efficacy of current tools and the supply and demand of health services are not sufficient to combat a disease in which infectious cases can arise spontaneously” from a vast reservoir of latently infected individuals (24).

This work illuminates a conceptually clear pathway to elimination: TB programmes must detect cases earlier, diagnose them accurately and achieve higher cure rates while also targeting LTBI directly. Accomplishing these tasks, however, will depend on developing new and improved technologies (24). Developments that would offer powerful new tools include a rapid point-of-care test for diagnosing TB and detecting drug resistance; safer, more effective regimens for treating DS-TB and DR-TB; and tests for LTBI that can identify the individuals most likely to progress to active disease. Ultimately, the development of these transformative tools will depend on funding for product development, as well as basic and translational science to sustain the pipelines with new candidate technologies (28, 29).

The epidemiological models discussed above open a window into the lives that might be saved by research. Complementing this, economic forecasts indicate that investing in TB research today will offer significant cost savings to health systems in the long run. The Copenhagen Consensus has identified spending on TB as a “best buy”, based on the calculation that reducing deaths from TB would be worth US$ 43 for every dollar spent (30). TB is even more than a best buy; estimates of the costs of inaction make clear that supporting TB R&D is a fiscal imperative. If the US$ 1 billion it took New York City to respond to a DR-TB outbreak in the early 1990s represents a fraction of the cost of lost opportunities accumulated over the 1980s, inaction today will incur even steeper expenses. The Stop TB Partnership’s 2016–2020 Global Plan to End TB: the Paradigm Shift estimates that the world needs to spend US$ 9 billion on TB R&D over the next 5 years to meet the End TB Strategy’s goal of introducing new tools by 2025 (31). According to the Global Plan to End TB, a 5-year delay in satisfying the R&D funding targets could result in an additional 8.4 million TB cases and 1.4 million TB deaths by 2030. This equates to US$ 5.3 billion in additional treatment costs and US$ 181 billion in lost productivity. Failure to increase support for TB R&D would have a devastating effect on lives, livelihoods and national economies.

Investing in TB research now will be necessary to avoid costs attributable to the looming threat of AMR. DR-TB was identified soon after the introduction of streptomycin in the 1950s, and in 2015 some 480 000 people newly developed multidrug-resistant TB (MDR-TB) and an additional 100 000 rifampicin-resistant TB (1, 6). Drug-resistant forms of TB account for a quarter of annual deaths due to AMR, and the United Kingdom Government’s Commission on Antimicrobial Resistance has called TB a “cornerstone of the AMR response” (5). Two independent models suggest that, if AMR is left unchecked, associated economic losses will grow over time, culminating in a 2.5–3% loss to global gross domestic product (GDP) that will be worth US$ 100 trillion by 2050. The estimations indicate that TB will be one of the three biggest drivers of the economic toll of AMR, alongside malaria and Escherichia coli (5).

In September 2016, the first-ever UN high-level meeting on AMR culminated in the adoption of a political declaration outlining broad intentions and actions to tackle AMR, including the need to resolve “the lack of investment in research and development … for new antimicrobial and alternative medicines, rapid diagnostic tests, vaccines, and other important technologies” (32). The revitalization of TB research over the past 2 decades has positioned the TB field to play a leading role in the AMR response. TB research has much to offer the global campaign against AMR, from basic-science insights into host–pathogen interaction and mechanisms of drug resistance, to the development of new tools to prevent, diagnose and treat DR-TB, to the refinement of public health strategies for promoting medication adherence and infection control in clinics and communities. In an age of antibiotic resistance, investments in TB research will continue to produce broad benefits to health and medicine that extend well beyond the fight against TB.
Key messages

- Global funding for TB research has not grown appreciably since 2009, and has lost ground in the face of inflation.
- Funding for TB research is heavily reliant on public-sector institutions. Across sectors and research areas, funding is highly concentrated in a handful of institutions from a few countries, highlighting the need to build a wider, more diverse funding base.
- The absence of strong market incentives for antimicrobial research has resulted in minimal industry engagement in TB R&D. Pharmaceutical industry spending on TB R&D has decreased each year since 2011, and total industry expenditures on TB research between 2009 and 2015 amounted to less than 0.25% of overall R&D spending by pharmaceutical companies over that period.
- Multisectoral collaborations have been instrumental in enabling scientific progress against TB. Public and philanthropic sources of funding for TB R&D often serve as catalysts for bringing different stakeholders together by signalling opportunities for collaboration and cost sharing.
- When research is conducted with the needs of patients and public health settings in mind, TB research and TB programmes can become two sides of the same coin. Forging stronger ties between research and programmes is a powerful way to confront DR-TB and its role in AMR, by ensuring that research strengthens TB programmes even as it responds to ongoing public health challenges.
3.1 FUNDING FOR TB R&D HAS NEVER EXCEEDED ONE THIRD OF THE REQUIRED NEED

Total funding for TB R&D increased from US$ 358.1 million in 2005 to US$ 620.6 million in 2015 (Fig. 2). However, growth over the period varied considerably. Spending on TB R&D peaked in 2013 at US$ 686.3 million, and in several recent years, expenditures fell compared with the year before. The biggest decrease occurred between 2014 and 2015 when funding fell by US$ 53.4 million (from US$ 674.0 to US$ 620.6 million). This marked the lowest level of funding for TB research since 2009. (Appendix 1 contains a detailed note on the methodology used to calculate these figures and conduct the analyses that follow.)

A single legislative act in a single country (the United States) produced the biggest increase in TB R&D funding in recent history; funding jumped by US$ 142.8 million from 2008 to 2009. Fifty-two per cent of this increase can be traced back to the NIH, which received a one-time 34% budget increase of US$ 10.4 billion under the American Recovery and Reinvestment Act, a US$ 787 billion economic stimulus package released by the US Government in response to the 2008 financial crisis (33, 34). This event demonstrates the power of fiscal policy to unlock additional resources for TB research, even when the policies at hand are not primarily aimed at TB or even at research.

Although funding for TB R&D has increased overall since 2005, the rate of growth slowed after 2009. The compound annual growth rate (CAGR) measures the average rate at which investments or other types of expenditures change over time by smoothing out the volatility seen from one year to the next. The CAGR for TB R&D funding for 2005–2015 was 5.6%, indicating that, on average, expenditures grew by 5.6% per year over the past 11 years. However, funding during the latter half of the period (2009–2015) had a CAGR of –0.4%, reflecting the mostly flat trend in recent years.
3.2 FUNDING FOR TB R&D HAS NOT KEPT PACE WITH INFLATION

Not all of the growth in nominal funding for TB R&D since 2005 is real growth. Fig. 2 compares TB research expenditures in nominal and inflation-adjusted terms (using 2005 as the base year). The US$ 620.6 million spent on TB research in 2015 is only worth US$ 464.5 million in 2005 constant dollars. When assessed in 2005 constant dollars, the CAGR for TB R&D funding drops to 2.63% for 2005–2015 and to –2.61% for 2009–2015. This suggests that the observed increases in funding for 2005–2015 are not buying as much additional purchasing power as the trend in nominal funding implies, because the costs of doing research have also gone up over the period.

The costs of biomedical research have also risen faster than general inflation. Fig. 2 shows expenditures on TB R&D adjusted for inflation using two measures: the biomedical research and development price index (BRDPI) and the consumer price index (CPI). The BRDPI indicates how much the NIH budget must change to maintain purchasing power given changes to the costs of research inputs (35). In contrast, the CPI is a general inflation measure of the price levels of consumer goods and services purchased by US households (36). The gap between the lines representing TB R&D funding adjusted for inflation using the BRDPI and the CPI indicates that the rising costs of research have outpaced the upward price movement of goods and services at large from 2005 to 2015.

3.3 MOST TB R&D FUNDING COMES FROM THE PUBLIC SECTOR, AND MULTISECTORAL COLLABORATIONS ARE COMMON

As shown in Fig. 3, 61% of total TB R&D funding over the period 2009–2015 came from the public sector. Funding was highly concentrated within each sector. The NIH gave 53% of the US$ 2.8 billion spent on TB research by public institutions since 2009. The Japanese pharmaceutical company Otsuka accounted for 60% of industry spending, the Gates Foundation comprised 89% of philanthropic expenditures, and Unitaid gave 47% of the total multilateral funding. Of note, the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) is probably the largest multilateral supporter of TB R&D, with estimated spending of US$ 120.2 million on TB operational research from 2002 to 2015, but this figure cannot be broken down by year (37).
3.3.1 In context: private-sector expenditures on TB R&D

Reduced spending by private-sector companies is one of the most alarming shifts in TB R&D funding over the past 6 years. Industry spending peaked in 2011 at US$ 145 million, before dropping to US$ 86.8 million in 2015, an amount lower than the US$ 100 million spent by private-sector companies in 2009 at the height of the economic crisis. This decrease is driven by two separate trends. Several major pharmaceutical companies closed their TB drug discovery programmes as part of an industry-wide shift away from anti-infectives research. Pfizer and AstraZeneca ended their anti-infectives programmes, and Novartis significantly scaled back its TB drug R&D activities during this period. These closures reflect the lack of a strong market incentive to attract and keep industry involved in TB R&D, in particular, and antibiotic development more generally.

Pharmaceutical companies that remained active in TB drug R&D began spending less as new compounds neared the end of clinical development and received regulatory approval. For example, Otsuka, the developer of TB drug delamanid and the largest private-sector investor in TB R&D, spent US$ 470.4 million over the period 2005–2015. Fig. 4 depicts Otsuka’s expenditures over time in relation to the clinical development milestones of delamanid (some of these costs supported discovery and preclinical projects for compounds other than delamanid, although these represent a minor share of Otsuka’s total investment). In 2005, soon after delamanid entered phase I trials, Otsuka spent US$ 12.3 million on TB drug R&D. Spending peaked at US$ 65.1 million in 2011, the year the phase III trial opened for enrolment, and decreased in subsequent years, reflecting the maturation of the drug’s development programme: by late 2014, the phase III trial reached the final date of data collection for its primary outcome measure; in that year, Otsuka reported spending US$ 53.2 million, an amount that dropped to US$ 29.0 million in 2015. Delamanid received conditional approval from the European Medicines Agency in 2014, and Otsuka expects to release results from the phase III trial in 2018.

3.3.2 In context: public-sector expenditures on TB R&D

The example of delamanid provides an indication of what Otsuka spent to bring this new TB drug through clinical testing to market without experiencing failure or major setbacks in early stages of testing. Cost estimates for developing new drugs vary widely; they depend on the disease or condition, adjustments for attrition and costs of capital, and the inclusion or exclusion of public incentives that support drug development. It is possible that different models of TB drug development would cost less than what Otsuka reports spending; examples of such models include research conducted by product-development partnerships or R&D advanced through novel mechanisms that pool intellectual property in order to facilitate the development of new TB drug regimens.

The development of the 3HP regimen for treating LTBI provides an apt example of how public funding underlies many cross-sectoral TB research projects. The 3HP regimen contains two TB drugs – rifapentine and isoniazid – taken together once a week for 12 weeks. Before 3HP, LTBI treatment relied on older drugs such as isoniazid (taken daily for up to 36 months) or rifampicin (taken daily for 4 months). Research to develop 3HP as a shorter alternative was primarily funded by the CDC’s TBTC in partnership with the Aids Clinical Trials Group (ACTG); the French pharmaceutical company Sanofi provided additional financial and in-kind support. Together, TBTC and ACTG conducted the pivotal phase III trial that established the safety and efficacy of 3HP and led the US Food and Drug Administration (FDA) to approve rifapentine for the treatment of LTBI in combination with isoniazid in 2014. In the same year, WHO included 3HP among the regimens recommended for treating LTBI in its first-ever Guidelines on the management of latent tuberculosis infection. On top of 3HP’s clinical advantages, mathematical modelling suggests that treating LTBI with 3HP instead of 9 months of daily isoniazid is cost effective and could result in 5.2 fewer cases of TB per 1000 people treated in the United States over a 20-year period.
Despite this success, funding for TB research at the CDC has fallen dramatically in both nominal and real terms. In 2005, the CDC Division of TB Elimination reported spending US$ 19.9 million on TB R&D, a figure that fell to US$ 14.1 million by 2015 (US$ 9.9 million in 2005 constant dollars). Flat appropriations in the face of inflation explain much of this decrease. In addition, the TBTC budget absorbed a 12% cut under sequestration, the automatic spending cuts to US federal agencies enacted by the US Congress in 2013 (51). As a result, the TB research agenda at the CDC appears more ambitious than is feasible to pursue given recent budget trends.

The TBTC provides a model for how clinical research can be integrated into TB programmes. Located within the division of the CDC that directs the domestic TB response, the TBTC has a mission to promote research within TB programmes through collaboration on clinical research of relevance to public health settings (18). When conducted this way, research and programmes are two sides of the same coin. At the same time, the TBTC experience illustrates how public expenditures on TB are vulnerable to larger budget-related policy changes and must be maintained against inflation. Strong public budgets for TB R&D – and the scientific and programmatic partnerships they make possible – depend on a policy environment that promotes TB research.
In context: multisectoral collaborations for TB R&D

The development of Xpert MTB/RIF, a test that can diagnose TB and resistance to TB drug rifampicin in less than 2 hours, provides a compelling illustration of the importance of even wider multisectoral collaborations in TB R&D. Xpert MTB/RIF resulted from a combination of resources from industry (Cepheid), public funders (NIH and the US Department of Defense [DOD]), philanthropic donors (Gates Foundation), academic partners (University of Medicine and Dentistry of New Jersey) and product-development partners (Foundation for Innovative New Diagnostics [FIND]). Upon the endorsement of Xpert MTB/RIF by WHO in 2010, Cepheid issued a statement that “the Xpert MTB/RIF test truly represents what can be accomplished in a successful academic-public-private partnership” (52).

The history of work behind the GeneXpert platform demonstrates how TB can benefit from R&D aimed at other health threats. Cepheid developed the GeneXpert platform in the late 1990s and early 2000s with an estimated US$ 120 million in funding from the DOD (53). The DOD was interested in using GeneXpert to detect anthrax in the wake of the September 11, 2001 attacks and the mailing of anthrax spores through the US postal system. Cepheid had received at least US$ 15 million from the DOD for an earlier system that predated GeneXpert (54). With an infusion of resources after September 11, 2001, Cepheid delivered the first prototype of its GeneXpert DNA detection system to the US Army Military Research Institute of Infectious Diseases (USAMRIID) by December 2001, fulfilling what the USAMRIID director called “a joint strategic vision dating back to 1996” (55). By combining three separate steps – sample preparation, DNA reproduction and amplification, and sample identification – GeneXpert offered a significant improvement over previous DNA detection systems.

In 2006, Cepheid entered into an agreement with FIND to develop a simple, rapid diagnostic test for TB and rifampicin resistance that could run on the GeneXpert platform. FIND spent US$ 15 million on the project, with funding from the Gates Foundation (56). Expenditures included contractually defined payments to Cepheid of US$ 7.23 million for development of the Xpert MTB/RIF cartridge and US$ 1 million for the test calibration kit. FIND spent an additional US$ 6.8 million on clinical trials and project management, and the NIH spent US$ 3 million on an evaluation of Xpert MTB/RIF assay in the United States, conducted by the ACTG. In addition to the ACTG study, the NIH National Institute of Allergy and Infectious Diseases reports spending about US$ 42 million between 1994 and 2016 on studies to support the development of Xpert MTB/RIF assay and its expansion to cover additional drug-resistance genes (57). Finally, Cepheid has indicated that it contributed “in excess of” US$ 25 million on a series of activities related to developing the Xpert MTB/RIF assay (52).

The multisectoral approach that facilitated the development of Xpert MTB/RIF also proved instrumental in making the test available and more affordable. A combination of private and philanthropic money reduced the price of the GeneXpert platform and the Xpert MTB/RIF cartridges in 145 developing countries in a 2012 market intervention agreement (58). This “buydown” involved US$ 3.5 million from the US President’s Emergency Plan for AIDS Relief and the United States Agency for International Development (USAID), US$ 4.1 million from Unitaid, and US$ 3.5 million from the Gates Foundation. This agreement reduced the price of the GeneXpert platform to US$ 17,000 and the Xpert MTB/RIF cartridge to US$ 10 a piece.
3.4 FUNDING FALLS SHORT OF NEED IN EVERY AREA OF TB R&D

Fig. 5 shows that TB drug R&D received more funding than any other category of TB research over the period 2009–2016, followed by basic science, vaccine R&D, operational research, infrastructure and unspecified projects, and diagnostics R&D. (Appendix 2 lists the research areas tracked by the Treatment Action Group [TAG] and their definitions.) The proportion of total funding received by each research area remained stable over this 6-year period, and no area experienced a sizeable jump in spending. Mirroring TB R&D funding by sector, most of the expenditures in each area came from two or three organizations. For example, the NIH accounted for 60% of the money spent on basic science since 2009 and three funders – Otsuka, the NIH and the Gates Foundation – comprised 58% of all expenditures on TB drug development. In vaccine R&D, the Gates Foundation, the NIH and the European Commission provided 67% of funding.

In the 2011–2015 Global Plan to Stop TB, the New Tools Working Groups of the Stop TB Partnership estimated the amount of funding required in each research area to enable the scientific progress needed to end TB as a public health threat. As Table 1 shows, actual expenditures fell well short of these targets in every category.

### Table 1: Actual Funding for TB R&D, 2011–2015 versus Global Plan Funding Targets

<table>
<thead>
<tr>
<th>Research Area</th>
<th>Actual Funding 2011–2015 (million USD)</th>
<th>Funding Target 2011–2015 (million USD)</th>
<th>Funding Gap (million USD)</th>
<th>Proportion of Target Unfunded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic science</td>
<td>$679</td>
<td>$2 133</td>
<td>$1 454</td>
<td>68%</td>
</tr>
<tr>
<td>Diagnostics</td>
<td>$300</td>
<td>$1 744</td>
<td>$1 444</td>
<td>83%</td>
</tr>
<tr>
<td>Drugs</td>
<td>$1 246</td>
<td>$3 680</td>
<td>$2 434</td>
<td>66%</td>
</tr>
<tr>
<td>Vaccines</td>
<td>$476</td>
<td>$1 925</td>
<td>$1 449</td>
<td>75%</td>
</tr>
<tr>
<td>Operational Research</td>
<td>$351</td>
<td>$359</td>
<td>$8</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$3 052</strong></td>
<td><strong>$9 841</strong></td>
<td><strong>$6 789</strong></td>
<td><strong>69%</strong></td>
</tr>
</tbody>
</table>

*Does not include the $243 million spent on infrastructure and unspecified projects.
### Table 2: Country Funding for TB R&D in Relation to GDP and GERD

<table>
<thead>
<tr>
<th>Country</th>
<th>TB R&amp;D Funding 2009–2015 (current USD millions)</th>
<th>GDP (2015 USD millions)</th>
<th>GERD (% GDP)</th>
<th>Average TB R&amp;D Funding as % of Average Annual GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>$1,783</td>
<td>$18,036,648</td>
<td>2.73</td>
<td>0.07%</td>
</tr>
<tr>
<td>European Union*</td>
<td>$269</td>
<td>$16,311,897</td>
<td>2.03</td>
<td>0.02%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>$269</td>
<td>$2,858,003</td>
<td>1.7</td>
<td>0.11%</td>
</tr>
<tr>
<td>France</td>
<td>$62</td>
<td>$2,418,836</td>
<td>2.26</td>
<td>0.02%</td>
</tr>
<tr>
<td>Germany</td>
<td>$59</td>
<td>$3,363,447</td>
<td>2.87</td>
<td>0.01%</td>
</tr>
<tr>
<td>India</td>
<td>$53</td>
<td>$2,095,398</td>
<td>0.82</td>
<td>0.04%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>$44</td>
<td>$750,284</td>
<td>1.97</td>
<td>0.05%</td>
</tr>
<tr>
<td>Australia</td>
<td>$43</td>
<td>$1,339,141</td>
<td>2.2</td>
<td>0.07%</td>
</tr>
<tr>
<td>Canada</td>
<td>$40</td>
<td>$1,550,537</td>
<td>1.61</td>
<td>0.03%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>$22</td>
<td>$670,790</td>
<td>2.97</td>
<td>0.03%</td>
</tr>
<tr>
<td>South Africa</td>
<td>$19</td>
<td>$314,572</td>
<td>0.73</td>
<td>0.07%</td>
</tr>
<tr>
<td>Sweden</td>
<td>$19</td>
<td>$495,624</td>
<td>3.16</td>
<td>0.02%</td>
</tr>
<tr>
<td>Norway</td>
<td>$15</td>
<td>$386,578</td>
<td>1.71</td>
<td>0.05%</td>
</tr>
<tr>
<td>Japan</td>
<td>$15</td>
<td>$4,123,258</td>
<td>3.58</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>$13</td>
<td>$1,377,873</td>
<td>4.29</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>Denmark</td>
<td>$13</td>
<td>$295,091</td>
<td>3.08</td>
<td>0.03%</td>
</tr>
<tr>
<td>Singapore</td>
<td>$12</td>
<td>$292,739</td>
<td>2.19</td>
<td>0.02%</td>
</tr>
<tr>
<td>Ireland</td>
<td>$10</td>
<td>$283,703</td>
<td>1.52</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

*Note: the European Union (EU) estimate primarily includes money directed through the European Commission and the European and Developing Countries Clinical Trials Partnership and does not include money spent by EU member states outside of joint EU mechanisms.

GDP, gross domestic product; GERD, gross domestic expenditure on R&D

#### 3.5 The Vast Majority of TB R&D Funding Comes from a Few Countries

Most public funding for TB R&D comes from a few high-income countries. **Table 2** shows the countries that contributed more than US$ 10 million to TB R&D between 2009 and 2015 in rank order, alongside GDP and gross domestic expenditure on R&D (GERD). Public institutions in the United States spent US$ 1.8 billion on TB research over the period 2009–2015, or 63% of total public funding. This is nearly seven times as much as the second and third largest contributors, the European Union (EU) and the United Kingdom. The United Kingdom spent more on TB research as a percentage of its annual GERD (0.112%) than any other country, followed by the United States, Australia and South Africa. Expenditures on TB research in the EU, United Kingdom and United States did not grow significantly over the period, pointing to the need to raise support from governments of other countries.

Fig. 6 and Fig. 7 show TB R&D funding in relation to GDP and GERD. Some countries such as Japan and South Korea have high GERD but spend relatively little on TB R&D. These are countries with highly developed research industries that might be well positioned to contribute to TB research, particularly in terms of basic science and discovery activities. Other countries such as India and South Africa have lower GERD as a percentage of GDP but rank above higher-GERD countries in terms of TB R&D expenditure. Countries at all levels of GDP and GERD have
room to increase their financial contributions to TB research in accordance with the strengths, capacities and priorities of their domestic R&D industries.

Given the low absolute level of funding, even modest increases in annual country funding for TB R&D can make a meaningful difference to the field. In 2015, an institution only needed to spend over US$ 10 million to rank among the 10 largest TB research funders, and US$ 4.8 million to land in the top 20. In 2014, the Government of Singapore spent more on TB R&D as a percentage of its GDP than any other country, providing funding of over US$ 8 million through its National Medical Research Council (59). A significant portion of this went to the Singapore Programme of Research Investigating New Approaches to Treatment of Tuberculosis (60). A few million dollars for a flagship TB research initiative or co-funding for an international TB trials network could unlock valuable additional resources and opportunities for TB R&D.

Combined, industry groups outspent most countries, but industry investments remain low as a proportion of companies’ overall R&D budgets. Total industry expenditures of US$ 779 million on TB R&D over the period 2009–2015 amounted to 0.22% of the US$ 359 billion spent by pharmaceutical companies on health R&D over the past 6 years (61). This is a clear indication that TB does not represent an attractive market from a pharmaceutical industry perspective, and reinforces the importance of public sector support for TB research.
FUNDING FOR TB R&D FLOWED TO AT LEAST 575 INSTITUTIONS IN 60 COUNTRIES BETWEEN 2011 AND 2015

Fig. 8 presents a first-time analysis of how money for TB research moves from funders to recipients. This analysis tracks funding received by organizations over the past 5 years from the subset of public and philanthropic institutions that belong to the 25 core funders who have participated in each year of the TAG survey (Appendix 3). In total, these funders awarded money to more than 575 institutions in 60 countries. The recipient organizations are deemed “principal recipients”, to reflect their status as the bodies receiving the initial award or investment; the funding flows analysis does not track how or where principal recipients spend money through subcontracts or sub-awards; therefore, it does not necessarily represent where TB research is conducted. Appendix 4 provides a matrix of the public and philanthropic funders included in this analysis with information on the largest principal recipient and the number of countries supported by each.

Funders from some countries primarily give to domestic institutions, while others support recipients around the world. Funders based in the United States, for example, gave US$ 1.6 billion to organizations headquartered in the United States, but also gave US$ 60 million to groups in South Africa. The European and Developing Countries Clinical Trials Partnership (EDCTP) supported organizations in 32 countries (21 in Africa and 11 in Europe), making it the funder with the most geographically diverse collection of recipient organizations.
Table 3: 15 Largest Principal Recipients of TB R&D Funding, 2011–2015

<table>
<thead>
<tr>
<th>Rank</th>
<th>Recipient Organization</th>
<th>Organization type</th>
<th>Country</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TB Alliance</td>
<td>PDP</td>
<td>USA</td>
<td>$259 279 914</td>
</tr>
<tr>
<td>2</td>
<td>Aeras</td>
<td>PDP</td>
<td>USA</td>
<td>$195 315 661</td>
</tr>
<tr>
<td>3</td>
<td>US. Centers for Disease Control and Prevention</td>
<td>P</td>
<td>USA</td>
<td>$81 988 864</td>
</tr>
<tr>
<td>4</td>
<td>US National Institutes of Health (intramural research programme)</td>
<td>P</td>
<td>USA</td>
<td>$68 645 337</td>
</tr>
<tr>
<td>5</td>
<td>Johns Hopkins University</td>
<td>A</td>
<td>USA</td>
<td>$66 282 510</td>
</tr>
<tr>
<td>6</td>
<td>University of Cape Town</td>
<td>A</td>
<td>South Africa</td>
<td>$65 283 333</td>
</tr>
<tr>
<td>7</td>
<td>FIND</td>
<td>PDP</td>
<td>Switzerland</td>
<td>$54 287 176</td>
</tr>
<tr>
<td>8</td>
<td>Harvard University</td>
<td>A</td>
<td>USA</td>
<td>$45 004 164</td>
</tr>
<tr>
<td>9</td>
<td>The International Union Against TB and Lung Disease</td>
<td>NP</td>
<td>France</td>
<td>$41 385 424</td>
</tr>
<tr>
<td>10</td>
<td>University of Medicine and Dentistry of New Jersey</td>
<td>A</td>
<td>USA</td>
<td>$40 680 010</td>
</tr>
<tr>
<td>11</td>
<td>National Institute for Research in Tuberculosis</td>
<td>P</td>
<td>India</td>
<td>$38 898 936</td>
</tr>
<tr>
<td>12</td>
<td>Medical Research Council</td>
<td>P</td>
<td>United Kingdom</td>
<td>$33 547 043</td>
</tr>
<tr>
<td>13</td>
<td>University of Pittsburgh</td>
<td>A</td>
<td>USA</td>
<td>$33 021 253</td>
</tr>
<tr>
<td>14</td>
<td>Albert Einstein College of Medicine</td>
<td>A</td>
<td>USA</td>
<td>$32 907 645</td>
</tr>
<tr>
<td>15</td>
<td>Case Western Reserve University</td>
<td>A</td>
<td>USA</td>
<td>$32 807 193</td>
</tr>
</tbody>
</table>

A, academic institution/university; NP, nonprofit organization, P, public/government institution; PDP, product-development Partnership.

With principal recipients belonging to more than 60 countries, TB research is truly global in scope and participation. However, a significant share of total TB research expenditure goes to a relatively small number of institutions primarily located in high-income countries. Table 3 lists the 15 largest principal recipients. Funding received by these 15 organizations accounts for 44% of funding disbursed by this subset of public and philanthropic funders between 2011 and 2015. Many of these organizations, although headquartered in the United States or other high-income countries, primarily conduct clinical trials or other research activities in other countries including those with high TB burden. Notably, only two of the 15 largest principal recipients are based in high TB burden countries: the University of Cape Town in South Africa and the National Institute for Research in Tuberculosis in Chennai, India.
This analysis tracks funding received by organizations from 2011 to 2015 from public and philanthropic institutions that have participated in each year of the TAG survey.

SAR, Special Administrative Region
4. ACHIEVEMENTS, GAPS AND CHALLENGES IN ADVANCING TB R&D

Key messages

- The End TB Strategy calls for the introduction of new tools to fight TB by 2025. Each area of TB product development has made significant strides over the past decade, but needs a major step up in financial support to bring game-changing diagnostics, drugs and drug regimens, and vaccines to market by the End TB Strategy deadline.

- The biggest advances in TB diagnostics R&D would be the advent of a rapid point-of-care test for diagnosing TB and detecting drug resistance at the primary health-care level, and a test to identify people with LTBI most at risk of disease progression. The Global Plan to End TB calls for US$ 676 million in funding for TB diagnostics R&D over the next 5 years and an additional US$ 3.4 billion to scale up new diagnostics.

- The ultimate breakthrough in TB drug R&D would be an ultra-short, safe, inexpensive regimen capable of treating all forms of TB. Making progress towards this long-term goal will require maintenance of a robust pipeline of new compounds and improvements in treatment of LTBI, DS-TB, MDR-TB and extensively drug-resistant (XDR)-TB using novel combinations of new and repurposed drugs. The Global Plan to End TB calls for US$ 4.15 billion in funding for TB drug R&D over the next 5 years.

- A new TB vaccine that is safe and more effective than BCG and protects against all forms of TB in adolescents and adults would be the most powerful tool for rapidly reducing TB incidence. The Global Plan to End TB calls for US$ 1.25 billion in funding for TB vaccine R&D over the next 5 years.

- Increased funding for TB operational and implementation research (OR/IR) will allow governments to leverage the most from their investments in basic science and product development. Funders should support the integration of OR/IR into routine programmatic activities, and build the capacity of TB programmes to use OR/IR to introduce new technologies efficiently and equitably.
4.1 THE CASE FOR NEW TB DIAGNOSTICS

4.1.1 Why do we need new TB diagnostics?

Rapid and accurate diagnosis is critical for starting TB treatment quickly, ensuring good treatment outcomes, and preventing transmission of TB to others. Yet current diagnostics have many limitations, including poor sensitivity or high complexity, and access to good TB diagnostics remains a persistent challenge for many people in low- and middle-income countries. As a result, up to 40% of the estimated 10.4 million new TB cases in 2016 were either not diagnosed or not formally notified to health systems (1). These “missing 4 million” people with TB were either treated late or not treated at all, allowing for continued TB transmission. Moreover, 75% of the estimated 580,000 cases of rifampicin-resistant TB and DR-TB globally were not diagnosed, and even among TB patients with the highest risk for DR-TB, 40% were never tested for drug resistance (62).

The Global Plan to End TB calls for early diagnosis of TB, including universal drug susceptibility testing and systematic screening of high-risk groups. The past decade has seen major advances in the development of new diagnostic technologies for TB. However, the TB field still lacks adequate tests for the simplified, rapid and accurate detection of TB and drug resistance. Meeting this need will require a sustained increase in funding for TB R&D in order to accelerate the development and deployment of improved tests.

Table 4 summarizes the TB diagnostics that are currently available for use globally, as endorsed by WHO. Some of these technologies are now over a decade old, and important diagnostic gaps and limitations remain, as indicated below.

- From a patient perspective, a central limitation is the lack of a rapid test to detect TB in all populations, including those who are difficult to diagnose with currently available tools. Most TB tests require a good sputum specimen, which some patients (e.g. children and people living with HIV) have difficulty producing. Moreover, there is no point-of-care test that can be used at the most peripheral levels of the health system, such as the primary care clinics where most patients first present for care.

- From a health systems perspective, most available tests need electricity, specialized equipment, trained technicians and specific infrastructure (e.g. high biosafety level laboratories, sample transport, or lots of space, spare parts and maintenance). These requirements are costly, and many governments rely on donor support to purchase and provide TB diagnostic tools. Affordability challenges are further compounded by the high add-on costs to many tests in the form of importation taxes, distribution costs, maintenance fees and other expenses.

- From a scientific perspective, major limitations include the low accuracy of some existing tests, either as a result of low sensitivity (high risk of false-negative results) or low specificity (high risk of false-positive results). There is no rapid test to detect resistance to drugs other than rifampicin and isoniazid. Moreover, there are no known, validated biomarkers that can reliably predict or serve as surrogate markers of immunity to TB, disease progression or cure.
### Table 4: WHO-endorsed diagnostics for TB detection and drug susceptibility testing

<table>
<thead>
<tr>
<th>WHO-endorsed technology</th>
<th>Method</th>
<th>Year</th>
<th>Use for detection</th>
<th>Use for DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial liquid culture, rapid speciation strip tests; DST</td>
<td>Culture (growth-based) phenotypic</td>
<td>2007</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Molecular LPA for first-line anti-TB drug-resistance detection</td>
<td>NAAT/genotypic</td>
<td>2008</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>LED microscopy</td>
<td>Microscopy</td>
<td>2010</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>NAAT/genotypic</td>
<td>2010</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Selected non-commercial DST methods</td>
<td>Phenotypic</td>
<td>2010</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>LAMP</td>
<td>NAAT/genotypic</td>
<td>2016</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Urine LAM rapid test</td>
<td>Antigen detection test</td>
<td>2016</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Molecular LPAs for second-line anti-TB drug-resistance detection</td>
<td>NAAT/genotypic</td>
<td>2016</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Xpert MTB/RIF Ultra</td>
<td>NAAT/genotypic</td>
<td>2017</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Source: adapted from (63)

DST, drug susceptibility testing; LAM, lipoarabinomannan; LAMP, loop-mediated amplification test; LED, light-emitting diodes; LPA, line probe assays; NAAT, nucleic acid amplification test

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### 4.1.2 What is the current status of TB diagnostics research?

According to WHO and a consensus of TB stakeholders, the highest priorities in TB diagnostics development include (64):
- a point-of-care, sputum-based test to replace smear microscopy;
- a point-of-care, non-sputum-based test capable of detecting all forms of TB;
- a point-of-care triage test, which should be a simple, low-cost test for use by first-contact health-care providers to rule out TB;
- rapid drug susceptibility testing suitable for microscopy centres;
- a test to identify persons with LTBI who are at the highest risk of progressing to active TB disease; and
- a test for monitoring TB treatment success through to cure.

At first appearance, the TB diagnostics pipeline looks robust, with several new TB diagnostics at various stages of development (Fig. 9). However, the most promising of these candidates will, if successful, primarily meet diagnostic needs at the upper levels of the health system – that is, well-equipped reference laboratories and secondary or tertiary care centres. There are few technologies under development at the low-complexity end of the pipeline that could lead to an inexpensive diagnostic tool for use in primary care centres, where most people with TB first seek care.

The identification and validation of TB biomarkers stands as the single biggest hurdle to developing a true point-of-care TB test as well as a test to identify people with LTBI at high risk of disease progression. Increased investments in basic science are necessary to support the discovery, validation and translation of biomarkers into clinical tools. Over 50 companies and product developers are active in the TB diagnostics R&D space, and many are interested in developing a biomarker-based point-of-care test. However, developers do not have the resources necessary to support biomarker discovery and validation in addition to financing product development and large, multisite clinical performance studies. Increased investment is urgently needed to take biomarker research through validation, and to translate potential biomarkers into clinically useful diagnostic tools (62).
How can we enhance support for TB diagnostics R&D?

The world cannot end the TB epidemic with the diagnostic tests available today. Each day the TB epidemic persists, the human and economic costs only increase. To avert these growing costs, the world must scale up investments in new diagnostic tests for TB. In the Global Plan to End TB, key stakeholders in the TB diagnostics field set the following objectives for the next 5 years of TB diagnostics research:

- develop a portfolio of new diagnostic tools, coupled with a package of accompanying solutions to ensure that results translate into patient treatment;
- evaluate the portfolio of new diagnostic tools and solutions, including new detection strategies, approaches for optimized use and innovative delivery mechanisms in order to demonstrate patient benefits and predict the likely impact of new tests within the health system;
- ensure that new diagnostic tools and solutions are widely available and appropriately used in endemic countries; and
- ensure that critical knowledge is available and shared widely, and explore alternative approaches to case finding.

Failure to make new investments in TB diagnostics R&D today will have major consequences for global TB prevalence in 10 years. There is a cost to complacency, and the funding required to develop new TB diagnostics is modest compared to the cost of inaction. The Global Plan to End TB calls for US$ 676 million in funding for TB diagnostics R&D between 2016 and 2020; additional investment up to US$ 3.4 billion would ensure that new diagnostic tools and solutions are widely available and appropriately used in endemic countries (31).
4.2 THE CASE FOR NEW TB DRUGS AND DRUG REGIMENS

4.2.1 Why do we need new TB drugs and drug regimens?

Despite being preventable, treatable and curable in most forms, TB kills more people every year than any other single infectious agent. Limitations to current TB treatment options – and the slow pace of research to develop new TB therapeutics – have contributed to the persistent magnitude and lethality of the TB epidemic. Over the past 4 decades, only two new drugs from novel classes (bedaquiline and delamanid) have been approved to treat TB. Most of the drugs used to treat TB are decades old, and several have never been studied for TB under the rigorous conditions of RCTs. There is an urgent need to develop safer, simpler, shorter and more effective regimens to treat TB in all its forms, from LTBI to DS-TB to DR-TB.

Standard first-line therapy for DS-TB consists of a four-drug regimen taken over 6 months, and the long duration of treatment makes it challenging for many patients to complete therapy. In addition, critical TB drugs – such as rifampicin, the backbone of the first-line regimen – are incompatible with current antiretroviral treatments for HIV, complicating the treatment of TB-HIV. The even greater length, complexity, cost and toxicities associated with MDR-TB treatment have hampered the scale-up of DR-TB programmes and contributed to poor treatment outcomes (65). The current treatment success rate for MDR-TB is about 50% globally, and even lower for people with extensively drug-resistant TB (XDR-TB), at around 28% (1).

Limited progress in TB drug R&D is a prime example of the crisis in antibiotic development. The conspicuous lack of activity and investment in developing new antibiotics by the pharmaceutical industry has generated warning cries for over a decade (38). Because newly developed antibiotics are not expected to generate blockbuster sales, most pharmaceutical companies have directed the bulk of R&D investments towards diseases with greater market potential, even though infectious diseases, and TB in particular, remain among the leading causes of death in many countries and require continuous innovation to outpace AMR (5). This challenge is compounded in TB drug development as TB disproportionately affects the poor, and most people with TB live in low- and middle-income countries. There is little commercial incentive to develop new TB drugs, given the strong association between TB and poverty, which has led to minimal investments in TB drug R&D by the pharmaceutical industry.

Even when drugs are provided for free, the cost of TB treatment for patients can be extreme. Shorter regimens could help to reduce health-care expenditures for both patients and health systems. A study that compared the standard 6-month DS-TB treatment regimen to a hypothetical 4-month regimen in Bangladesh, Brazil, South Africa and the United Republic of Tanzania estimated that the shorter regimen would reduce direct costs to patients by 5–30% (66). The same economic models suggest that shortened regimens can drive costs savings to health systems, even in the presence of substantially increased drug costs. In particular, reducing the cost of treating MDR- and XDR-TB to the level of the current DS-TB regimen would produce dramatic savings to health systems globally. For example, in South Africa, the per patient cost of MDR-TB treatment was shown to be 103 times greater than treatment of DS-TB, and XDR-TB four times greater than MDR-TB (67).

Finally, new regimens for MDR-TB and XDR-TB are needed to eliminate the serious toxicities imparted by some current TB drugs (e.g. hearing loss, depression, psychosis, and liver and kidney damage). Shorter, safer, more effective and affordable TB regimens will enable TB programmes and health systems to dramatically improve the care they provide, and will increase the likelihood that patients complete treatment, are cured, and avoid the unacceptable financial and personal hardships associated with current therapies.

4.2.2 What is the current status of TB drug research?

In 2000, there were almost no drug candidates in the TB pipeline. By 2017, the pipeline had expanded to include more than 30 compounds, spanning early-stage research to late-stage product development (Fig. 10). The past 5 years saw
the approval of two new drugs (bedaquiline and delamanid) to treat DR-TB as additions to existing regimens. Six compounds, including some repurposed from other disease indications, are in late phases of clinical development. However, the high attrition rate in drug development – and the requirement to treat TB using multidrug regimens – means that a greater number of novel experimental compounds are needed to ensure progress.

Breaking with the past, the field is increasingly focused on developing wholly new drug regimens as opposed to single new chemotherapeutic agents. A number of large trials are underway to identify shorter regimens to treat LTBI, DS-TB, MDR-TB and XDR-TB using combinations of new and repurposed drugs.

- **LTBI treatment trials**: Most LTBI treatment trials are focused on optimizing the drug rifapentine. The NIH and USAID are supporting several phase III trials that are studying the effectiveness of the combination of rifapentine and isoniazid when given to different patient groups in different settings for various durations of time and frequency. The first-ever clinical trials of MDR-TB prophylaxis are also underway, looking at the new drug delamanid or the repurposed drug levofloxacin, with support from the NIH, the Australian National Health and Medical Research Council, the Government of Viet Nam, and the South African Medical Research Council (SAMRC).

- **DS-TB treatment trials**: Researchers are following a number of novel approaches to improve DS-TB treatment, but the overriding focus remains on reducing the duration of therapy. For example, the ACTG and the TBTC are collaborating on a phase III clinical trial to test whether two rifapentine-containing regimens can shorten DS-TB therapy to 4 months. With support from the Government of Singapore, the SPRINT-TB programme is seeking to reduce DS-TB therapy to just 2 months using different combinations of new and old drugs.

- **DR-TB treatment trials**: Multiple groups are testing novel approaches that could lead to all-oral, 6-month regimens for DR-TB. Among them is the STREAM study, funded by USAID, in which The Union is comparing a 9-month regimen first developed in Bangladesh to the longer 24-month approach to treatment previously recommended by WHO. Stage 2 of STREAM will examine whether the addition of bedaquiline to the regimen can further shorten treatment duration to 6 months while eliminating the injectable agent (which causes deafness in many patients). Other trials are being conducted by various groups (including, among others, Médecins Sans Frontières, Partners In Health, Interactive Research and Development, South Africa MRC) to evaluate the safety and efficacy of different combinations of new drugs (including bedaquiline, delamanid and pretomanid) and re-purposed drugs for the treatment of adults with MDR-TB or XDR-TB.

- **Progress towards pan-TB treatment regimens**: For some in the field, the ultimate breakthrough in TB drug R&D would be a 1 month or less treatment regimen that could safely, effectively and affordably treat all forms of TB (68, 69). The TB Alliance is investigating the potential of two regimens – BPAL (bedaquiline, pretomanid and linezolid) and BPaMZ (bedaquiline, pretomanid, moxifloxacin and pyrazinamide) – to provide a way to treat every person with TB (i.e. DS-TB, MDR-TB and XDR-TB) with one of two, all-oral, 4–6 month regimens (70). If successful, these development programmes could move the TB community closer to the advent of an entirely new TB treatment paradigm.
The formation of new platforms for coordination and collaboration across drug developers stands as another significant achievement of the past decade. Early-stage development activities have benefited from the TB Drug Accelerator, which is supported by the Gates Foundation and brings together academic institutions, pharmaceutical companies, the TB Alliance, and other researchers to share results of early-stage discovery programmes, and accelerate those that demonstrate high potential. On the clinical side of the pipeline, the Critical Path to TB Drug Regimens convenes partners from across sectors to advance enabling technologies, as well as the most promising compounds and regimens. 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 to identify important features of new regimens for rifampicin-susceptible TB, rifampicin-resistant TB and pan-TB treatment (71).

4.2.3 How can we enhance support for TB drug R&D?

The rejuvenation of the TB drug pipeline since 2000 is a tremendous tribute to the relatively small number of dedicated governments, research institutions, pharmaceutical companies and individuals involved in TB drug development. Yet current TB treatments remain woefully inadequate, and if left unimproved will forestall progress towards ending the TB epidemic. The Global Plan to End TB set the following objectives for the next 5 years of TB drug research:

- sustain the pipeline through the basic discovery of TB drugs;
- increase clinical trial site capacity;
- develop a shorter regimen for DS-TB;
- develop a safer, shorter and higher efficacy regimen for MDR-TB;
- improve treatment for children in parallel to efforts in adults;
- develop a shorter, high-efficacy regimen for LTBI;
- ensure adoption of new TB drugs and regimens at the country level; and
- engage communities and civil society in the entire process of drug development and access.

Together, these activities will require an estimated US$ 4.15 billion in funding. This is US$ 1 billion less than the estimated US$ 5.3 billion in extra treatment costs that would result from not adequately investing in all areas of R&D over the next 5 years, according to the Global Plan to End TB (31).

4.3 THE CASE FOR NEW TB VACCINES

4.3.1 Why do we need a new TB vaccine?

Vaccines are one of the most successful and effective public health interventions to reduce and even eradicate life-threatening infectious diseases (72). However, the only licensed TB vaccine, BCG, has been inadequate in halting the global TB epidemic, despite its almost global administration. BCG provides moderate protection against severe forms of TB in infants and young children, but does not adequately protect adolescents and adults, who account for the majority of TB transmission. New, more effective vaccines that protect against all forms of TB in all age groups will be essential to end the TB epidemic for the following reasons:

- Public health impact of new TB vaccines. New vaccines may work in multiple ways, including by preventing establishment of an initial infection (pre-exposure) or by preventing progression to disease (post-exposure). A vaccine might also serve as an immunotherapeutic agent by shortening TB treatment or reducing the risk of recurrence following treatment completion. Mathematical modelling suggests that a new TB vaccine for prevention of disease that is 60% efficacious and delivered to just 20% of adolescents and adults globally could avert 60–70 million cases in its first 25 years of use (73). A significantly improved infant vaccine (relative to BCG) would avert about 6–7 million new cases of TB over the same time period. Other models indicate that vaccinating adolescents and adults would be at least as effective in reducing TB in children aged 0–4 years as directly vaccinating infants (e.g. by interrupting TB transmission in households) (74).

- Cost-effectiveness of new TB vaccines. Multiple health economic evaluations have shown that new TB vaccines would be highly cost effective and offer substantial cost savings to health systems and society (75). In addition, new vaccines that are effective in preventing TB disease will reduce or eliminate the often-catastrophic costs of TB shouldered by patients and their families.

- Role of new TB vaccines in addressing AMR. An effective vaccine would play an important role in tackling DR-TB, since new vaccines are likely to be equally effective against both drug-resistant and drug-sensitive strains. By preventing disease, vaccines would reduce the need for antibiotics, an essential step for curbing AMR. Therapeutic vaccines, used in combination with drugs, could also reduce treatment duration and the risk of recurrence, thus reducing the development and spread of AMR (5).
4.3.2 What is the current status of TB vaccine research?

In 2000, there were no preventive TB vaccine candidates in clinical trials. Today, there are 12 candidates under active clinical development and several more in preclinical development (Fig. 11). These candidates include subunit vaccines that pair different combinations of MTB antigens with immune-modifying adjuvants; viral-vectored vaccines; and whole-cell vaccines based on genetically attenuated MTB or closely related mycobacterial species.

An example of the last type is MTBVAC, the only TB vaccine candidate in clinical development based on live-attenuated MTB. MTBVAC is being developed as a replacement for BCG, with infants as the primary target population and BCG-vaccinated adolescents and adults as a secondary population (76). MTBVAC will begin a phase IIa trial in infants and adolescents in the second half of 2017 (77). Two subunit vaccines – M72 + AS01E (owned by GlaxoSmithKline) and H4:IC31 (developed by Denmark’s Statens Serum Institut) – will report results from phase II trials in early 2018. Several other candidates are completing or preparing to initiate phase II trials in various populations, including adolescents (Dar-901, H56:IC31), infants (VPM1002) and adults previously treated for TB (VPM1002).

Despite significant progress in rejuvenating the TB vaccine pipeline since 2000, the current candidates display little antigenic and immunological diversity. It is therefore imperative that funders continue to invest in early-stage research to diversify strategies (78). A more diverse preclinical pipeline is under development, and scientists are exploring alternative routes of vaccine administration (e.g. aerosol delivery). One of the more promising candidates finishing preclinical development is a viral-vectored TB vaccine based on an attenuated version of cytomegalovirus (CMV). CMV is believed to be a potent inducer of novel and persistent immune responses, and has shown the strongest protection to date of any candidate evaluated in non-human primates. Work is ongoing to identify the basis of its protection against TB and understand whether this mechanism can be induced in humans. A CMV-based TB vaccine could enter clinical trials as early as 2019 (77).

Alongside efforts to advance the pipeline, research is underway to develop new tools to overcome the scientific challenges holding back TB vaccine R&D. These efforts include refinement of the animal models used in preclinical development and work to create a controlled human infection model (79) of TB (80, 81). CHIM studies involve intentionally infecting healthy adult volunteers with weakened strains of a pathogen to get early glimpses of a vaccine’s protective ability before commencing expensive, large-scale clinical trials. CHIMs have proven pivotal in accelerating vaccine development for other major infectious diseases (e.g. malaria and influenza).

The lack of biomarkers that can act as prospective signatures of risk of developing TB or as correlates of protection remains the greatest challenge to developing new TB vaccines (82). The identification of biomarkers could accelerate TB vaccine R&D by allowing investigators to detect signals of efficacy at earlier stages of development. In turn, early suggestions of efficacy could improve the selection of candidates for late-stage trials and, once validated, might enable shorter, smaller (and therefore less costly) trials by serving as surrogate endpoints for TB disease. TB vaccine developers are introducing novel trial designs – that is, prevention of infection (POI) and prevention of recurrence (60) studies – to help determine efficacy at earlier time points in the development process (78). The first POI study of a TB vaccine candidate (H4:IC31) results are expected early 2018.
4.3.3 How can we enhance support for TB vaccine R&D?

The TB vaccine field is at an inflection point. An increased focus on early-stage research is leading to a more robust and diverse pipeline, and new approaches and technologies are positioning the field to take advantage of unprecedented scientific opportunities. However, a constrained funding environment has slowed progress. The Global Plan to End TB calls for about US$ 250 million per year over the next 5 years to advance TB vaccine R&D, but the average annual investment for the past 5 years (2011–2016) was only US$ 95 million (59). By comparison, the HIV vaccine field received significantly more funding than TB vaccine R&D between 2007 and 2015 (US$ 6.2 billion versus US$ 943 million) and has conducted six efficacy trials with a seventh soon to begin (83). TB vaccine R&D will only be able to achieve similar milestones with greater global support.

Additional support will need to come from all sectors and take advantage of innovative financing mechanisms that can help to de-risk the inherent uncertainties of vaccine development. Vaccine R&D is a lengthy and expensive process, and timelines and success rates can vary considerably between disease areas and among candidates in the same disease area. Table 5 presents estimated success rates for TB vaccine development by phase. Mitigating the risks inherent to vaccine R&D could help to attract increased support from the pharmaceutical industry. Towards this end, Aeras and the TuBerculosis Vaccine Initiative (TBVI) developed a set of “stage gate criteria” to help ensure that only the most promising candidates advance through the pipeline (84). These criteria are part of an overall portfolio management process designed to mitigate risk, direct limited resources efficiently and increase the overall probability of success.
Despite the compelling global health need for a new vaccine, there is limited industry engagement in TB vaccine development due to the lack of market incentives to invest in a disease that is concentrated in low- and middle-income countries and disproportionately affects the poor. Yet mathematical modelling suggests that TB vaccines could be an attractive market if development is de-risked. Mechanisms for accomplishing this could include grant funding for early, high-risk stages of development or incentives such as advanced price or purchase commitments (85). Using relatively conservative estimates on price and vaccine coverage, one study projected the 10-year worldwide market opportunity for a preventive vaccine targeted at adolescents and adults to be at least US$ 12–13 billion (85).

Public and philanthropic sources of funding are essential since the pharmaceutical industry will probably remain cautious with investments in TB vaccine R&D until early scientific hurdles are overcome. Public and philanthropic support should be directed to enhance the full continuum of vaccine R&D, from early-stage research to translational science to clinical trials. In the Global Plan to End TB, key stakeholders in the TB vaccine field set the following objectives for the next 5 years of research (31):

- continue to advance the clinical pipeline of TB vaccines by conducting clinical trials, exploring novel trial designs, ensuring sufficient manufacturing capacity and conducting epidemiological research at trial sites;
- enhance knowledge by conducting small, early-phase human studies of TB vaccine concepts to address specific scientific hypotheses and provide data to inform future vaccine development;
- increase the emphasis on early-stage and discovery research, including the development of novel vaccination targets;
- improve animal models to better mimic human disease and reflect natural TB transmission;
- improve preclinical and clinical readouts, standardize reagents and harmonize assays used in TB vaccine research; and
- lay the groundwork for adolescent and adult vaccination campaigns.

The TB epidemic costs an estimated US$ 20 billion per year in diagnosis, treatment and lost productivity (1, 86). A US$ 1.25 billion investment in TB vaccine R&D over the next 5 years would represent a fraction of the annual cost of the TB epidemic while dramatically increasing the probability of success and the speed at which researchers can bring this transformative, lifesaving intervention to the countries, communities and people who need it most.
4.4 OPERATIONAL AND IMPLEMENTATION RESEARCH TO END TB

4.4.1 Why do we need TB operational and implementation research?

Ineffective implementation of existing tools is one of the key reasons why progress towards TB elimination remains slow. To date, there has been limited published evidence on the development and comparative evaluation of strategies to deliver evidence-based TB interventions in programmatic settings (87). The lack of such evidence precludes effective programme-wide implementation of interventions known to be effective in improving patient and public health outcomes. Countries and funders will not realize the full benefits of their investments in TB without strengthening country capacity for conducting operational and implementation research (OR/IR) (88).

4.4.2 How has operational and implementation research contributed to TB elimination?

OR/IR is intended to assist in improving programme performance; assessing the feasibility, effectiveness and impact of new strategies or interventions; and collecting evidence to guide policy-making (89).

TB programmes generate substantial amounts of data as part of routine surveillance and clinical care, but the use of this information to improve programme quality is often neglected. A primary goal of OR/IR is to identify ways to close programme performance gaps (i.e. the difference between what is recommended and what actually is delivered in routine practice) in context-specific ways. In turn, quantifying performance gaps and linking them to outcome gaps (the difference between expected and observed impact on health outcomes) becomes a jumping off point for research on strategies to optimize TB care, as shown in Example 1 (90).

Example 1: Using OR/IR to identify performance gaps in MDR-TB case detection in Cambodia (91)

Less than one quarter of MDR-TB patients worldwide are diagnosed and reported to health authorities. To quantify gaps in MDR-TB case finding among previously treated, smear-positive TB patients in Cambodia, the National TB Programme (NTP), the WHO country office and academic investigators conducted a mixed-methods study. Data sources included NTP case notification data and semi-structured interviews with health-care workers. The results revealed multiple points of attrition along the cascade of care for previously treated TB patients: only 50% of patients were registered as previously treated; 36% of patients registered as previously treated did not have their sputum collected or successfully delivered to the laboratory for drug susceptibility testing; 45% of patients whose specimen reached the laboratory had negative culture results; and 5% of those with a positive culture did not have DST performed. Based on these findings, investigators estimated that eliminating attrition early in the cascade of care could nearly double the number of MDR-TB cases detected. Complementing this, interviews with providers identified key barriers to treatment classification. Through this simple and low-cost study, Cambodia’s NTP and its partners revealed a significant performance gap, identified steps in the cascade of care accounting for the largest share of this gap, and pinpointed barriers to completing these steps that could be targeted by specific interventions.

In addition to identifying and filling performance gaps, OR/IR is crucial for understanding the conditions and strategies likely to facilitate implementation and enhance scale-up of new interventions at the country level, as shown in Example 2.
Example 2: Using OR/IR to identify performance gaps in TB case finding and Xpert MTB/RIF implementation in Uganda (92)

Over 4 million of the estimated 10 million people who newly develop TB each year go “missing”, representing a failure of the public health system to either diagnose or report TB cases (1). To improve the TB diagnostic cascade, the Uganda National TB and Leprosy Program joined forces with local and international researchers. Monitoring routine data at six health centres across Uganda revealed that nearly 80% of patients with chronic cough were not referred for TB testing; 20% of those referred did not complete testing; and 30% of smear-positive patients were not initiated on treatment. Similar monitoring at eight health facilities that had implemented Xpert MTB/RIF assay demonstrated that the devices were only being used at 8% of capacity, and that Xpert MTB/RIF testing did not significantly increase the number of patients starting TB treatment. These findings contributed to TB policy changes in Uganda, including the roll-out of a presumptive TB register to document TB screening at microscopy centres, and Xpert MTB/RIF replacing microscopy as the first-line TB test at health facilities.

Example 3: Evaluating the feasibility and effectiveness of China’s “Free TB” policy (93)

Although China has instituted free TB care since the 1990s, recent integration with a TB care delivery model centred at designated hospitals has prompted concern about the feasibility for scale-up and the true impact of this policy on patient costs. To address these concerns and generate data to inform scale-up, the NTP and the Gates Foundation collaborated on a mixed-methods study in three Chinese districts. Data were collected through a patient cost survey, review of case notification and surveillance data, and key informant interviews to elucidate barriers to care. The results demonstrated that TB care continued to burden patients with high costs, mainly due to spending on non-recommended services, examinations and drugs. Qualitative interviews with providers revealed that most ordered medications and tests that were not covered under the free care policy because they lacked trust in the drugs, tests and other supplies provided. These data suggest that the current policy alone is unlikely to achieve zero catastrophic costs for Chinese TB patients. The results offer insights into health service delivery and provide a tool for advocacy on behalf of true universal health coverage.

OR/IR can also be used to evaluate the impact of implementation strategies. Evaluations of this type focus not only on programme performance and health outcomes, but also on understanding whether the selected implementation strategies modify targeted barriers and facilitators, as shown in Example 3. Through these iterative phases, OR/IR generates data to guide, inform and adapt TB-related policy recommendations to specific settings and contexts.

Finally, OR/IR can involve collecting data on the feasibility, benefits and harms of new interventions as they are deployed under routine programmatic conditions. Such “real world” data are often lacking and are an important complement to data from RCTs, as shown in Example 4 (87).
Example 4: Evaluating the effectiveness of using bedaquiline to treat MDR-TB in programmatic settings

In 2013, WHO issued interim guidance on the use of bedaquiline to treat MDR-TB following conditional approval of the drug by the FDA in December 2012, based on phase IIb clinical trial data. Questions about the generalizability of trial results and the lack of phase III clinical trial data led to a conditional recommendation to use bedaquiline in a limited portion of patients with MDR-TB. Operational research has helped inform national guidelines on the use of bedaquiline pending the completion of the drug’s phase III trial (anticipated by the end of 2021). For example, the International Bedaquiline Study Group assessed data from 428 MDR-TB patients at 25 centres in 15 countries, and found promising rates of sputum smear and culture conversion among those receiving bedaquiline (81% and 57% at 60 days, respectively), and relatively low rates of adverse events (~6%) (94). Additionally, the South African NTP analysed over 2000 patients given bedaquiline under routine programmatic conditions and found a mortality benefit associated with bedaquiline use (95, 96).

4.4.3 How can we enhance support for TB operational and implementation research?

Increased funding for OR/IR and its integration into programmatic activities is essential for speeding progress towards TB elimination by allowing TB programmes to leverage the most from investments in basic science and new product development. In addition, conducting OR/IR at the country level is a critical way to improve TB care using a health systems approach that takes into account the patient experience within the larger contexts of health care and development. OR/IR thus gives governments a way to advance TB research and programmes simultaneously. WHO Member States and other stakeholders, including research funders, should take the following actions to support OR/IR:

- support activities for OR/IR capacity-building among programme staff and local researchers through training programmes;
- incorporate rigorous, programme-based OR/IR into proposals for programmatic support as a critical part of programme evaluation (97);
- engage in North–South and South–South research collaborations to conduct programme-focused OR/IR, with the goal of improving programme performance and policy;
- support the call for additional domestic and global TB research funding to help address evidence-practice gaps; and
- advocate for context-specific, evidence-based policy-making and programmatic practice (98).

Without taking these steps, the short- and medium-term targets of the End TB Strategy cannot be met, nor can potentially game-changing innovations be effectively adapted and implemented to meet the long-term goal of TB elimination.
Key messages

- A bibliometric analysis of TB publications and citations over the past decade provides important insights into the contribution of different countries to TB R&D, the dynamics of international collaboration in TB research, and the overlap between TB research outputs and research priorities set by stakeholders in the field.

- Between 2007 and 2016, the United States produced nearly twice as many TB research publications (as measured by country of the first author) as the next highest country, India. The other countries in the top five were China, the United Kingdom and South Africa.

- Compared with research published over the previous decade (1997–2006), there was a major increase in TB publications with a first author from one of the BRICS countries in the 2007–2016 period. The average year-on-year increase in publications from the BRICS countries was nearly double the overall year-on-year increase across all countries.

- North–South collaborations between researchers in high-income and low- and middle-income countries increased during the period 2007–2016, particularly between the United States and high TB burden countries such as India and South Africa. However, South–South collaborations occurred less frequently.

- Across the 10-year period, basic science and epidemiology were the most common TB research areas as measured in an analysis of a random subset of abstracts from TB publications. The same analysis found only a modest correspondence between published TB research and the priority questions outlined in the 2011 International roadmap for tuberculosis research.
It is important to ensure that increased investments in TB research generate knowledge in key areas that will quicken progress towards ending the TB epidemic. Publications can serve as an important measure of knowledge generation in biomedical research, with the important caveat that not all published research is successfully translated into policies with public health impact. Bibliometric analysis (a statistical analysis of citations and publications) is a tool used to map the landscape of knowledge generation in a specific area. It can provide valuable insight into the orientation of knowledge generation with respect to public health needs, the respective contributions of different countries to this knowledge pool and the dynamics of international scientific collaboration.

Previous bibliometric analyses of TB research have shown that research activity has increased over time, with most publications produced by high-income, low TB burden countries such as the United States (99, 100). The bibliometric analysis presented here builds on these earlier efforts – particularly a study by Ramos et al. (2008) that examined TB papers indexed in PubMed for the period 1997–2006 by looking at publications indexed in Web of Science from 2007 to 2016, with the aim of describing TB knowledge generation over the past decade. In addition, an analysis of a random subset of abstracts from these publications assessed the relationship between global TB research outputs and the research priorities outlined in the International roadmap for tuberculosis research (the Roadmap) published in 2011 by WHO and the Stop TB Partnership (101). Appendix 5 describes the methodology of the bibliometric and abstract analyses in detail.

5.1 The United States produced the most TB publications of any country, but the rate of publication increased fastest among the BRICS countries

There was an average 7.3% year-on-year increase in the number of TB publications indexed in Web of Science between 2007 and 2016 (Fig. 12). The top five publishing countries (as measured by first author's country) included two low TB burden countries (United States and United Kingdom) and three high TB burden countries belonging to the BRICS nations (China, India and South Africa). The United States produced the most publications of any country, with nearly twice as many as the second highest country, India (Table 6).

A notable trend since the previous bibliometric analysis by Ramos et al. (2008) is the emergence of the BRICS countries as major research producers. A quarter (25.5%) of all publications in the past decade have a first author from a BRICS country, and the annual proportion of papers with a BRICS country first author increased from 19.3% in 2007 to 30.7% in 2016 (Fig. 13). The average year-on-year increase in publications was 13.1% for BRICS countries, nearly double the overall year-on-year increase across all countries. Comparing these data with the earlier work by Ramos et al. (2008) indicates that South Africa published almost twice as many publications in this decade as it did in the previous decade. In comparison, the United States only published an additional 215 articles. China climbed from the fifth largest producer of TB research publications over 1997 to 2006 to number three for the 2007 to 2016 period.

With 46% of incident TB cases and 40% of all TB-related mortality, the BRICS countries constitute a significant portion of the global TB burden (102). BRICS countries have experienced significant economic expansion over the past 10 years and, accordingly, their domestic research capacity appears to have grown (103). For example, science and technology features prominently in China's new national spending plan (104). In
recent years, the BRICS countries have each taken steps to organize and promote TB research at the country level. In 2016, the Government of India launched the India TB Research Consortium, which aims to bring together all major national and international stakeholders to develop new tools for TB (105). In 2015, Brazil established its National TB Research Strategy, which builds on the decade-long experience of the Brazilian TB Research Network (REDE-TB), a group whose members represent universities, industry, the public health system and civil society (79). In South Africa, the Strategic Health Innovation Partnerships, a special product-development initiative managed by the SAMRC, has flagged TB as a priority research area (106).

Table 6: Top 10 producing countries of TB research publications, 2007–2016

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>6 365</td>
<td>18.4</td>
</tr>
<tr>
<td>India</td>
<td>3 342</td>
<td>9.7</td>
</tr>
<tr>
<td>China</td>
<td>2 534</td>
<td>7.3</td>
</tr>
<tr>
<td>England</td>
<td>2 244</td>
<td>6.5</td>
</tr>
<tr>
<td>South Africa</td>
<td>1 348</td>
<td>3.9</td>
</tr>
<tr>
<td>Brazil</td>
<td>1 298</td>
<td>3.8</td>
</tr>
<tr>
<td>Spain</td>
<td>891</td>
<td>2.6</td>
</tr>
<tr>
<td>Republic of Korea</td>
<td>885</td>
<td>2.6</td>
</tr>
<tr>
<td>France</td>
<td>827</td>
<td>2.4</td>
</tr>
<tr>
<td>Italy</td>
<td>776</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Figure 12: Number of published TB articles by year, 2007–2016

Figure 13: Number of published TB articles by year, stratified by BRICS countries versus non-BRICS countries
### 5.2 North–South TB Research Collaborations Are Increasingly Common

Fig. 14 shows an increasing number of research collaborations between the top five publishing countries over time (where collaboration is defined as having at least one author from the relevant country income strata on the same paper). Of note, the number of collaborations between the United States and high TB burden countries such as India and South Africa increased between 2007 and 2016, as did the number of papers with authors from high-income and low- and middle-income countries. As discussed in Section 4, most R&D investment is concentrated in high-income countries where the TB burden is lowest. In this context, North–South collaborations not only allow for the sharing of resources, but also enable the vital exchange of technical and geographic expertise as well as access to TB patients, samples and trial sites in the places where TB is most common. North–South research collaborations may also help to ensure that research principally funded by institutions in high-income, low TB burden nations reflects the insights of scientists from high TB burden countries (and, perhaps, the priorities of communities heavily affected by TB).

While North–South collaborations increased over the past decade, the network analysis presented in Fig. 14 suggests that South–South collaborations occurred less frequently. Many papers with authors from the United States included coauthors from India and South Africa, but comparatively few were published between authors from these countries alone. Given the rising contribution of individual BRICS countries to TB knowledge generation, a clear next step would be for BRICS countries to increase collaborative research activities with one another.

Most articles on TB were published in specialty journals focused on TB, respiratory diseases or infectious diseases (Table 7). Only a minority appeared in high-impact, general medical journals, as would be expected given the broader scope and higher publishing requirements of such outlets.

### Table 7: Top journals publishing TB research, 2007–2016

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Number of articles</th>
<th>2016 5-year impact factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>International Journal of Tuberculosis and Lung Disease</td>
<td>2,021</td>
<td>2.38</td>
</tr>
<tr>
<td>2</td>
<td>PLoS One</td>
<td>1,726</td>
<td>3.39</td>
</tr>
<tr>
<td>3</td>
<td>American Journal of Respiratory and Critical Care Medicine</td>
<td>946</td>
<td>13.08</td>
</tr>
<tr>
<td>4</td>
<td>Tuberculosis</td>
<td>773</td>
<td>2.93</td>
</tr>
<tr>
<td>5</td>
<td>European Respiratory Journal</td>
<td>716</td>
<td>8.49</td>
</tr>
<tr>
<td>6</td>
<td>International Journal of Infectious Diseases</td>
<td>514</td>
<td>2.59</td>
</tr>
<tr>
<td>7</td>
<td>Journal of Clinical Microbiology</td>
<td>504</td>
<td>3.85</td>
</tr>
<tr>
<td>8</td>
<td>BMC Infectious Diseases</td>
<td>469</td>
<td>2.96</td>
</tr>
<tr>
<td>9</td>
<td>Respirology</td>
<td>404</td>
<td>3.18</td>
</tr>
<tr>
<td>10</td>
<td>Antimicrobial Agents and Chemotherapy</td>
<td>398</td>
<td>4.33</td>
</tr>
</tbody>
</table>
IS TB RESEARCH ADDRESSING KEY RESEARCH PRIORITIES?

In 2011, WHO and the Stop TB Partnership published the *International roadmap for tuberculosis research (the Roadmap)* (101). The *Roadmap* sought to present a coherent list of research priorities on the road to TB elimination; identify knowledge gaps stymying progress; and highlight key areas in which to encourage greater, more coordinated investment. The *Roadmap* identified and described priority research questions in six areas of research: epidemiology; basic science (referred to in the *Roadmap* as “fundamental research”), diagnostics, treatment, vaccines, and operational and public health research (Appendix 6). These areas encompass the full spectrum of TB research and correspond to the research categories presented in the analyses of TB research funding trends in Section 4.

In order to explore how current knowledge generation in TB aligns with the *Roadmap*, a detailed analysis was conducted on a random 5% year-stratified subset (n=1725) of the TB publications indexed in Web of Science between 2007 and 2016. Abstracts were analysed and original research articles (n=878) were categorized according to the research areas and priority questions described in the *Roadmap*. A small proportion of articles (1.7%) did not fall under any of the six research areas; these were categorized as ‘other’.

This subset analysis is not without limitations. The ability to draw strong conclusions from the 5% random sample is limited, because the analysed abstracts represent a small number of the total TB publications indexed in Web of Science over the period 2007–2016. As a result, this analysis may miss some key publications and overlook less obvious trends. Additionally, neither the subset analysis nor the bibliometric analysis captures the quality, depth or size of a given study. For example, the high-quality evidence produced by RCTs of new drugs and vaccines may be the product of years of work and millions of dollars while only resulting in a single publication. Despite these limitations, the random sampling methodology enables inferences to be made about the proportion of research being conducted in key areas and to what degree high-priority research questions are being addressed.

The proportion of articles published in each research area remained relatively stable across the 10-year period (Fig. 15). Table 8 shows the proportion of abstracts that addressed various priority questions under each research theme, as identified in Appendix 6. Across the 10-year period, basic science and epidemiology were the most dominant research areas, with 33.8% and 29.6% of articles, respectively. However, only a small proportion of articles in the 5% subset addressed priority questions in the *Roadmap* (see summaries for each area below). If confirmed by more detailed analyses, this would suggest a need to better align ongoing TB research to meet the main needs identified in the *Roadmap*, and to increase efforts to ensure that basic-science research is successfully translated into products and policies that can help end the TB epidemic.

**Epidemiology**

Within the domain of epidemiology, 17.9% of articles addressed the burden of TB (priority question 1.1), while 25.6% addressed TB transmission dynamics (1.2). In comparison to trends observed in other research areas, the proportion of articles addressing either priority question varied minimally over the decade.

**Fundamental research**

The greatest proportion of articles in the subset (33.8%) fell under fundamental research. Of these, 7.4% addressed the characterization of human TB (2.1), 20.1% addressed host-
pathogen interaction (2.2), and 3.7% addressed biomarker discovery (2.3). There was little variation over the decade in the proportion of articles addressing any given priority questions.

**Diagnostics**

Among the articles categorized as diagnostics (10.1% of the subset), the most commonly addressed priority question was the evaluation of new TB diagnostics (3.4) followed by designing and validating new tools for TB diagnosis in high-burden settings (3.2). Of note, only 6.7% of diagnostics articles addressed biomarkers for TB diagnosis (3.1). The lack of validated biomarkers for TB has been identified as the greatest translational challenge for the development of new tools (62). These data may suggest a need to increase investment in TB biomarker research to address this important knowledge gap.

**Treatment**

Among the articles categorized as treatment, the proportion addressing any one priority question varied greatly from year to year. Overall, 12.1% of articles addressed the development of new drugs and treatment strategies (4.1) and 10.3% addressed more effective and safer drugs for DR-TB (4.3). In this domain, no studies were identified for priority question 4.5 on TB drugs for TB-HIV coinfected individuals. However, major clinical trials investigating TB-HIV coinfection have been published in the past decade, highlighting the limitations of the 5% subset analysis. Articles on TB treatment constituted only a small portion (6.6%) of the overall subset (107-110).
Articles related to TB vaccine research constituted only 5.1% of the subset, the least of any research area. Over half (55.6%) of the articles identified in this research area addressed fundamental questions such as how to best prime, boost or modulate the immune response needed to control MTB infection (5.1). Priority question 5.2 on conducting research and clinical testing to better understand the safety and efficacy of BCG and of new candidate vaccines was addressed by 37.8% of articles categorized as ‘vaccines’. The 5% subset did not contain any articles addressing biomarkers that can act as correlates of protection (5.3). As with diagnostics, the identification of TB biomarkers (particularly those that can act as signatures of risk of developing disease or as correlates of protection) is a significant challenge to vaccine R&D (82). Within the subset, no articles related to TB vaccine research addressed priority questions 5.5 and 5.6 on new vaccine efficacy and improved testing of vaccines, respectively. However, several vaccine candidates are under active clinical development, and the first efficacy trial of a TB vaccine since the 1960s published results in 2013 (78).

Operational and public health research

Of the articles in the subset, 13.1% were categorized as operational and public health research, and among these 17.2% addressed TB case detection and diagnosis (6.1). The second most commonly addressed question was the improvement of measurement of disease burden (6.8). This research area encompasses a large variety of research topics, including implementation of new technologies, capacity-building and programmatic research. In contrast to the other research areas, many of the operational and public health priority questions are quite specific and therefore are less likely to be common topics of TB research publications.

### Table 9: Most Frequently Listed Funders among a Random Sample of TB Papers Published between 2007 and 2016

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top Funders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>National Institutes of Health, USA</td>
</tr>
<tr>
<td>2</td>
<td>National Natural Science Foundation of China</td>
</tr>
<tr>
<td>3</td>
<td>Bill &amp; Melinda Gates Foundation</td>
</tr>
<tr>
<td>4</td>
<td>European Commission</td>
</tr>
<tr>
<td>5</td>
<td>USAID</td>
</tr>
</tbody>
</table>

USA, United States of America; USAID, United States Agency for International Development
Key messages

- TB is emblematic of the persistent “gross mismatch” between burden of disease and investments in health research first described as the 10/90 gap. Despite accounting for nearly 2% of DALYs and 2% of deaths globally, TB only receives 0.25% of the estimated US$ 265 billion spent on medical research annually.

- TB research receives less funding per fatal case than HIV and malaria, and less funding per DALY than HIV. Research funding per DALY and fatal case stayed flat for TB between 2010 and 2015 but increased for HIV and malaria.

- Limited funding in TB has influenced both the speed and composition of TB research. The pace of new product development for TB has lagged behind HIV and malaria. Between 1970 and 2016, fewer new TB products came to market and most of these represented new formulations, indications or combinations of products developed decades earlier. The TB field saw fewer new chemical entities approved than either HIV or malaria.
The 1990 Commission on Health Research for Development first described the gross mismatch between the global burden of disease and investments in health research that would come to be known as the 10/90 gap. At the time, the 10/90 gap described a situation in which less than 10% of worldwide resources for health R&D were put towards solving health issues prevalent in developing countries, where over 90% of preventable deaths occurred (111). A 2013 synthesis of available health R&D funding data found that “although the nature of the 10/90 gap has changed since the 1990s, the gap itself very much remains” (112). The estimated US$ 2.4 billion for research on neglected diseases in 2010 amounted to 1% of the US$ 240 billion spent on health R&D in that year. Where does TB fall within this persistent gap, and how does funding for TB R&D compare to spending on research responding to other global epidemics such as HIV and malaria?

6.1 TB RECEIVES JUST 0.25% OF GLOBAL HEALTH R&D SPENDING

A recent analysis by Moses et al. (2015) found that global medical research expenditures grew from US$ 208.8 billion in 2004 to US$ 265.0 billion in 2011 (113). In the same year, TB accounted for 1.78% of total DALYs and 2.24% of total deaths worldwide, but expenditures of US$ 675.3 million on TB research amounted to just 0.25% of total medical R&D spending.

Looking at medical R&D expenditures over time, Moses et al. observed a number of patterns that accord to trends in TB R&D. First, medical research funding is highly concentrated among a limited number of institutions – for example, the NIH accounted for 12% of global funding in 2011 (113). Second, between 2004 and 2011, investments by the pharmaceutical industry shifted away from basic discovery and preclinical research towards late-stage clinical trials (113). Third, in the view of the authors, the combination of diminished investments in basic discovery by pharmaceutical companies, and flat funding by the US Government and major philanthropies, presages that “difficulties may soon appear in the ability of clinicians to realize the value of past investments in basic biology” (113). TB research could encounter a similar challenge if chronic underfunding slows the translation of promising findings into products with clinical and public health applications (114).

6.2 TB RECEIVES LESS R&D FUNDING PER DALY THAN HIV AND MALARIA

Comparing research funding for TB, HIV and malaria shows that progress – assessed in terms of research spending in relation to burden of disease – has not been equal for the three diseases over time. The combination of relatively stable funding for research and significant progress in reducing morbidity and mortality means that HIV and malaria receive more research dollars per DALY and per fatal case than TB, a discrepancy that has grown over the past 5 years. At the same time, all three diseases have serious unmet research needs.

Between 2010 and 2015, research funding decreased for TB and HIV and stayed flat for malaria. Assessed in 2015 constant dollars, spending on TB R&D fell from US$ 713.2 million in 2010 to US$ 620.6 million in 2015, a 13% decrease. Similarly, HIV research funding decreased by 15%, dropping from US$ 1.2 billion in 2010 to US$ 1 billion in 2015. (Of note, the figures for HIV research significantly underestimate total spending, given that the source of these estimates, the G-FINDER report, excludes most forms of HIV drug development and some types of HIV basic-science activities.) Malaria R&D spending of US$ 565 million in 2015 was just slightly under the US$ 573 million expended in 2010.

Fig. 16 shows the change in R&D dollars spent per DALY for TB, HIV and malaria between 2010 and 2015. In 2010, for each DALY attributable to TB, the world spent US$ 12 on research compared with US$ 14 for HIV and US$ 8 for malaria. By 2015, R&D expenditures per DALY remained unchanged for TB. For malaria and HIV, flat funding for research between 2010 and 2015, coupled with substantial reductions in DALYs, resulted in higher per DALY R&D expenditures. Malaria research spending per DALY increased to US$ 10 (a 30% increase) and HIV to US$ 15 (a 10% increase). Research spending per DALY would be even higher for HIV if accounting for the research categories excluded from the G-FINDER report.
Analysing R&D expenditures in relation to attributable mortality for the three diseases reveals a similar trend (Fig. 17). In 2010, TB research received US$ 475 for each fatal case of TB while HIV research received US$ 767 and malaria US$ 602. R&D spending per fatal case decreased slightly for TB from 2010 to 2015, while spending increased for both HIV and malaria. Over 2010–2015, TB research received an average of US$ 492 per fatal case compared to US$ 809 for HIV and US$ 694 for malaria.

There is significant overlap between the 10 largest funders of TB, HIV and malaria research (Fig. 18). Given the considerable overlap among major funders, increasing resources for TB R&D will require cultivation of a wider, more diverse funding base.
### Figure 18: Change in Top 10 Funders for TB, HIV, Malaria over Time

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</thead>
<tbody>
<tr>
<td>1</td>
<td>US NIH ($158M)</td>
<td>US NIH ($214M)</td>
<td>US NIH ($679M)</td>
<td>US NIH ($664M)</td>
<td>Gates Foundation ($124M)</td>
<td>Gates Foundation ($124M)</td>
</tr>
<tr>
<td>2</td>
<td>Gates Foundation ($57M)</td>
<td>Gates Foundation ($111M)</td>
<td>Gates Foundation ($92M)</td>
<td>Gates Foundation ($107M)</td>
<td>Gates Foundation ($124M)</td>
<td>Gates Foundation ($124M)</td>
</tr>
<tr>
<td>3</td>
<td>Industry ($43M)</td>
<td>Industry ($81M)</td>
<td>USAID ($67M)</td>
<td>USAID ($58M)</td>
<td>US NIH ($84M)</td>
<td>Industry ($147M)</td>
</tr>
<tr>
<td>4</td>
<td>US CDC ($20M)</td>
<td>USAID ($34M)</td>
<td>United Kingdom DFID ($31M)</td>
<td>Industry ($55M)</td>
<td>US DOD ($33M)</td>
<td>Gates Foundation ($108M)</td>
</tr>
<tr>
<td>5</td>
<td>European Commission ($13M)</td>
<td>UK DFID ($23M)</td>
<td>US DOD ($28M)</td>
<td>US DOD ($29M)</td>
<td>European Commission ($22M)</td>
<td>UK DFID ($19M)</td>
</tr>
<tr>
<td>8</td>
<td>USAID ($7M)</td>
<td>UNITAID ($14M)</td>
<td>Irish Aid ($14M)</td>
<td>Inserm ($11M)</td>
<td>US NIH ($19M)</td>
<td>Australian NHMRC ($8M)</td>
</tr>
<tr>
<td>9</td>
<td>United Kingdom MRC ($6.2M)</td>
<td>United Kingdom MRC ($11)</td>
<td>DGIS ($13M)</td>
<td>CIHR ($6.3M)</td>
<td>USAID ($9M)</td>
<td>USAID ($9M)</td>
</tr>
<tr>
<td>10</td>
<td>Inserm ($5.7M)</td>
<td>ICMR ($9M)</td>
<td>United Kingdom MRC ($13M)</td>
<td>United Kingdom MRC ($5.3M)</td>
<td>DGIS ($5.5M)</td>
<td>ICMR ($7.7M)</td>
</tr>
</tbody>
</table>

Funders appearing in green are new to the list in 2015. Investments from industry groups are aggregated.

CDC, Centers for Disease Control and Prevention; CIHR, Canadian Institutes of Health Research; DFID, Department for International Development; DGIS, Dutch Directorate for International Cooperation; DOD, Department of Defense; Gates Foundation, Bill & Melinda Gates Foundation; HIV, human immunodeficiency virus; ICMR, Indian Council of Medical Research; M, million; MRC, Medical Research Council; NHMRC, National Health and Medical Research Council; NIH, National Institutes of Health; TB, tuberculosis; UK, United Kingdom; US, United States; USAID, United States Agency for International Development.
6.3
TB PRODUCT DEVELOPMENT HAS LAGGED BEHIND HIV AND MALARIA

A comparison of new quality-assured products developed and brought to market shows that the pace of product development in TB has lagged behind HIV and malaria. This analysis updates two earlier studies assessing drug development for neglected diseases over two time periods: 1975–1999 and 2000–2011 (115, 116). For these studies and the following analysis, new products include quality-assured treatment options or biologics. A product counts as quality-assured if it has received regulatory approval from the FDA, European Medicines Agency, WHO prequalification programme (WHO PQ) or Global Fund Expert Review Panel. New products include new chemical entities (NCEs), new indications, new formulations and new fixed-dose combinations (FDCs).

Two thirds of the TB products approved between 1970 and 2016 were new formulations, indications or FDCs of products developed decades earlier; only one third were NCEs (Table 10). By contrast, nearly 63% of HIV product approvals and 50% of malaria approvals were for NCEs or FDCs that contained an NCE not approved as a standalone product (e.g. lopinavir and tenofovir alafenamide fumarate). In contrast to HIV and malaria, a sizeable fraction of new TB product approvals were expanded indications for drugs developed for other conditions – for example, the WHO prequalification of the fluoroquinolones in 2010 and 2011.

Fig. 19 shows the number of NCEs approved annually for each disease since 1970. The figure reveals a 22-year gap between the approval of pyrazinamide in 1970 and the next TB NCE to receive marketing authorization (i.e. rifabutin in 1992). Another rifamycin – rifapentine – followed in 1997, but it took 15 more years until the 2012 accelerated approval by the FDA of bedaquiline, the first new TB drug from a novel class since pyrazinamide. Compared to TB, the development of NCEs for treating HIV proceeded rapidly following the approval of zidovudine in 1987. In 2003 alone, HIV had more NCE approvals than TB saw in two decades. NCE approvals for malaria picked up after 2000 with the WHO prequalification of artemisinin-based combination therapies.

Although the pipelines for TB, HIV and malaria started in different places over this period – indeed, HIV drug development did not begin until the mid-1980s – this analysis suggests that limited funding in TB has influenced both the speed and composition of TB research. While TB drug developers brought two new compounds from novel classes to market, the bulk of activity in the past 15 years focused on repurposing existing compounds, many of which were first introduced decades ago. To a certain extent, this is a consequence of limited pharmaceutical industry investment in TB drug R&D due to the lack of adequate market incentives. Dramatically reduced public funding for TB research in the 1980s also left TB drug development with an unfinished agenda that developers needed to complete during the field’s revitalization in the 2000s. For example, the PanACEA research network is conducting studies to establish the optimal dose of rifampicin, the backbone drug of first-line TB treatment, with

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### Table 10: New Quality-Assured Products Developed and Brought to Market for TB, HIV, and Malaria, 1970–2016

<table>
<thead>
<tr>
<th>Product Type</th>
<th>TB</th>
<th>HIV</th>
<th>Malaria</th>
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<tbody>
<tr>
<td>New Chemical Entities (NCE)</td>
<td>5</td>
<td>30*</td>
<td>9</td>
</tr>
<tr>
<td>New Formulations</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>New Indications</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>New Fixed-Dose Combinations (FDC)</td>
<td>5</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>New Biologics</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td><strong>47</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>

*Includes two NCEs only approved as part of FDCs (lopinavir and tenofovir alafenamide fumarate). The total number of approved HIV products does not double count lopinavir and TAF.

Detail on TB products: TB NCEs include pyrazinamide, rifabutin, rifapentine, bedaquiline, and delamanid. Other TB products include first-line FDCs; new indications (e.g., the quinolones, linezolid); and new formulations (e.g., PAS granupas).

HIV, human immunodeficiency virus; PAS, para-aminosalicylic acid; TAF, tenofovir alafenamide
Figure 19: New Chemical Entity Approvals by Year for TB, HIV, and Malaria, 1970–2016

Detail on new TB product approvals (new chemical entities appear shaded in blue)

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<tbody>
<tr>
<td>PZA</td>
<td>Rifabutin (FDA)</td>
<td>Rifapentine, active (FDA)</td>
<td>HRZE FDC (WHO PQ)</td>
<td>HRE FDC (WHO PQ)</td>
<td>HRZ FDC (WHO PQ)</td>
<td>Moxifloxacin (WHO PQ)</td>
<td>Levofloxacin (WHO PQ)</td>
<td>Bedaquiline (FDA)</td>
<td>PAS granupas (EMA)</td>
<td>Delamanid (EMA)</td>
<td>Pediatric FDC (Global Fund ERP)</td>
<td></td>
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<tr>
<td>(FDA)</td>
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</table>

Support from the European Commission (EDCTP). By contrast, HIV drug development has enjoyed steadier progress thanks to more stable, robust levels of public and private investment. The year 2016 marked 20 years since the introduction of combination-based antiretroviral therapy in 1996. The years that followed saw a period of unprecedented drug discovery. Between 1996 and 2006, competition between at least eight major pharmaceutical companies improved HIV regimens to the point of offering three-in-one FDCs, and the field is now pursuing long-acting antiretroviral therapy formulations (117).
7. DISCUSSION AND RECOMMENDATIONS
The next decade will be a critical period in the global TB response. Meeting the End TB Strategy targets of a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030 compared with 2015 will only be possible through research and innovation. The low absolute level of funding for TB research is insufficient to support such needs, despite the strategic use of limited resources to date. Under the status quo, one institution within each sector accounts for over half of all money spent on TB research by public, private, and philanthropic actors. This degree of concentration leaves the field vulnerable to sudden shifts in priorities among leading donors or policy changes by country governments. Funding must also make progress against inflation, which has steadily eroded the real value of TB research dollars.

Reversing these trends poses a formidable challenge, but there are many points of entry and reasons for governments and other stakeholders to get involved.

- The fact that in 2015 an institution only needed to spend US$ 10 million to rank among the 10 largest TB research funders worldwide means that an investment in a new flagship TB research programme, or a grants portfolio earmarked for TB within a larger science and technology funding envelope, can make a meaningful difference that is felt by the field at large.

- The experience of TB research over the past 10 years indicates that early public investments often attract co-funding from other sectors. Public institutions including the NIH, CDC, USAID, European Commission, EDCTP, Japanese Ministry of Health, Labour and Welfare, and others have formed public–private research partnerships with drug, diagnostic and vaccine developers. By signalling opportunity, public money may help to raise resources for TB research outside the public sector. Philanthropic investments in TB research have had a similarly catalytic effect and have proven indispensable for keeping industry groups engaged in the field and supporting the work of the product-development partnerships involved in TB R&D, including Aeras, FIND and the TB Alliance.

- The TB community has taken steps in recent years to organize collaborative research platforms that combine and coordinate the contributions of different funders to tackle big challenges. For example, the vaccine field has explored forming a Global TB Vaccine Partnership to identify new funding and better align resources with scientific priorities (118). Further along is the Life Prize, an innovative investment framework to incentivize TB drug research first proposed by Médecins Sans Frontières and now hosted by The Union. By combining push, pull and pool mechanisms, the Life Prize seeks to attract new investors and re-engage traditional funders in the development of new TB drug regimens (119). In a similar vein, the Medicines Patent Pool recently expanded its mandate to include TB, and in January 2017 it announced its first license for TB treatment in an agreement with Johns Hopkins University to facilitate the development of the TB drug compound sutezolid (120). These platforms and others provide ample opportunities to invest in joint initiatives, combine financial and scientific resources, and leverage investments across governments and sectors.

- The costs of research pale in comparison to the costs of inaction. According to the Stop TB Partnership, a 5-year delay in funding R&D at the targeted level of US$ 9 billion between 2016 and 2020 could result in over 8 million additional TB cases and more than 1 million excess TB deaths, equating to billions of dollars in extra treatment costs and lost productivity (31). Research on TB will be essential for averting future costs from AMR, which, if left unchecked, could cause the global economy to incur losses worth US$ 100 trillion by 2050 (5). That TB accounts for nearly 2% of DALYs and deaths worldwide, yet in recent years has only received 0.25% of total global spending on health R&D, indicates that current research funding is not commensurate with the heavy toll TB exacts on lives, livelihoods and national economies.

- Despite a critical shortage of resources, the money that has been invested in TB R&D has produced significant returns. Early advances in TB research helped to define modern medicine, and only the disappearance of funding in the 1970s and 1980s halted this momentum. Since the field’s revitalization at the turn of the century, TB research has produced several historic advances, including a rapid test that can detect TB and resistance to rifampicin (Xpert MTB/RIF), two new drugs to treat DR-TB (bedaquiline and delamanid), and a safer, shorter regimen for treating LTBI (3HP). With promising candidates in the pipeline and a better understanding of the basic science of TB, the TB research community is well positioned to make further advances. An injection of funding for high-quality R&D would enable TB scientists to build on these recent advances and accelerate progress towards producing the high-impact innovations required to meet the SDG and End TB Strategy targets.

Building on the accomplishments of the past decade will require the securing of additional resources and the development of new ways of working together to maximize efficiencies and avoid
duplication of efforts. Governments and stakeholders from all sectors should join forces to enable scientific progress on TB and ensure that all people with or at risk of TB have access to the benefits of scientific advancement, whether these come in the form of new tools or improved models of service delivery, care and support.

Multiple international initiatives and declarations have recognized the need to create new ways of jointly financing health research and innovation to meet the challenges posed by TB and other global health threats:

- In its final report, issued in September 2016, the UN Secretary-General’s High-Level Panel on Access to Medicines wrote that “it is imperative that governments increase their current levels of investment in health technology innovation to address unmet needs” and urged governments and other stakeholders to “test and implement new and additional models for financing and rewarding public health R&D” (121).
- In parallel to this, the political declaration of the UN high-level meeting on AMR called for “joint action” to resolve the lack of investment in R&D (32). Importantly, this political declaration, adopted by UN member states, discusses R&D by referencing particular norms and principles for promoting innovation to address pressing public health needs. In the words of the declaration, “research and development efforts should be needs-driven, evidence-based, and guided by principles of affordability, effectiveness, and efficiency and equity, and should be considered as a shared responsibility”. The declaration acknowledges the importance of delinking the costs of R&D investments from the price of resulting products, and calls on “all relevant stakeholders” to explore innovative R&D models. Many of the norms and principles included in the political declaration on AMR and voiced in the final report of the UN Secretary-General’s High-Level Panel on Access to Medicines have been progressively developed and articulated by WHO Member States working together through initiatives such as the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) (122).

In line with these UN-level initiatives, multiple intergovernmental forums have raised the need for increased cooperation and joint action on health R&D. The BRICS ministers of health have called for coordinated action on TB R&D on several occasions. In the 2012 Delhi Communiqué, the BRICS countries resolved to collaborate to develop “capacity and infrastructure to reduce the prevalence and incidence of TB through innovation for new drugs, vaccines, diagnostics and promotion of consortia of TB researchers to collaborate on clinical trials of drugs and vaccines” (123). These ideas were reiterated in 2014 when the BRICS ministers of health met in Brazil and agreed to cooperate on research and innovation for TB, identifying technology sharing, manufacturing capacity and TB financing as key priorities (124). In December 2016, the BRICS ministers of health returned to Delhi, where eight of the 25 points in the resulting communiqué concerned research. Most importantly, the BRICS health ministers “agreed to the setting up of a BRICS network on TB research and creation of a research and development consortium on TB, HIV and malaria including the possibility of international fund raising” (125).

These multiple resolutions by the BRICS health ministers to work together on TB research were echoed by leaders of the BRICS nations when they met in Xiamen, China, in September 2017. In the declaration released at the summit, the BRICS heads of state agreed to “foster the development and improve the availability of innovative medical products through promotion of research and development”. Importantly, the declaration specifically referenced efforts to establish new global frameworks to advance TB research in line with the SDGs. BRICS leaders welcomed “the decision to set up the Tuberculosis Research Network”, an initiative described in the recommendation section of this policy paper, and that will be presented at the First WHO Global Ministerial Conference on Ending Tuberculosis in the Sustainable Development Era: A Multisectoral Response, in Moscow in November 2017.

In addition to garnering support in BRICS country dialogues, TB research has received welcome attention at wider diplomatic forums in the context of AMR. At their July 2017 summit in Hamburg, Germany, the G20 nations recognized the imperative of supporting research on TB and other infectious diseases in order to tackle AMR. The 2017 G20 Leaders’ Declaration highlighted “the importance of fostering R&D, in particular for priority pathogens as identified by WHO and TB” (126). Notably, the specific mention of TB marked only the second time a G20 declaration singled out a particular disease threat by name (the first was in response to Ebola in 2014) (127). To foster this research, G20 leaders called for “a new international R&D Collaboration Hub to maximize the impact of new and existing anti-microbial basic and clinical research initiatives as well as product development” (126). They further stated their intention to examine practical market incentives for antimicrobial research together with WHO and the Organization for Economic Co-operation and Development (OECD). By naming this new platform (i.e. the R&D Collaboration Hub) and “inviting all interested countries and partners to join this new initiative”, the G20 set forth a tangible proposal for advancing research and innovation to overcome TB and other drug-resistant infections.
7.2 RECOMMENDATIONS

To turn these declarations of intent into a reality, and to ensure that the next decade of TB research delivers the innovations required to end the TB epidemic, governments should pursue a series of actions at the national and international levels, detailed in the recommendations below. These recommendations acknowledge that ending the TB epidemic and averting the looming crisis of AMR will require breaking out of business-as-usual approaches. States must work together and in concert with other stakeholders to develop and deploy innovative interventions for supporting and financing research.

1. At the national level, countries should take steps to create research-enabling environments that nurture and facilitate TB R&D. This will involve reducing structural impediments to research where they exist, increasing TB research capacity, developing national strategic plans for TB research, and activating domestic research financing mechanisms. In creating research-enabling environments, countries can seek guidance from the detailed blueprint in the WHO Global action framework for TB research (the WHO Action framework) (128). Priority steps to be taken include:

a. **Streamlining regulatory processes for the review of clinical trials and other research activities in order to expedite research.** This can involve creating a streamlined, predictable process for ethics and regulatory approvals, and providing a simple pathway for the transfer of biological samples, study drugs and other equipment in and out of a country. Lack of such logistical considerations can increase the cost and complexity of clinical trials and result in avoidable delays. The need to address these issues has been raised by many funders, industry groups, scientists and advocates as an important priority. The particular challenges will vary by setting, and there is much that countries can learn from one another in creating regulatory and administrative frameworks that facilitate research while ensuring the safety of research participants. At a minimum, countries should develop or enhance their capacity to evaluate products studied elsewhere, to allow for their importation for the benefit of their constituents.

b. **Developing country-specific TB research agendas and strategic plans to expand and accelerate TB research at the country level through capacity-building and multisectoral partnerships.** The WHO Action framework encourages countries to create national TB research networks that can serve as platforms for bringing together stakeholders to develop country-specific research plans and advocate for TB R&D. The development of these plans should proceed through a broad consultation of stakeholders and assessment of existing research capacity, and consider the specific unmet innovation needs arising from local TB epidemics. Capacity-building – in the form of training a sustained cohort of TB researchers and developing required infrastructures – should be a key element of any plan. Importantly, the TB research plans should be incorporated into larger national TB strategies in keeping with the End TB Strategy’s insight that promoting research is of equal concern for states as ensuring patient-centred TB care and prevention, and advancing bold policies and supportive systems. To evaluate the success of such efforts, national TB research networks should set up observatory systems to report on TB research undertaken at the country level. In pursuing these objectives, countries can draw on the experience of pathfinder nations that have already organized national TB research networks and developed national TB research plans, including Brazil, Ethiopia, India, Swaziland and Thailand.

c. **Activating domestic financing mechanisms to increase funding for TB research.** Dedicated resources for TB research within bigger health R&D funding envelopes managed by ministries of health and ministries of science and technology will be critical for success. One way to accomplish this is for countries to set a target of spending a particular proportion of GDP or GERD on health R&D, and within that amount, earmark a certain percentage of funding for TB research. As a starting point, the WHO CEWG has recommended “all countries should commit to spend at least 0.01% of GDP on government-funded R&D devoted to meeting the health needs of developing countries”. In addition to budgetary appropriations for TB research, governments can draw on a number of policy levers
Table 11: Possible fiscal policy and regulatory incentives to promote TB research

The tools below represent a range of legislative, policy and regulatory approaches to stimulate research and development on diseases of high public health importance left unaddressed by market forces. Many have been tried in other disease areas, and some have been used to promote investment in other types of public goods (e.g. environmental conservation, public infrastructure). Each comes with its own strengths and weaknesses, and the appropriateness of each for TB research may vary by setting, stage of research, and how each is designed and implemented.

<table>
<thead>
<tr>
<th>Fiscal policy options</th>
<th>Description</th>
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<tbody>
<tr>
<td>Tax levies</td>
<td>Taxes on particular products, services or activities instituted with the goal of generating resources for health R&amp;D. The international solidarity levy on airline tickets that supports Unitaid is one prominent example. Other possibilities include taxes on types of financial transactions, carbon emission taxes, or the proposed Solidarity Tobacco Contribution.</td>
</tr>
<tr>
<td>Biomedical research bonds</td>
<td>Bonds issued by federal, state or local governments to finance research.</td>
</tr>
<tr>
<td>Research innovation trusts</td>
<td>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.</td>
</tr>
<tr>
<td>Tax check-off programmes</td>
<td>Tax payment systems that allow individuals to specify a portion of their tax payment to be directed to medical research.</td>
</tr>
<tr>
<td>Foreign capital repatriation</td>
<td>Tax provisions that allow companies to return funds held outside a country if used for research.</td>
</tr>
<tr>
<td>Budgetary set asides</td>
<td>A proportion of budget envelopes set aside or earmarked for research into a particular disease. For many years, the NIH had a 10% set aside for HIV-related research.</td>
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<tr>
<th>Regulatory incentives</th>
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<tr>
<td>Priority review vouchers</td>
<td>Regulatory incentive programme that grants a voucher to manufacturers for expedited review of a future product following successful approval of a drug or biologic for an eligible condition.</td>
</tr>
<tr>
<td>Orphan product legislation</td>
<td>Offers incentives, or adjusts registration requirements, for developers to enter an otherwise unattractive market. Incentives can include waived registration fees, development grants, priority review eligibility, tax credits or extended periods of data exclusivity.</td>
</tr>
<tr>
<td>Breakthrough therapy designation</td>
<td>Regulatory incentive intended to expedite development programmes for breakthrough therapies that show preliminary clinical evidence of improvement over existing therapies. Breakthrough therapy designation could entail expedited or rolling review in advance of full submission, or opportunity for frequent guidance from regulators.</td>
</tr>
<tr>
<td>Fast-track designation</td>
<td>Similar to breakthrough therapy designation, but granted at earlier stages of development with nonclinical or clinical demonstration of potential to address unmet need.</td>
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<tr>
<th>Other research incentives</th>
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<tbody>
<tr>
<td>Grant funding</td>
<td>Upfront financing awarded through competitive, peer-reviewed processes – particularly important during early, high-risk stages of research. Grant funding is a type of “push funding”.</td>
</tr>
<tr>
<td>Prize funds</td>
<td>An example is milestone prizes awarded to compounds or technologies that meet certain criteria when they advance from one stage of research to the next. End prizes can also be issued for products that receive regulatory approval. Prize funds are an example of “pull mechanisms”.</td>
</tr>
<tr>
<td>Patent pools</td>
<td>Often combined with the above incentives, patent pools encourage open, collaborative development through pooling of intellectual property and associated clinical trial data in exchange for certain awards, incentives or other conditions. The Life Prize is an example of a mechanism that combines grant funding, prize funds and patent pooling.</td>
</tr>
<tr>
<td>Advance purchase agreements</td>
<td>A commitment by purchasers to finance the purchase of new health products at an agreed-upon price in advance of development.</td>
</tr>
</tbody>
</table>

Sources: information in this table was compiled from a number of sources, including (113, 122, 129)
to raise money. Special tax levies, biomedical research bonds, research innovation trusts or tax check-off systems are some of the fiscal tools that governments can test and deploy (113). The 2012 WHO CEWG report provides a comprehensive overview of other incentive structures that governments can use to promote innovation (see Table 11 for a summary of possible options). Governments need not employ identical fiscal policies and incentives, because the combination of different financing mechanisms implemented across countries will probably produce the most sustainable effect (5).

2. At the international level, countries should work together and in collaboration with WHO and other stakeholders to establish a new Global Strategy for funding and coordinating TB research. The development of this strategy should proceed in line with other existing and proposed initiatives, such as the TB Research Network stated in the BRICS Leaders Xiamen Declaration and the R&D Collaboration Hub named in the 2017 G20 Leaders' Declaration on AMR.

The aims, scope and means of the new global TB research strategy should be cooperatively determined by countries, civil society, donors and other committed stakeholders. To be effective, the strategy should function on a fully inclusive and coordinated consultative basis. It should be developed together with countries and stakeholders (including global partners, research organizations, NGOs, civil society, donors and the scientific community at large). To earn the trust and buy-in of Member States and stakeholders, the strategy must be developed through transparent procedures matched by a rigorous accountability framework for evaluating implementation and impact – the best option is to establish a core Steering Committee that will be hosted by an existing UN organization (e.g. WHO).

The new global TB research strategy should include the following components:

a. Development of a mechanism for collaboration and coordination of research activities. The strategy should determine mechanisms to facilitate collaborations between researchers in different countries around common research goals, and promote multisite and multidisciplinary research. This should rely on existing or new international TB research networks and consortia dedicated to investigating specific questions of importance that combine discovery, preclinical, clinical and operational research. Such knowledge networks could complement existing international TB research networks by focusing on understudied areas. As outlined in the WHO Global action framework, these networks could be coordinated from a hub located in an institution with expertise in the relevant focus area (128).

b. Reinforcement of TB research priorities. A priority-setting exercise could improve the coherence of global and national TB R&D investments by helping to focus resources on pressing needs or neglected research areas (or both). The International TB research roadmap,
published by WHO and the Stop TB Partnership in 2011, would offer a natural starting place (101). The Roadmap seeks to identify key research questions that need to be answered in order to achieve TB elimination, with a view towards encouraging investment in these topics. Updating the Roadmap in the context of the goals and targets of the End TB Strategy to reflect recent advances and the current state of TB science could be among the first priorities of the new global strategy for coordinating and advancing TB research. Importantly, the updated Roadmap should be linked with the wider landscape of country-specific TB research agendas, with special efforts to address socioeconomic barriers that are critical to reaching the missing TB cases, and mitigating the health and social impact of TB.

c. Development of mechanisms for a wider, more diverse funding base for TB research. The strategy should aim to mobilize further resources for TB research funding, including through innovative financing mechanisms and incentive strategies, and a more diverse funding base, with a view to including new resources rather than merely re-appropriating existing funding streams. The strategy should consider ways of bringing on new funders – whether they be country governments or philanthropic or industry partners – that would commit to taking certain actions to support TB research through financial or other contributions (e.g. technical expertise, material transfer or in-kind support). It should reflect and make concrete proposals to increase and diversify R&D funding through diverse modalities – for example, a mix of prizes, grants, loans and other incentives – to deploy funding efficiently according to the unique financing requirements of different development stages.

d. Creation of a framework for monitoring, evaluation and reporting. The ability to monitor, evaluate and report on the outcomes of projects is a critical component of accountability and transparency. The potential development of a monitoring and reporting framework embedded in the global strategy would enable tracking of progress in major ongoing research projects at the global, regional and national levels; the dissemination and publication of completed studies; and research that leads to significant policy and practice changes. Monitoring and reporting should not only satisfy an internal audit function, but should also serve as a communication channel to the larger TB research field. In this respect, it should be linked with a global accountability framework that may be developed within the wider context of the End-TB Strategy and the SDGs. This outward-looking orientation to monitoring and reporting would support the strategy’s important role in the dissemination of research and knowledge generated through its support for the benefit of contributing stakeholders and all people with TB.

e. Stimulation of actions over a targeted duration of time. To have an impact, the global strategy for TB research must be ambitious and achievable over a predictable time horizon. The business case put together for the Life Prize provides an exemplary benchmark for the amount of financing that would be required. The Life Prize estimates that it will take an average of US$ 200 million per year – on top of existing resources for TB drug R&D – for 10 years in order to achieve its goal of delivering a 1 month or less cure that works for all forms of TB everywhere (130). The exact amount required varies by year; for example, early in the Life Prize, prize money will be awarded to developers for promising TB drug compounds that satisfy early-stage criteria, whereas grant funding will predominate in later stages when new treatment regimens enter clinical trials. Accelerating progress on new diagnostics, drugs and vaccines may therefore require even higher levels of investment through 2025, the date by which the End TB Strategy indicates new tools must be introduced in order to reach the 2030 targets.
In many ways, this strategy would build on the trend towards bilateral agreements between TB research funders in different countries. In 2013, the NIH and the SAMRC formed the South Africa–US Program for Collaborative Biomedical Research to support South African researchers at eight institutions and link them with peers in the United States (131). In addition, the SAMRC and the Indian Council of Medical Research formed a bilateral Science and Technology Cooperation Agreement to support a collaborative research programme on HIV and TB (132). Brazil and China have also held a joint meeting on TB R&D (79). RePORT International – a platform for coordinated TB research organized between the NIH and research entities in Brazil, India, Indonesia and South Africa – is another prominent example of country-to-country cooperation on TB research (133). A global strategy for TB research would amplify such collaborations by expanding what can be achieved through country-to-country bilateral agreements alone.

Although developing a new global strategy for TB research will need substantial investment by various stakeholders, the collaborative approach embodied by this type of initiative could lead to outputs that save costs and increase efficiencies over the long run by reducing the duplication of research efforts. In addition, if the strategy facilitates the sharing of data among product developers, NTPs and the scientific community at large, it could further advance the rapid development and deployment of innovative tools and strategies.

The Ministerial Conference in Moscow marks a pivotal moment in TB research. Despite great strides made over the past decade, the TB R&D field faces a critical shortage of resources that, if left uncorrected, will constrain opportunities in the future and put the world off-track towards achieving the SDG targets. Epidemiological models and economic forecasts of the cost of inaction make clear that the status quo in TB research is not enough to meet the SDG targets or avert the toll of AMR. Given the scale of these costs, the least expensive option for governments is to act now by financing R&D and taking steps to create research-enabling environments at the national, regional and global levels. New tools to fight TB must be introduced by 2025, and preferably sooner – a time horizon that calls for invigorated funding and new, innovative research models. Without these concerted efforts, there is a danger of repeating the mistakes of the past, when TB research programmes were scaled back after premature declarations of success. In the SDG era, old frameworks that divide the world into donor countries and recipient countries will not be up to the task of enabling the scientific progress needed to end the TB epidemic by 2030. Meeting the SDG targets and realizing the End TB Strategy's vision of a world without TB will require that all countries and stakeholders move forward with the understanding that TB research is a shared responsibility and a global endeavour.


GLOBAL INVESTMENTS IN TB R&D PAST, PRESENT, AND FUTURE


How were the data on TB R&D expenditures handled?
The TAG survey asks recipients to report spending in local currencies, which TAG converts into US dollars using the interbank exchange rates published by OANDA. All dollar figures represent disbursements, or the actual transfer of funds, rather than commitments or budgetary allocations for future years. For the following analyses, all figures are reported in current (i.e. nominal) dollars of a given year unless otherwise noted. Where adjusted for inflation, the adjustment was made using the biomedical research and development price index (BRDPI), a measure of how much the budget of the US National Institutes of Health (NIH) must change each year to maintain purchasing power. The US Bureau of Economic Analysis developed and maintains the BRDPI for the NIH Office of Budget, and the BRDPI is commonly used as a measure of inflation for biomedical research in related studies (113).

Limitations
Working with global health and economic data collected by different organizations for varying purposes poses a number of methodological challenges. For example, data on expenditures specific to health R&D are notoriously sparse (112). Although UNESCO and the Organization for Economic Co-operation and Development (OECD) collect information on GERD from countries, many countries do not report annually, and even those that do may not always specify the proportion of GERD that goes towards health research. In addition, each source of data reflects the priorities and purpose of the institution collecting it. The G-FINDER report, for example, collects information on R&D spending for neglected and poverty-related diseases that primarily affect low- and middle-income countries. Consequently, its estimates of HIV R&D expenditures do not include spending on most HIV drug R&D or on some types of HIV basic-science activities. The exception is research that is deemed relevant to developing country settings, including the development of paediatric or slow-release formulations, fixed-dose combinations, and low-dose drug formulations for prophylaxis. The money devoted to types of HIV research excluded from the G-FINDER report is substantial. For example, the NIH reports spending US$ 3 billion on HIV research in 2015, more than double the worldwide estimate of US$ 1 billion spent on HIV R&D published in the G-FINDER report. These and other limitations to the data used in this policy paper are noted and discussed in the text.

Limitations also apply to the TB R&D funding data that form the heart of the following analyses. The comprehensiveness of...
estimates of TB R&D expenditure depends on the proportion of organizations funding TB research that participate in the TAG survey. This proportion cannot be calculated, because the true number of TB research funders worldwide is unknown. To address this limitation, TAG takes several steps to ensure that the survey has a wide reach and high yield. First, the sampling frame is updated annually, and each year TAG conducts outreach to organizations that have not previously participated in the survey. Most of these organizations do not have known TB R&D investments, but either support health research generally or invest in related diseases. Second, given the high degree of concentration of TB research funding, TAG makes a special effort to collect data from the 30 largest funders from one year to the next. In any given year, the top 30 funders of TB R&D account for more than 90% of known total spending. On average, the survey achieves a 95% response rate from the top 30 funders. Finally, 25 organizations have participated in each year of the TAG survey since 2009 and comprise a ‘core funders’ group. For each of the following analyses, data were first analysed using the full TAG dataset and then re-analysed using only information from the 25 core funders to see whether the results differed. In all cases, the two datasets produced similar results. Appendix 3 lists the 25 core funders.

### APPENDIX 3:
**25 Core TB R&D Funders That Have Reported to TAG Each Year Since 2009**

| National Institutes of Health (United States) | Department for International Development (United Kingdom) | Wellcome Trust | Company Y* | Ministry of Health, Labour and Welfare (Japan) |
| Bill & Melinda Gates Foundation | Company X* | Indian Council of Medical Research | Institut Pasteur (France) | Swedish Research Council |
| Otsuka | Centers for Disease Control and Prevention (United States) | Dutch Directorate-General for International Cooperation (DGIS) | National Health and Medical Research Council (Australia) | Department of Science and Technology (106) |
| European Commission | Medical Research Council (United Kingdom) | Federal Ministry of Education and Research (Germany) | Statens Serum Institut (Denmark) | Irish Aid |
| United States Agency for International Development | European and Developing Countries Clinical Trials Partnership | Canadian Institutes of Health Research | Eli Lilly | US Food and Drug Administration |

* Company X and Company Y are pharmaceutical companies that report data to TAG anonymously

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### APPENDIX 2:
**Research Areas Tracked by TAG**

1. **Basic science**: undirected, investigator-initiated research to discover fundamental knowledge about *Mycobacterium tuberculosis* and closely related mycobacterial organisms (sometimes called “fundamental research”).

2. **Diagnostics**: preclinical and clinical trials of diagnostic technologies and algorithms.

3. **Drugs**: preclinical and clinical research on treatments and treatment strategies for TB infection and disease.

4. **Vaccines**: preclinical and clinical research on new TB vaccines, including both preventive and immunotherapeutic vaccines.

5. **Operational and implementation research**: evaluations of new or existing TB control tools and strategies to guide their effective implementation in programme settings. Operational research may include randomized controlled trials, surveillance, and epidemiological and observational studies.

6. **Infrastructure/unspecified projects**: TB research that the funder is unable to further classify.
## APPENDIX 4:
FUNDING FLOWS FOR TB R&D EXPENDITURES BY SELECT* PUBLIC AND PHILANTHROPIC INSTITUTIONS, 2011–2015

<table>
<thead>
<tr>
<th>Funding Organization</th>
<th>Total TB R&amp;D Expenditure 2011–2015 (USD millions)</th>
<th>No. Countries Represented by Principal Recipients</th>
<th>Country in which Principal Recipients Received the Most Funding Name (Amount)</th>
<th>Largest Principal Recipient Name (Amount)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian NHMRC</td>
<td>$22</td>
<td>1</td>
<td>Australia ($22M)</td>
<td>University of Sydney ($11M)</td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation</td>
<td>$635</td>
<td>16</td>
<td>USA ($488M)</td>
<td>TB Alliance ($172M)</td>
</tr>
<tr>
<td>Canadian Institutes of Health Research</td>
<td>$28</td>
<td>4</td>
<td>Canada ($27M)</td>
<td>McGill University ($13M)</td>
</tr>
<tr>
<td>United Kingdom Department for International Development</td>
<td>$111</td>
<td>7</td>
<td>USA ($70M)</td>
<td>TB Alliance ($53M)</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership</td>
<td>$73</td>
<td>33</td>
<td>South Africa ($28M)</td>
<td>University of Cape Town ($20M)</td>
</tr>
<tr>
<td>European Commission</td>
<td>$107</td>
<td>18</td>
<td>The Netherlands ($27M)</td>
<td>TuBerculosis Vaccine Initiative ($22M)</td>
</tr>
<tr>
<td>Dutch Directorate-General for International Cooperation</td>
<td>$27</td>
<td>4</td>
<td>USA ($17M)</td>
<td>Aeras ($17M)</td>
</tr>
<tr>
<td>German Federal Ministry of Education and Research</td>
<td>$31</td>
<td>2</td>
<td>Germany ($29M)</td>
<td>Max Planck Society ($11M)</td>
</tr>
<tr>
<td>Indian Council of Medical Research</td>
<td>$39</td>
<td>1</td>
<td>India ($39M)</td>
<td>National Institute for Research in Tuberculosis ($38M)</td>
</tr>
<tr>
<td>South African Department of Science and Technology</td>
<td>$9</td>
<td>1</td>
<td>South Africa ($9M)</td>
<td>South African Technology Innovation Agency ($5M)</td>
</tr>
<tr>
<td>Pasteur Institute</td>
<td>$15</td>
<td>1</td>
<td>France ($15M)</td>
<td>Pasteur Institute ($15M)</td>
</tr>
<tr>
<td>Irish Aid</td>
<td>$7</td>
<td>1</td>
<td>USA ($6M)</td>
<td>TB Alliance ($6M)</td>
</tr>
<tr>
<td>Japanese Ministry of Health, Labour and Welfare</td>
<td>$12</td>
<td>1</td>
<td>Japan ($12M)</td>
<td>Japan Anti-Tuberculosis Association ($5M)</td>
</tr>
<tr>
<td>Wellcome Trust</td>
<td>$56</td>
<td>10</td>
<td>UK ($40M)</td>
<td>Imperial College London ($39M)</td>
</tr>
<tr>
<td>Statens Serum Institute (SSI)</td>
<td>$5</td>
<td>1</td>
<td>Denmark ($5M)</td>
<td>SSI ($5M)</td>
</tr>
<tr>
<td>US Centers for Disease Control and Prevention (US CDC)</td>
<td>$77</td>
<td>1</td>
<td>USA ($77M)</td>
<td>US CDC ($77M)</td>
</tr>
<tr>
<td>US Food and Drug Administration</td>
<td>$5</td>
<td>2</td>
<td>USA ($5M)</td>
<td>TB Alliance ($3M)</td>
</tr>
<tr>
<td>Swedish Research Council</td>
<td>$10</td>
<td>1</td>
<td>Sweden ($9.7M)</td>
<td>Karolinska Institute ($4M)</td>
</tr>
<tr>
<td>United Kingdom Medical Research Council (United Kingdom MRC)</td>
<td>$67</td>
<td>5</td>
<td>United Kingdom ($59M)</td>
<td>United Kingdom MRC ($32M)</td>
</tr>
<tr>
<td>US National Institutes of Health (US NIH)</td>
<td>$1,046</td>
<td>20</td>
<td>USA ($989M)</td>
<td>US NIH Intramural Research Program ($69M)</td>
</tr>
<tr>
<td>US Agency for International Development</td>
<td>$118</td>
<td>24</td>
<td>USA ($46M)</td>
<td>International Union Against TB and Lung Disease ($41M)</td>
</tr>
</tbody>
</table>

*The organizations appearing in the table represent the public and philanthropic funders that have participated in each year of the TAG survey.

M, million; NHMRC, National Health and Medical Research Council; R&D, research and development; TAG, Treatment Action Group; TB, tuberculosis; US, United States; USA, United States of America
A bibliometric analysis of publications indexed in Web of Science from 2007 to 2016 was performed with the aim of describing TB knowledge generation over the past decade. The Web of Science database was searched on 8 June 2017 for papers with “tuberculosis” in the title and a date restriction of between 2007 and 2016, inclusive. The resulting 34,512 papers were downloaded from the database by year. A year-stratified 5% (n=1725) random subset was then drawn using a random number generator.

How was the bibliometric analysis conducted?
A bibliometric analysis was performed on the full search results using the bibliometrix package in R. This package uses the metadata in the Web of Science citations to calculate and rank country production, journal sources and country collaborations. Country production was defined using the first author’s country. Using World Bank country classification for the 2018 fiscal year, countries were divided into low-, middle- and high-income strata (upper- and lower-middle income countries were classified as middle income). The author affiliation strings in the Web of Science citations were searched for the presence of countries named in each classification strata. A high-income and low- and middle-income country collaboration was defined as having at least one author from the relevant strata on the same paper.

How was the 5% subset analysis conducted?
The 5% subset of the full search results was screened for papers that were related to human Mycobacterium tuberculosis (MTB) and were original research articles (i.e. not meeting abstracts, book chapters, narrative reviews, news items, editorial material, or case reports/series). Systematic reviews/meta-analyses were included as original research. A sensitivity analysis reclassifying systematic reviews/meta-analyses as non-original research made no substantive impact. Data was extracted from these original research articles (n=878) to determine year of publication, journal, study design, country of first author, field site country and funding source(s). The papers were then classified into one of the six research areas identified in the International roadmap for tuberculosis research, or into “other” if none of the six were appropriate. Where relevant, one of the priority questions within the chosen research area was assigned. Screening, extraction and classification were performed independently by two reviewers, and discrepancies were resolved by consensus. Fig. 20 shows a workflow schematic for the 5% subset analysis.

If authors acknowledged funding sources in the full text of the paper, those data were also extracted. The full text could not be retrieved for 25 of the 878 original TB articles. In the event that authors did not mention funding or stated that no funding was received, the paper was excluded from the subsequent funding analysis. Top funders overall and by research area represent the funders most frequently acknowledged. All analyses were performed in R.

Limitations
This subset analysis has some limitations. The ability to draw strong conclusions from the representative 5% random sample is limited, because the abstracts analysed represent only a small number of the total publications indexed in Web of Science over the period 2007–2016. As a result, key publications and potentially less obvious trends may have been missed. Additionally, both the subset analysis and the greater bibliometric analysis do not capture quality or scope/depth or size of the study. For example, large randomized drug and vaccine clinical trials produce critical high-quality evidence, but may be the product of years of work and millions of dollars while only resulting in a single publication. Despite these limitations, using random sampling methodology makes it possible to infer the proportion of research being conducted in key areas and to what degree high-priority research questions are being addressed.
Figure 20: Workflow for the 5% subset analysis

Records identified through database searching
n = 34,512

5% year-stratified subset randomly generated
n = 1,725

Abstracts screened
n = 878

Roadmap research area identified
Epidemiology
(n = 262)
Fundamental research
(n = 299)
Diagnostics
(n = 89)
Vaccines
(n = 45)
Treatment
(n = 58)
Operational and public health
(n = 116)
Other
(n = 9)

Non TB-related publications
(n = 100)
Editorial material excluded
(n = 738)
Articles without abstract excluded
(n = 9)
### 1. Epidemiology
1.1 Determine the burden of TB ('TB burden')
1.2 Understand variations in the dynamics of TB in different settings and identify the social and biological drivers of M. tuberculosis transmission at population level ('TB dynamics')

### 2. Fundamental research
2.1 Characterize human TB by modern biochemical, clinical and epidemiological approaches ('characterize TB')
2.2 Better understand the host–pathogen interaction ('host–pathogen')
2.3 Use ‘discovery science’ to identify biomarkers that can better differentiate the stages of the disease spectrum ('biomarker discovery')

### 3. R&D of new diagnostics ('diagnostics')
3.1 Evaluate biomarkers identified in fundamental studies for use as diagnostic tools ('diagnostic biomarkers')
3.2 Design and validate a set of tools for diagnosis of active drug-sensitive and drug-resistant TB and latent TB infection that are feasible and applicable at various health-care levels in high-burden settings ('diagnostic validation')
3.3 Improve existing diagnostic tests for active drug-sensitive and drug-resistant TB and latent TB infection at various health-care levels in high-burden settings ('improve diagnostics')
3.4 Evaluate new diagnostic tools, and conduct demonstration studies, followed by evaluation of the programmatic impact of all diagnostic tools ('diagnostic evaluation')

### 4. R&D of new drugs ('treatment')
4.1 Develop new drugs and treatment strategies ('new drugs')
4.2 Develop a shorter regimen for drug-susceptible TB that can be used in combination with HIV treatment ('drugs for DS TB')
4.3 Develop a safer, more efficacious, shorter regimen for drug-resistant TB that is compatible with HIV treatment ('drugs for DR TB')
4.4 Develop safe, reliable, user-friendly drug regimens suitable for all forms of TB in children and compatible with HIV treatment ('drugs for pediatric TB')
4.5 Develop safer, more effective, shorter regimens for TB infected individuals ('drugs for TB')
4.6 Develop safer, shorter, highly effective regimens for drug-susceptible and drug-resistant latent TB infection that are compatible with HIV treatment and suitable for children ('drugs for LTBI')

### 5. R&D of new vaccines ('vaccines')
5.1 Conduct fundamental research as a basis for the development of effective TB vaccines ('fundamental vaccine research')
5.2 Conduct research and clinical testing to better understand the safety and efficacy of BCG and candidate vaccines ('BCG and candidate vaccines')
5.3 Develop standardized assays and find biomarkers for use in clinical trials to identify correlates of protection ('protection biomarkers')
5.4 Develop new pre- and post-exposure vaccines, new adjuvants and new delivery platforms ('vaccine development')
5.5 Improve and standardize preclinical assays to evaluate immunogenicity and potential protective efficacy of new TB vaccines ('vaccine evaluation')
5.6 Improve and standardize testing of TB vaccines in clinical trials ('TB vaccine trials')

### 6. Operational and public health research
6.1 Improve TB case detection and diagnosis ('detection/diagnosis')
6.2 Investigate methods to improve access to treatment and treatment delivery for drug-sensitive and drug-resistant TB ('treatment access/delivery')
6.3 Institute sustainable collaboration with all private and public providers of TB care and control ('public/private collaboration')
6.4 Address priority operational research questions at global, regional or national level to improve implementation of collaborative TB and HIV activities, and also in respect of other diseases or conditions in which the risk for TB is increased ('TB/HIV OR')
6.5 Design collaborative activities in other disease programmes or situations in which TB risk is increased ('programme collaboration')
6.6 Investigate methods to encourage community participation, to increase the effectiveness of all interventions (e.g. case-finding, access to treatment and delivery) ('community participation')
6.7 Optimize infection control to reduce TB transmission ('infection control')
6.8 Improve measurement of disease burden by effective surveillance, monitoring and evaluation of TB programmes ('measurement of TB burden')
6.9 Ensure that countries have the capacity to perform TB-related operational research to improve TB programme performance ('country capacity')