Lancet Commission on TB:

Building a TB-free world

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Introduction: Tuberculosis in the 21st Century

'Knowing is not enough; we must apply. Willing is not enough; we must do.'
Goethe

Progress against tuberculosis: moving forward, but not fast enough

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a public health emergency.[1] WHO urged governments worldwide to significantly scale up their TB control efforts and within a year unveiled 'directly observed treatment, short course,' or DOTS, as its solution to the problem. DOTS, which used direct observation to improve adherence to a rifampicin-based standardized treatment regimen of 6-9 months, also required diagnosing TB by sputum smear and reporting cases and treatment outcomes to public health authorities. Unfortunately, the original DOTS framework largely ignored smear-negative TB, extrapulmonary TB, latent tuberculosis infection (LTBI), childhood TB, and drug-resistant TB (DR-TB). The DOTS approach, while perhaps fit to budget constraints, was neither comprehensive enough nor sufficient to curtail ongoing TB transmission. The emphasis on directly observed treatment was also inimical to delivery of person-centered care. The expanding HIV epidemic and the growth of DR TB further undermined the DOTS strategy, which was hampered by imprecise diagnostic tools and passive case detection.

Despite gains made against the TB epidemic since the introduction of DOTS—and subsequently, an enhanced strategy by WHO to intensify TB control efforts[2]—the potential to dramatically reduce the rates of TB incidence and mortality worldwide as first proposed 25 years ago has not been realized. Dismayed by this lack of progress, 2014, the global TB community outlined The End TB strategy, that has been incorporated into the UN Sustainable Development Goals (SDGs). By 2035, the strategy aims to reduce TB deaths to 95% of 2015 levels by 2035 and cut TB incidence to 90% of 2015 levels by 2035, and to ensure that no families face catastrophic costs due to tuberculosis.[3,4] Tragically, the global burden of TB in 2019 remains substantial and, for reasons outlined below, those targets will not be attained without urgent corrective action.

TB-related mortality and the persistent burden of TB infection and disease

TB-related mortality: TB remains a global public health emergency, responsible for more deaths than any other infectious disease. While globally, the TB mortality rate has declined approximately 3 percent

per year since 2000, or 37 percent overall between 2000 and 2017,[5] this decline reflects a substantial progress in the number of patients diagnosed and treated. Moreove, it aslo occurred as poverty-related drivers of TB decreased and economies grew. As evidence of this Ethiopia, Viet Nam, Zimbabwe and Côte d'Ivoire all achieved annual average rates of decline in TB mortality of more than 6% between 2000 and 2017 (Table 1). This progress aside, however, TB mortality rates, especially among people living with HIV and in children are still substantial.[5,6] Furthermore, rates of TB mortality have declined much more slowly than for most other infectious diseases (Appendix Table xx), and the declines are far less in low- and lower-middle income countries compared with elsewhere (Table 2). Three-quarters of all TB deaths occur within just eight countries (Appendix Figure xx). In many parts of sub-Saharan Africa and Southeast Asia, TB remains a leading cause of years-of-life lost. Moreover, TB ranks as the 9th leading cause of death and the 12th leading cause of years-of-life lost worldwide.[7]

TB incidence: An estimated 10 million people (90 percent adults, 58 percent male) became ill with TB in 2017. Eight countries in Southeast Asia and Africa (India, Indonesia, China, the Philippines, Pakistan, South Africa, Bangladesh and Nigeria) accounted for two-thirds of all new cases worldwide. Overall, TB incidence has fallen approximately 1.4% per year since 2000 and 2% per year since 2015 – far less than the rate needed to achieve WHO End TB targets[5] (an annual incidence rate decline of 4-5% by 2020 and 10% by 2025 to achieve the milestone case reductions) and less than declining trends in mortality. The overall slow decline in TB burden suggests that TB programs, while reducing deaths, are insufficient to overcome poverty-related drivers that substantially impact the epidemic.[8] Modeling suggests that to avert transmission, individuals at risk must be identified and provided effective preventive therapy, *and* individuals with less infectious, early TB must be diagnosed and provided immediate treatment.[9,10]

TB Prevalence: Between 2000 and 2016, 32 national TB prevalence surveys were performed in 26 countries.[5] These studies consistently found a higher prevalence of TB than previous estimates based on less precise information such as case notifications. The upwardly revised incidence estimates highlighted large numbers of undiagnosed or unreported TB cases in many countries. Prevalence surveys also revealed that people with TB often sought care for TB symptoms that health care workers failed to identify. Other individuals did not recognize the seriousness of their symptoms and had not sought care. All prevalence surveys in the last decade have found a higher burden of TB among men, with male:female ratios ranging from 1.2 (in Ethiopia) to 4.6 (in Viet Nam). [5] The higher global disease burden in men—estimated to be 1.8 times higher than in women[5]—combined with larger detection and

reporting gaps highlight gender differences in accessing care that may be related to both financial barriers and stigma.[11] The differences also suggest that male-friendly strategies to improve access to and use of health services are required.[12]

Why haven't we made more progress over the last quarter century?

The lack of progress against TB over the last 25 years has resulted from a mix of political, societal, scientific, and strategic shortcomings. These include health system frailties; lack of investment in control efforts, and in research towards developing new medical tools; reliance on simplified, one-size-fits-all approaches that fail to meet the different needs of individual patients; biological factors, such as HIV co-infection and the spread of drug resistance; and the huge and persistent reservoir of latent TB infection are all to blame. Moreover, TB is also 'a disease of the shadows,' disproportionately affecting those communities with the least powerful constituencies to effect change.

Lack of investment and political will -Deaths from TB fell rapidly in western Europe and the United States as living standards improved. The combination of a decline in TB cases in high-income countries and the lack of a powerful civil society voice in high-burden countries has undermined efforts to garner the same political support or domestic investment as for other diseases. Failure to appreciate the profound negative economic impact of the epidemic and advocate for increased donor financing in high-burden, low-income countries has hampered efforts. In many of the highest burden countries, chronic under-funding and lack of political will have profoundly disabled TB programs, and also explain why, 40 years after the Alma Ata Declaration,[13] half the world's population still lacks access to comprehensive health care services.

Under-investment in TB research and development – Funding for TB R&D has been stagnant for many years, despite that TB remains a major global health threat.[3] A reflection of this under-investment is the continued reliance upon tools such as smear microscopy and the BCG vaccine developed nearly a century ago.[14] While global funding for TB research received more funding in 2018 than ever before ($772 million), the pace at which scientific discovery progresses has been greatly hindered by lack of sufficient funding dedicated to research priorities that have been defined ad nauseam. [15-17]

Broken care cascades and poor quality of care - Turning the tide on TB requires early, accurate case detection together with the rapid initiation of and adherence to effective treatment that prevents *Mtb* transmission, especially in high-burden countries. To achieve this, national TB programs in such settings must first invest to ensure that all patients with TB seeking care have access to TB diagnostics and treatments. Unfortunately,TB care is frequently delivered with little attention to patient needs and preferences, poorly coordinated with other services, and undermined by lack of access to essential services.[18] A recent assessment of patient pathways in 13 countries accounting for 92% of the world's missed TB cases revealed that even among people who actively sought care, fewer than one-third sought care at a facility that had the capacity to diagnose and/or treat people with TB.[18-21] Referral systems to access diagnostic technologies also were limited. These findings confirm those of numerous other studies from various settings demonstrating the many programmatic and financial barriers[22,23] that prevent people with TB from accessing healthcare.[24] Furthermore, they highlight how it is critical to align the availability of services to where people seek care.

Not only is *access* highly variable, so too is the quality of TB care in many high-burden countries. Although the DOTS strategy emphasized the importance of quality-assured drugs and diagnostics, it neglected to ensure prioritizing the quality of TB care. The Lancet Global Health Commission on High-Quality Health Systems (HQSS) recently highlighted that the vast majority of TB deaths result from poor quality care..[25]. As Figure 1 demonstrates, the care quality is undermined by chronic under-funding, limited access to new tools, and inadequate implementation of policies.

Numerous studies have highlighted substantial gaps in the TB care continuum for all forms of TB cases: active disease, DR-TB, latent infection, and childhood TB.[26-30] For patients with multidrug-resistant TB (MDR-TB), only 14% completed treatment, and 11% remained disease-free at one year. A similar study in South Africa found that only 82% of 532,005 TB cases were diagnosed, and less than 54% of drug-susceptible TB cases completed treatment.[29] Of those with rifampicin-resistant TB, only 22% completed treatment (Appendix Figure xx). Simulated patient studies in three countries show that most primary care providers are unable to diagnose TB and referral linkages to the National TB Program (NTP) are weak. In India, China and Kenya, only 28% to 45% of simulation patients were correctly managed by primary care providers.[31-33]

Simply put, the current global capacity to diagnose, link to care, treat, and cure TB patients is woefully inadequate for the massive burden of disease that exists. The public health implications, as well as the

poor clinical and financial implications[34] for patients, are self-evident. Substantially reducing TB mortality and incidence will require significantly increasing both the coverage and the quality of TB services across the entire care continuum.

Failures to optimize private sector engagement Of the 3.6 million unreognized or "missing" TB patients in 2017, 63% of them are in six countries where primary care is dominated by private providers and >67% of initial care-seeking is in the private sector (Table 3). However, in these countries, private provider notifications are just 18% of total TB notifications and 9% of estimated TB incidence. Based on data from TB prevalence surveys and private sector drug sales,[35] a considerable proportion of TB patients are treated in the private sector, with largely unknown levels of quality and patient outcomes. . Given the dominance of private health care in countries with the largest share of "missing" TB patients, to meet national and indeed global TB goals, private providers must be engaged to provide high-quality, patient-centered care on a scale equal to their role in primary care.

Modeling studies also suggest that untreated or poorly-treated patients in the private sector are a major source of Mtb transmission.[36] This is due to delay in diagnosis and treatment initiation among private patients, as well as recurrent TB among private patients who were inadequately treated. Therefore, improving the diagnosis and treatment of patients seeking care in private facilities is an opportunity to rapidly reduce TB transmission. Engaging private providers can also reduce unnecessary morbidity and mortality caused by inappropriate treatment, drug resistance caused by undetected MDR TB and incomplete treatment, and catastrophic expenditures and impoverishment.

Failure to target resources at hot spots and high risk populations - Global and regional data camouflage localities where the TB epidemic continues to grow unabated. Many different micro-epidemics exist, and the risk of both acquiring and dying of TB are unevenly distributed across society. Even adjacent neighborhoods may have markedly different TB prevalences, as recent analysis from Chennai, India, illustrates.[37] Such regional variations reflect social and environmental determinants, which include living in densely populated areas[38-40] and working in occupations, such as health care or mining, that increase the risk for TB.[41-43] Turning the tide on TB requires early, accurate case detection together with rapid initiation of and adherence to effective treatment (both preventive and curative) that prevents transmission. To achieve this, national TB programs in high-burden regions must scale up active case finding strategies for those people and populations at the highest risk, rather than relying on passive

case finding alone. Unfortunately, active case finding strategies, even in the highest risk populations, are not widely implemented because of cost concerns and lack of research consensus on what best practices should include.[44]

Neglecting to implement TB prevention strategies **-** Ending TB as a disease of public health significance must entail a comprehensive, cogent prevention agenda. Because the human reservoir of M. tuberculosis infection is enormous,[45] overwhelmingly asymptomatic, and long-lived, identifying individuals who are at highest risk of progression to disease, who would thus benefit the most from preventive therapy, is crucial.The benefits of preventive TB therapy have been known for more than 60 years. Pioneering studies in the 1950s–1960s provided overwhelming evidence of the efficacy of isoniazid in preventing active TB in children,[46] Alaskan Native populations, residents of congregate living facilities such as mental hospitals, and household contacts of TB patients. [47] Subsequent work has further documented the benefits of preventive therapy for individuals with evidence of recent infection, those with radiographic evidence of prior untreated TB, [48]people with HIV infection,[49] recipients of immunosuppressive therapy such as TNF-alpha inhibitors,[50] and other immunocompromised individuals.[51]

Large population-based studies of TB preventive therapy and mathematical models both suggest that preventive treatment of TB infection—as part of a comprehensive approach that includes active case-finding and prompt, effective treatment—can sufficiently reduce population-level transmission to interrupt the cycle of infection, illness, and death.[52,53] Unfortunately, despite abundant evidence of its efficacy, the use of preventive therapy globally has been limited,[54] as TB control programs in LMICs have focused almost exclusively on detection and treatment of individuals with active TB disease.

The problem of drug-resistant TB - Among the 558,000 individuals currently estimated to develop rifampicin-resistant (RR-TB) each year, most are thought to be infected with multidrug-resistant TB (MDR-TB, resistance to both rifampicin and isoniazid).[55] Despite this large burden, only a quarter of the estimated number of individuals with MDR/RR-TB were diagnosed and notified in 2017.[5] The remainder either form part of the 'missing millions' or were placed on largely ineffective first-line treatment in the absence of a drug-resistant TB diagnosis. Among those diagnosed, 87% were reported to have been enrolled on treatment, with only 55% of these successfully treated. This simple cascade leaves only 12% of the global MDR/RR-TB burden successfully treated. While there are significant variations in the prevalence of DR-TB between countries, MDR-TB prevalence can vary by a factor of 10 at the sub-district level and even more from one health centre to the next. [56,57] The largest number of DR TB cases are in India (which, along with other high burden countries, has witnessed the emergence of so-called 'totally drug-resistant' strains)[58] and China (where one-quarter of all active TB disease cases are resistant to either isoniazid or rifampicin).[59] Importantly, increasing evidence demonstrates that the majority of DR TB cases reflect transmission rather than initial acquisition.[60-62] Thus, a high priority for curbing DR TB is to interrupt DR TB transmission through early diagnosis and prompt initiation of effective treatment.[63] In parallel, an urgent need exists to develop and trial preventive treatment strategies that are effective against DR-TB.

Addressing social determinants - Fundamentally, TB is a disease of poverty.[64-67] Most often it causes substantial losses in productivity for already poor individuals (3-4 months of work) and families (30% of yearly household earnings).[68] Social determinants that contribute to TB risk are linked both directly and indirectly to social and economic vulnerabilities.[65] Surveys in seven countries demonstrate that patients who develop TB often face catastrophic costs (>20% of household income) just to access care to diagnose and treat their TB.[22,23,69-72] In Viet Nam, for example, 63% of TB-affected households experienced catastrophic costs, 38% took out loans or sold assets (so-called "dissavings"), and 27% reported serious financial burdens related to TB-related costs.[73] Significant social and economic burdens make TB patients less likely to present for care, complete TB testing, and initiate and adhere to treatment,[66,74] leading to increased Mtb transmission, morbidity, and mortality.[75-81] The financial impacts of TB disease are significant and long lasting; as we highlight in Panel 3, individuals suffering from TB in rural India experienced profound financial hardship even seven years after completing TB treatment.

As history demonstrates, the global TB epidemic is not homogenous, characterized by a gradual decline in incidence. Rather it is a heterogeneous collection of micro-epidemics in which transmission in each setting is driven by different catalysts,[82] from HIV-induced immune defects to inadequate diagnosis and treatment.[83] In settings where increased attention and resources have been devoted to controlling TB (for example, New York City,[84] Alaska,[85] and China[59]), remarkable successes have been achieved. But in regions where facilitators of transmission have been left unaddressed (incarceration in eastern Europe, for example), TB has resurged. To prevent the 'worst of history' repeating itself, TB control programs must anticipate and respond to dynamic demographic, environmental, and socio-economic trends, mapping each micro-epidemic to clearly understand its drivers and how it is evolving. In addition, anticipating the threats of vulnerable aging populations, global plofieration of urban slums and the increasing incidence of non-communicable diseases, such as diabetes and chronic long disease, is essential. In the Sustainable Development Goal (SDG) era, ending TB must be framed within a broader health and development agenda.[86] This agenda includes understanding that reducing TB mortality and improving the health system are inextricably linked with ensuring gender equality (SDG 5), improving working conditions (SDG 8) and urban planning, (SDG 11) and mitigating the impact of air pollution and food insecurity caused by climate change (SDG 13). Purely biomedical or public health solutions are not enough to end the tuberculosis epidemic;[87] economic development and exigent investment in social policy strategies that can alleviate the drivers of TB disease are also important.

Global Leaders have made a strong political commitment to ending the TB epidemic

The High Level Meeting on Tuberculosis at the United Nations (UNHLM) in September, 2018 endorsed an ambitious and powerful declaration to accelerate progress towards the goals outlined in the End TB strategy (Panel 1). Taken together, programmatic innovations, new health technologies, sustained global economic growth, increasing commitment to attaining UHC, and mounting political momentum to definitively address TB can all contribute to achieving that goal. A long-term political pledge, however, requires a clearly defined endpoint and a road-map for how to achieve it. For the purposes of this Report, the Commission focused primarily on the goals outlined in the HLM declaration and the End TB Strategy mortality target: a reduction by 90% from the worldwide level in 2015, which was about 24 TB deaths per 100,000 population per year (including TB deaths in persons living with HIV). We recognize that efforts to reduce TB mortality must occur in tandem with strategies that prevent ongoing transmission, and lead to reductions in incidence. However, focusing on mortality rather than incidence

is motivated by a desire to make the recommendations of the report relevant to a broad audience of policy-makers and public health practitioners, for whom change in mortality is a more useful metric of progress than TB incidence.

The Commission concluded that achieving that goal within a generation and at a feasible cost, is realistic in many settings, but it will require substantial investment in resources. Countries like Japan,[88] China,[89,90] and Peru[91] have all demonstrated that rapid declines in TB mortality can occur with sufficient political will and financial investment, and when multisectoral steps to alleviate poverty occurred in tandem with efforts to reduce TB mortality. If other countries can replicate the trends in TB mortality decline achieved in these countries, then a 90% reduction in TB-deaths worldwide within a generation is possible (Figure 2). For some high burden countries, however, even sustained investment will be insufficient; transformative innovations in service delivery and increased investment in new tools is necessary to end the epidemic in these settings. Thus, our commission set out to answer two questions as the foundation for creating a roadmap for countries to reduce TB mortality: (1) *How should TB high-burden countries and their development partners target their future investments to ensure that ending TB is achievable? (2) What policy priorities are necessary to ensure that the HLM political declaration leads to rapid and sustained progress towards ending the epidemic?*

Report Roadmap

Section 1, of the report highlights proven strategies to reduce TB mortality in high burden countries. We focus first on high-priority strategies needed to close gaps in the care continuum, including person-centered approaches to diagnosis and adntreatment, active case-finding approaches to reach high-risk populations and the urgent need to implement TB prevention interventions. We emphasize the critical need for new models of private sector engagement to deliver high-quality care, and innovative ideas to optimize care for patients with DR TB.

The challenge TB now presents also has in part resulted from neglecting to identify TB research as an integral, critical priority during the last quarter century.[92] While ending TB with existing tools is possible, new products are essential to reduce cost, simplify implementation and accelerate progress. In Section 2, we describe why current funding for TB research and development (R&D) must increase to expedite transformative innovations in point-of-care diagnostics; safer, less toxic, shorter treatment regimens;

chemoprevention; and a more effective TB vaccine. The economic rates of return on greater TB R&D investment are both substantial and invariably beneficial to poor and marginalized communities.[93]

Section 3 highlights how effective TB control represents one of the 'best buys' in global development, one that can produce considerablel economic dividends for high-burden countries. We examine the potential to expand domestic TB financing through increased revenue generation and prioritizing health care, as well as from more innovative sources, including loans, gains in efficiency, and complementary non-TB resources. Efforts to end TB within a generation need to differ dramatically from those in the past. Rather than relying on a global campaign funded and led by foreign donors and focused on specific interventions, increasingly TB control efforts will require domestic resources and full country ownership.[94] We discuss how foreign donor support can still play a critical role in 'transitioning' countries to full country ownership by targeting resources to address DR-TB, investing in TB R&D, and strengthening strategies that ensure sustainable domestic funding for TB control efforts.

Section 4 calls for a new era of accountability and a reinvigorated cadre of political leaders committed to doing their part to accelerate efforts to end TB worldwide. Heads of States, national TB programs and even regional and site-level clinics must be held accountable for their performance in contributing to ending the epidemic. We advocate for an independent review mechanism to evaluate the performance of all major global stakeholders engaged in TB programming.

Section 1: Scaling up proven strategies

Several high-performing countries have demonstrated that substantive declines in TB mortality, while difficult to achieve, can be reached by using existing tools to scale up evidence-based, best-practice interventions. To substantially reduce TB deaths, we must prioritize delivering patient- and family-centered programs to individuals with active TB, while also reaching high-risk populations with TB screening and preventive services. This comprehensive, integrated approach requires first focusing resources to ensure the availability of high quality services to diagnose, treat, and prevent all forms of TB in both the public and private sectors. It then requires investing in strategies to find those suffering from TB in high-risk communities and scaling up preventive interventions in these communities. Although no one approach fits all countries, we highlight policy priorities that can inform domestic budget allocations and donor investments in high-burden countries (section 1.1-1.3), and we also discuss the specific challenges faced by high-burden countries where private sector care is significant (section 1.4) and where DR-TB is prevalent or emerging (section 1.5). To complement these recommendations, we present modeling analysis from three countries with different epidemiologic profiles – Kenya, India, and Moldova.

1.1 Ensuring delivery of high quality, person-centred services

1.1.1 Defining person-centered care

To respond effectively to people suffering with TB and to reduce delays in their diagnosis, treatment, and cure, TB services must be person-centered; that is, they must be holistic, individualized, empowering, and respectful, encouraging informed decision-making and self-determination.[95] Given that TB commonly affects families, and family members of persons with TB are at high risk for developing TB disease, services must be family-centred[96] in addition to person-centred. Thus a thorough assessment of care-seeking behavior, TB epidemiology, as well as local demographic and health system data, is necessary to determine where to prioritize resources and what 'delivery gaps'[97] to address first. In all contexts, the first priority must be ensuring universal access to high quality, person-centred TB care for individuals who are already in the health system.

Unfortunately, in many high-burden settings, health system frailties are inimical to delivery of person-centered TB services: first, individuals with TB often are neither identified nor appropriately evaluated in a timely manner;[98,99] second, once a diagnosis is established, they are not started or supported to complete treatment that ensures a durable cure. TB services must align with care-seeking behavior to bring about person-centred care and prevention. Optimizing alignment of services, both in national TB programmes (NTPs) and in the non-state sector (private providers, nongovernmental organizations, etc.), can help ensure higher TB cure rates and improve the efficiency of care delivery to ensure greater equity and control costs. By redressing inequities in access, improving efficiencies in delivery, and protecting patients from physical and financial hardships, these interventions are also integral to robust health systems and to the broader UN Sustainable Development Goal (SDG) agenda.[100]

1.1.1. Re-thinking TB service delivery

As the UNHLM declaration illustrated, there is strong political commitment to promote person-centred policies. There are also solid ethical and moral rationales for adopting a people-centered approach to TB care. Providing patients with choices about where they access care and giving them ownership over clinical decisions can have important beneficial clinical consequences, as recent work in Russia illustrates. In one study, persons who were lost to follow up in Tomsk, Russia, where alcohol abuse is a major comorbiditiy with MDR-TB, were offered alcohol reduction interventions along with nutritional support, transportation support and a choice of where they would prefer to receive ongoing care

(inpatient, day hospital or at home). After the intervention, adherence improved from 52% to 81% and treatment success of 71% was achieved.[101]

To be successful, person-centered TB care demand a radical re-thinking of how treatment is delivered. Unfortunately, many national TB programs have been slow to embrace new models of care, constrained by limited technical capacity, scarce resources and a myriad competing priorities. This Commission stresses that TB programs need to learn to continuously evolve, responsive to changing demographics, patient preferences and available data. Differentiated HIV service delivery has demonstrated not only how service delivery innovations can improve efficieny and effectiveness, but also how communities can shape and inform systems. Marked disparities in particular demographic groups, such as the elderly and working-age men, highlight how the one-size-fits-all is untenable. The case for implementing responsive models of person-centered care that can reduce suffering and end TB within a generation is clear.[95]

1.1.1 Aligning TB services with care seeking patterns

To realize the vision of sustainable health for all, we must ensure that health systems are fully resourced so all of those at risk for TB care can access TB diagnostic, curative and preventive services. Immediate and incremental steps are are needed to strategically required to ensure that available resoureces are appropriately allocated, with a longer-term goal of creating optimally integrated, patient-centered health systems. To do this requires that TB programs pivot resources so that they align with how and where people with TB, and those at risk of developing TB, seek care. Patient pathway analysis (PPAs) mapping the continuum of care for people with TB, using existing population-based surveys and routine programmatic data, can enable programs to better understand how well patient care-seeking and TB service availability align, highlighting system-level obstacles to patients accessing care. This is an essential step to prioritizing efforts and planning the placement of services to meet patient needs and preferences. This methodology is well characterized,[102] and in 2017, results from five countries implementing PPAs and two countries implementing care cascades were published.[18] These analyses revealed marked mismatches between diagnostic capability and TB care-seeking behavior, with less than 30% of facilities where TB patients initiate care able to perform sputum smear microscopy and even fewer having the capacity to conduct an GeneXpert test or refer a sample for GeneXpert testing[19]. These results also highlighted the need to prioritize deployment of rapid molecular tests in certain places and strengthen specimen referral mechanisms in others. In addition, these PPAs demonstrated

the importance of facility-level data to ensure efficient, targeted allocation of resources and improving the primary health care network to find the missing cases.

In 2016, WHO's Strategic and Technical Advisory Group for Tuberculosis recommended that all countries complete PPAs as part of their priority-setting and planning processes.[103] Implementation guidelines have been published. However, to date, fewer than 10 countries have completed subnational PPA or care cascades.[102]

Person-centred care requires evidence-based priority-setting

Robust person-centred prioritization and planning demands a paradigm shift in how data is collated and translated. Currently, myriad data collection requirements often leave NTPs with numerous data points that are disjointed, overwhelming, and difficult to apply to decision-making. Furthermore, in most settings planning efforts have primarily used epidemiological data to inform resource allocation, rather than also considering how and where they should target resources to meet patient preferences. Several recent evaluations have enhanced our understanding of TB patient care seeking patterns, and health system TB capacities. However, few of these data are being routinely incorporated into planning processes yet. Unfortunately, evidence generation has been heavily driven by top-down planning rather than by key programmatic questions from NTPs. In addition, donor requests for evidence-based plans are not harmonized or synchronized with country-level planning processes. Consequently, countries can be locked into perpetual planning cycles without time for implementation and learning, which makes a robust data consolidation process for each plan nearly impossible.

Designing patient-centered programs will require that data and evidence are consolidated so that gaps in the care continuum are identified. It also demands that TB survivors and their advocates play an integral role in how TB care programs are designed, implemented and evaluated. A systematic and uncompromisingly person-centred approach to the use of this data, [Appendix Figure xx and Appendix Case xx], can enable NTPs to take the steps necessary to overcome the obstacles that prevent people with TB from reaching health services, not being diagnosed when they do reach a facility, or not being notified and/or completing treatment.

To support countries in moving toward person-centred planning, the global architecture of TB, including surveillance, technical assistance, and donor financing, will need to better align with this step-wise, person-centred approach. Currently, global TB results frameworks do not monitor gaps closed along the

patient pathway or specific health interventions optimized to the patient experience. To address this, PPAs need to be routinely deployed as key components of a package of evidence that informs priorities and donor assistance. While it follows that realignment of resources with care-seeking behavior should improve the efficiency of allocating NTP resources, further research is warranted to validate this assumption.

1.1.2 Utilize network optimization and big data analytics to ensure all patients have access to services

Network optimization is one strategy that can be utilized in high-burden countries to ensure that patients presenting with TB symptoms, many of whom drop out of the TB patient pathway during the 'diagnostic phase'[104], have access to rapid and accurate diagnostic services. Borrowing analytic approaches from manufacturing industries, network optimization seeks to solve how to ensure the selection of the best network configuration from available alternatives based on selected criteria and subject to constraints. Applied to TB diagnostic services, it can help balance the need to increase access to diagnostic services for those most in need while ensuring cost efficiency and feasibility , informing instrument placement, sample transportation, referral mechanisms, staffing and geographical prioritization. Furthermore, by integrating data from other diagnostic tools, e.g. chest radiography and HIV testing, and other disease programs, e.g. HIV care and treatment services, network optimization can enable more precise resource utilization across health sectors and programs.

One example of this approach comes from Lesotho, where diagnostic network mapping was used to analyze the NTP's testing and care cascade and inform procurement decisions. Despite a high unmet need, less than half of GeneXpert testing capacity was being used in 19 of 25 sites where it was available. Initially the NTP planned to procure and deploy additional instruments within the network. However, an analysis found that network capacity could be better optimized by improving referral flows and adjusting where the placement of existing instruments should be. The analysis also identified a "sweet spot" where patient demand would make it most worthwhile to place point-of-care diagnostics. The analysis led to recommendations that 62% of the country's GeneXpert instruments be re-allocated for maximal impact. Referral flows between and across district borders were also adjusted to improve efficient use of GeneXpert instruments, obviating the need to purchase additional instruments.

In the near future, big data aggregated from routine Ministry of Health reports, donor-agency operating plans, private health systems, and social media, as well as other sectors of government, will help transform the efficiency of TB programs, enabling targeted scale up of services and providing unprecedented situational awareness and analytic capability to Ministers of Health and NTP managers. At present, examples of aggregated data being employed to enhance the delivery of person-centred programs are scarce in resource-limited settings. However, integrated data platforms, in combination with simulation technology, could enable NTPs to create detailed real-time models of the TB case continuum, incorporating variability in patient care-seeking behaviors, diagnostic capacities, gaps in linkages and health care costs. In the future, such data systems could provide user-friendly 'dashboards' at each level of the health system, with a single interface for both static and real-time analysis of complex systems, enabling NTPs to predict changes in patient-demand, anticipate stock-outs, determine utilization of diagnostic and treatment assets and, ultimately, improve patient care. Such use of aggregated, 'big data' sources will demand specialized equipment, interoperability standards, coherent data collection and analysis systems, as well as regulatory oversight.[105] However, these approaches are being successfully applied to address other complex health system problems in the US[106,107] and elsewhere.[108] Thus, they couldbe successfully employed to help close delivery gaps for TB programmes as well.

1.1.3 Improving quality management to ensure high quality service delivery

In addition to PPA and network design analyses to ensure *access* to services for all patients presenting with TB, we must improve the *quality* of care that patients receive. Unfortunately, cascade of care analyses show large gaps in the quality of care for both adults and children, and for both drug-susceptible and DR TB in many high-burden countries. Simulated patient studies in India, Kenya, South Africa and China[26,28,29] have all demonstrated that the quality of TB care is poor. In a study in China, for example, health care providers failed to correctly manage the 'mystery-shopper' TB patients 59% of the time.[33] In an Indian study, only 21% of practitioners correctly managed TB when presented with a text-book simulated patient. [32]

Traditionally, programmatic impacts and outcomes have been defined primarily by epidemiological measures. Such a focus, however, overlooks that outcomes tied to improving quality by closing gaps along the care cascade are more relevant operationally and can accelerate progress. Quality

management (QM) tools can help front-line providers and NTP managers address those gaps to improve care quality as well as address the drivers of ongoing TB transmission. [109]

Implementing quality improvement: lessons learned from tackling HIV

Over the past few decades, HIV programs in sub-Saharan Africa, the Caribbean, and Asia have implemented QM programs to optimize the use of limited resources available from governments and donor agencies.[110] The basic elements of quality management include a formal QM plan, a technical working group or committee, a set of performance measures, expectations for implementing quality improvement (QI) activities, staff capacity building, and patient/community involvement. These elements are necessary to achieve sustainability in the face of expected staff turnover and environmental changes that affect the stability of healthcare organizations and the workforce. By leveraging a four-step continuous cycle of improvement ('plan-do-check-act,' or PDCA), these programs have driven substantive change by developing local solutions to improve the quality of HIV/AIDS care. Improvements have been demonstrated across different facets of care, including treatment adherence,[111] reducing mother-to-child transmission of HIV,[112] pediatric services,[113] enhancing fidelity to treatment guidelines,[114] and strengthening the clinical capacity of front-line providers.[115]

Similar approaches can be used to improve the quality of care for patients with TB, while also enabling increased levels of accountability at all levels of NTPs. (Appendix Case studies xx,yy and zz provide examples from the public and private sector, at facility and regional level, of how QI approaches have been deployed to improve TB outcomes).

Using the cascade of care as an organizing framework, NTPs can measure quality at the facility-level using a set of indicators that represent key steps in the care cascade or that reflect the International Standards of TB Care[116] (Appendix Table xx). National reporting of these quality indicators can help NTPs identify low-performing facilities that may require more support or resources. Furthermore, health facilities can use the tools of root cause analysis to identify specific barriers and generate ideas for addressing them.

However, as pointed out by the Lancet Global Health Commission on High Quality Health Systems, improving quality will require system-wide action that goes beyond facility-based QI efforts.[25] These actions include better governance for quality; adopting competency-based clinical education and

training in ethics and respectful care; and creating demand for quality in the population to empower people so they can hold systems accountable and actively seek high-quality care.

Implications for national and global stakeholders in implementing a quality management program

Quality management programs must become part of NTPs and ideally integrated into existing national quality management programs. Ensuring that NTP managers and their teams have access to this expertise will facilitate the development of ways to measure and improve quality in their NTP. Nonetheless, a culture change in how TB data are used to improve care must occur at every level of the health system, including greater accountability of local TB clinics to patients they serve. Globally, a quality management program that embraces improvement methodologies can be a powerful lever to improve donor-recipient accountability and enhance donor efficiency. WHO plays a crucial role in supporting a quality management agenda and creating a global culture that supports QI and accelerates dissemination of learning through peer exchange. Linking donor support to quality indicators could also improve efficiencies in donor financing and enhance transparency.

1.1.4 Assessing the impact of strategies to deliver high-quality, person-centered services

Together, the strategies described in this section share the common objective of accurately diagnosing TB as early as possible: they reflect ways of realising the maximum potential impact of a system of TB services that is contingent on cases presenting for care. What are the potential epidemiological implications of these measures? Modelling analysis, commissioned for this report, casts some light on the potential value of these and other measures in three different country settings, each with distinct challenges in TB control: India (with a large private sector); Kenya (with HIV confection); and Moldova (with a high burden of MDR TB). The full analysis is provided in (Vesga Gaviria et al, in press, 2018). Figure 3 Illustrates the example of Kenya: in this setting, patient pathway analysis has already identified the lack of diagnostic facilities as a key challenge.[20] The figure shows the potential impact of measures that could increase the probability of diagnosis per provider visit to 90%: the impact is to reduce cumulative TB cases from 2018 – 2045 by 25% (95% credible intervals 11-39%), and cumulative TB mortality over this time by 38% (95% CrI 17 – 50%). As described in this section, such measures are not limited to diagnostic tools: they also involve network optimisation, correcting misalignments of TB services; and other such measures to maximise the effective uptake of rapid, accurate diagnostics. As the modelling illustrates, these measures are necessary but insufficient to end TB. However, in concert

with the other strategies outlined in section 1, they can enable countries to make substantial progress towards ending the epidemic.

1.2 Prioritized active case finding

Besides targeting resources and analyses to ensure high-quality, person-centred care for those individuals with TB disease that present, another high priority is finding persons with TB, especially among high-risk populations, who have not yet presented for care. Strategies to find these "missing persons" must occur together with scaling up access to preventive interventions. These two strategies—*active case finding and prevention*– must be programmatically inseparable and not divorced by budget allocation decisions. While active case finding (ACF) mainly seeks early detection of and prompt treatment for people with active TB, thereby reducing mortality, morbidity, patient costs, and ongoing transmission, it also aims to identify people eligible for treatment of latent TB infection.[117] In this section we discuss ACF; in Section 1.3 we highlight the importance of prevention interventions.

1.2.1 ACF: Closing the 'know-do' gap

Prevalence surveys in high-burden countries[118-120] provide abundant evidence that despite scaling up and decentralizing TB diagnosis and treatment services, undetected TB cases loom large, especially for high-risk groups.[121-124] Unfortunately, most high-burden countries have not widely implemented strategies to find these individuals because these countries lack funding, political will, and scientific consensus.[125-127] As a result, the impact of ACF strategies on TB epidemiology in high-burden settings is limited; only a few studies have been published, with mixed results.[126-129] Nonetheless, recent clinical research,[130] mathematical modeling[131,132], and considerable programmatic experience[132,133] suggest that these strategies can be taken to scale. In the Russian Federation in 2015, for example, almost half of the TB burden was detected by actively screening 68% of the prison population. In Brazil TB screening of the prison population yielded 6021 new cases, 8% of the total national burden in 2015.[134]

While implementing ACF requires a systematic approach, ministries of health and their partners also need to consider how to scale up targeted ACF interventions. Important considerations include setting clear goals and objectives based on a thorough assessment of the situation; identifying and prioritizing risk groups; and choosing simple algorithms and accurate, effective technologies. [133,135] In addition, consideration should be given to using best practices to disseminate innovations;[97,136] establishing and using networks for change; actively engaging the community; and ensuring strong leadership and

governance to guarantee the success of ACF activities. Linking ACF strategies to accountability frameworks and funding predicated on meeting case-finding targets may also play a role.

1.2.2 Prioritizing high risk groups

Several groups with diseases or exposures that put them at high risk for TB should always be systematically screened for TB (see Appendix Table xx). Among them, household contacts must always be a programmatic priority, given the strength of evidence demonstrating the impact of strategies targeted to them.[137] The importance of a family-centered approach – and recognition that TB is a disease that affects families, as much as it affects individuals – has important implications for ACF, insofar as NTPs need to understand the family, not the individual, as the 'unit of intervention.'

Other risk groups may warrant targeted screening programs based on epidemiology, health system capacity, availability of resources, and feasibility. Given higher rates of TB in men compared to women in almost all high-risk groups,[12] male-friendly strategies, such as workplace interventions should be employed where feasible. In preparing ACF scale-up strategies, the risk of discrimination and stigmatization should be carefully addressed. In addition, the legal status of migrants, with regard to both access to health services and risk of expatriation in case of TB diagnosis, needs to be considered.[138] Engaging with civil society groups to better understand the expectations and concerns of high-risk groups when planning and implementing TB screening activities is critical to their success.

Opportunities for integrating ACF with other essential services for these populations should be exploited where possible, especially when high-risk groups are already served by vertical, facility-based programs[139] or private providers[140] and where ACF activities can be aligned with other health promotion activities.[141] For some high-risk populations—such as people living in slums, the homeless —innovative, multipronged case-finding strategies, leveraging m-health technologies, and incorporating social protection strategies, may be necessary to maximize yield and rationalize costs[140,142]

1. 2.3 Anticipating costs and using planning tools

Scaling up ACF strategies will require substantial additional resources. The cost of screening can be high per case identified,[143-145] especially when compared with other health promotion interventions.[146] Nonetheless, as highlighted in Section 3, evidence on the cost-effectiveness and benefits of expanded financing for ACF suggests that such investments will yield a high return. Modelling performed as part of

the South African government's investment case for TB (Figure 7) also illustrates that the declines in TB transmission resulting from higher case detection and optimal treatment will be highly cost-effective if major and durable reductions in TB incidence and prevalence are achieved. Other modeling studies that include the benefits from reduced rates of transmission also confirm that even where active screening costs are high, ACF strategies still can be highly cost-effective.[131,145]

Planning tools, such as the WHO's online ScreenTB tool,[147] can help NTPs plan their case-finding activities and prioritize risk groups for screening by modeling the potential case yields and costs of different screening approaches. The ScreenTB tool allows the user to select risk groups of interest and compare estimates of the yield of screening (including true-positive and false-positive cases found), the total costs, and the cost per case detected across the selected risk groups and across different screening algorithms.

1.2.4 Leveraging technology to improve the efficiency of case-finding strategies

The tools used to screen for and diagnose TB are crucial in determining the efficacy of systematic screening. A rapid triage test that would enable active screening in the community would be a more efficient, person-centered approach to case-finding than current approaches and warrants substantial investment (Appendix Panel xx). Mobile, automated, digital chest radiography units, to detect lung lesions in people who are relatively asymptomatic[148,149], may also help detect many more patients with TB than is possible through passive case finding or self-reporting. While data are sparse,[150] computer aided detection tools, used in concert with digital radiography, could substantially increase diagnostic sensitivity while also saving money. Clearly, this technology will also enhance sensitivity for detecting other pathology, in addition to pulmonary TB, underscoring the importance of incorporating ACF in the setting of comprehensive primary care services.

In addition to new diagnostic technologies, better use of available data—aggregated and anonymized, and collected from a variety of sources, including social media, pharmacies,[35] and the private sector—have the potential to enhance both the precision and efficiency of ACF interventions. Already, social network data, mobile phone records, and spatial data have been combined to improve HIV testing rates in Uganda[151] and to show that imported malaria contributes significantly to disease burden in urban centers in Kenya.[152] Notably, the impact of these additional data to address TB ACF efforts will be small unless they can be captured and integrated into existing data systems.

1.2.6 Finding cases in lower-risk populations

Reaching the general population through ACF should remain a low priority until high-risk populations are successfully covered. Nonetheless, recognizing that ACF is a high-value intervention, both epidemiologically and economically, lower-risk populations in high-burden countries should not be ignored. The identification of the most effective mix of interventions and strategies that NTPs can use to detect patients in both high risk and lower risk populations, and the empowerment of NTP managers to select the most appropriate combination of approaches in their unique settings, are key for success. Within a country, different provinces or districts might use various methods, depending on population sociodemographics, civil society engagement, and health system assets. Selecting appropriate interventions and strategies hinges on a rigorous, ongoing process of scientific research, knowledge sharing, and monitoring and evaluation.

1.2.5 Recognizing that ACF in high-risk populations will not be enough

ACF alone will be insufficient to eliminate TB in high-risk populations. Even if we identify more individuals with TB in at-risk populations, those patients will return to their high-risk pools where the prevalence of TB risk factors are high. A multisectoral approach is essential to ensure that drivers of TB risk such as malnutrition and air pollution are addressed. It is also vital that ACF interventions are programmatically inseparable from interventions targeted at preventing TB disease in those latently infected and at greatest risk of developing active TB. Such interventions are discussed in more depth in the next section.

1.3 Prioritizing TB prevention

As noted in Section 0, TB prevention is a crucial but neglected component of global control of the TB epidemic. For the past 50 years, global strategies for controlling TB have focused on passive case detection and treatment of active disease. However, mathematical modeling shows that this approach alone, while averting deaths and relieving suffering, will not end TB. Rather, ending TB will require multiple different preventive interventions to interrupt transmission, treat latent infections, immunize close contacts, and treat or prevent comorbidities, such as HIV, that increase susceptibility to developing active TB. Table 4 illustrates some populations that may benefit from prevention interventions.[153] While this subsection focuses primarily on TB preventive therapy (TB PT), TB Infection control in healthcare facilities and congregate settings such as prisons is also critical to TB prevention efforts: healthcare centers and hospitals are often hotspots of TB transmission, and instituting environmental control measures and rigorous administrative and personal protective strategies is likely to reduce the transmission risk substantially.[154]

1.3.1 Targeting preventive therapy

TB preventive therapy (TB PT) likely offers one of the most effective interventions to reduce TB incidence globally. In addition, by preventing TB and reducing mortality by treating those with latent infection who are greatest risk of becoming ill, TB PT is a necessary component of a comprehensive strategy to end the epidemic. Even improved strategies for diagnosis and treatment will not address the large reservoir of latently infected people (estimated to be approximately 2 billion globally) who may develop TB at any point in their lifetimes.[45] Clearly targeted TB PT could significantly reduce rates of TB disease in the highest risk groups. These groups include people with HIV infection; household and other close contacts of persons with infectious TB; and persons working or living in settings that foster the transmission of *M. tuberculosis*, such as congregate living settings, prisons, healthcare facilities,[155,156] and underground mines, especially those in which there is silica exposure, which, in itself greatly increases risk[123,157]. Moreover, the process of providing TB PT will uncover active cases, as candidates for PT undergo screening to rule out disease before beginning treatment, which identifies previously undetected cases of TB disease.

Although the effectiveness of TB PT in preventing active TB disease is well-established,[48] public health programs have prioritized TB case finding and treatment rather than implementing this inexpensive and highly effective intervention. HIV programs have focused primarily on rolling out lifesaving antiretroviral

703 therapy, not least because of compelling evidence of its efficacy as TB prevention intervention.[158,159]
704 Recent studies have shown that TB PT using isoniazid significantly reduces rates of death in people with
705 both early and advanced HIV infection. [160-162] People with HIV and household contacts of active TB cases
706 can benefit substantially from TB PT. Globally, modeling studies find that wider uptake of TB PT, coupled
707 with improved case-finding and treatment, is more important than an effective vaccine for reaching TB
708 elimination by 2050[162], and that household contact evaluations and use of TB PT would avert 99,000-
709 117,00 deaths per year in children <15 years of age.[163] This data underscore the importance of a family-
710 centered approach to TB care to ensure that these contacts are routinely screened as part of the routine
711 management of all persons diagnosed with TB.
712
713 Numerous obstacles have hindered the scale-up of TB PT, and innovative approaches must be taken to
714 overcome these barriers (Appendix Table xx).[153] Improved diagnostic tests to document TB infection,
715 including point-of-care (POC) tests, would facilitate treatment of infection in persons with an increased
716 risk of developing TB, such as household contacts, though young (<5 years) child contracts and all people
717 living with HIV in high-burden areas could potentially be treated without testing. Prognostic biomarkers
718 that identify latently infected people who are most likely to progress to active disease would allow more
719 targeted use in high-risk populations and broader use of PT in lower-risk populations. Global supplies of
720 essential drugs such as isoniazid (INH) and newer agents such as rifapentine are unreliable, and stock-
721 outs are frequent; improving the supply chain of inexpensive and quality-assured drugs is therefore
722 critical. The duration of PT using INH, now 6-9 months, often results in non-adherence and is leading to
723 widespread concerns, largely unfounded,[164] about TB PT causing drug resistance. Novel short-course
724 regimens, such as 12 weeks of weekly rifapentine and INH, or a 4-week regimen of daily rifapentine and
725 INH, could transform prevention efforts, [165-167] reduce the risk of resistance emergence, while also
726 saving money and lives. [165,168,169] Nonetheless, rather than waiting for new diagnostics and shorter
727 courses, this Commission asserts that NTPs should increase access to TP PT now. (While scarce, there
728 are examples of how NTPs and their partners have successfully implemented TB PT at scale; we highlight
729 these in cases Appendix xx and Appendix yy).
730
731 To realize the full impact of preventive therapy, NTPs must devote resources to ensuring that ACF and
732 TB PT are integrated into existing programs for specific high-risk populations. Integrating TB screening
733 and preventive services into care for people living with HIV (PLWH) is particularly important, especially
734 given extensive, high quality research demonstrating the life-saving benefits of this strategy.[160,170] Global

efforts to provide antiretroviral therapy have now reached 20 million individuals with HIV, but another 17-19 million remain untreated. Fewer than four million people with HIV have ever received TB PT, highlighting the opportunity to substantially scale-up this intervention. Failure to scale up TB PT in people living with HIV has likely caused several million deaths over the past decade.[170].

In collaboration with the Lancet Commission, a team at Imperial College, School of Medicine, London conducted an analysis to determine the impact of TB PT using isoniazid as currently recommended in countries with high rates of TB/HIV co-infection. By increasing TB PT among PLWH in Kenya to 90% (Figure 4)TB mortality could be reduced by 17% between now and 2045. In South Africa, a similar increase in TB PT coverage would lead to an even greater reduction in mortality over the same time frame. To achieve this impact, as well as to extend TB PT to other eligible groups recommended by WHO,[171] will require additional investment. The incremental cost to the TB program of increasing TB PT in Kenya and South Africa would be relatively modest (estimated to be US$66 million per annum between 2018 and 2045 to achieve results highlighted in Figure 4), especially when compared to the economic costs of avoidable deaths resulting from failure to implement this strategy. The efficiency of that investment can be enhanced by optimal use of health systems data to enable NTPs and their partners to plan interventions and monitor the impact of prevention strategies.[172,173] TB report card tracking progress on these data at regional and local levels may also help accelerate TB PT scale up efforts and ensure that NTPs and their partners are more accountable to civil society organizations and funders. The success of scale up TB PT efforts will also be contingent on recognition of the importance of shared responsibility (Appendix Table xx) from across health programs and community stakeholders.

1.4 Importance of private provider engagement: from acknowledgment to prioritization

In most low- and middle-income countries, private providers are an important source of healthcare for people of all socioeconomic groups, often offering accessibility and convenience not provided in the public system. Strictly speaking, “private” is synonymous with “non-state” and includes the for-profit as well as the non-profit sectors, i.e., non-governmental organizations (NGOs) and faith-based organizations (FBOs). While most countries could improve their engagement of public and NGO/FBO providers, engaging for-profit private providers, which is even more important for TB control, has been much more difficult. In this section, we discuss some reasons for the failure to engage private providers, recent progress in how they can be engaged on a large scale for TB care, and the critical actions countries must take to prioritize private provider engagement as part of their TB programs. We highlight

767 strategies to enable high quality TB care in the private sector, opportunities for greater syngergy
768 between NTPs and private providers, and how the extended capability that the private sector provides
769 can be leveraged to find those people with TB disease that are being missed by current NTP surveillance
770 efforts.

771 **1.4.1 Making engagement of private providers a priority**

772 The need to engage private providers for TB control has been acknowledged in various global strategies
773 since the early 1990s.[174] Unfortunately, NTPs and their development partners have not focused
774 sufficiently on engaging private providers in TB, and resources have not been adequate to meaningfully
775 tackle this issue. Before the most recent funding allocation, the Global Fund to Fight AIDS, Tuberculosis,
776 and Malaria (GFATM), which provides 56% of international development assistance for TB, had allocated
777 less than 5% of grant budgets to engage a range of non-NTP providers defined as part of the "public-
778 private mix."[175] Because the GFATM responds to country requests for how its grant funds will be used,
779 ultimately this small percentage reflects the low priority that countries place on engaging their private
780 providers. Although data on how much NTPs spend to engage private providers is scant, an example
781 from India is illustrative: until recently, only 1.5% of the state-level TB expenditure was allocated to
782 engage NGOs and private providers.[176]

783 Failure to engage private providers is often blamed on NTP staff shortages, but clearly the constraints
784 are much more profound.[177] Most health systems in low- and middle-income countries are weak in
785 areas essential for effective private provider engagement, such as regulatory enforcement, strategic
786 purchasing, and health information systems. NTPs often lack basic information on the number of
787 private providers, their role in TB patient care-seeking, and the drivers of patient and provider
788 behaviors. Therefore, NTPs find it difficult to engage hundreds and thousands of independent private
789 providers with widely varying capabilities. For their part, private providers are often wary of engaging
790 with government programs and, given competitive market dynamics and financial imperatives, unwilling
791 to adhere to guidelines promoted by NTPs.

792 Failure to meaningfully engage private providers reflects a strong preference for the public sector
793 among those who manage TB programs, those who fund them, and those offering technical support.
794 The TB community has successfully embraced many innovations, including new diagnostics, treatment
795 tools, and approaches to address TB/HIV and multidrug-resistant TB (DR -TB). These innovations,
796 however, should be adopted in the private sector without challenging the basic public-sector business

models. Private provider engagement can succeed at scale only when NTPs acknowledge that they cannot continue using the current business model (Table 5). Nonetheless, such engagement must occur in tandem with strategies that protect patients and their families from catastrophic financial losses that can arise from accessing care in the private sector.[178,179] In working towards ending the TB epidemic in countries with a large private sector, it will be essential to protect the interests of poor people by ensuring that public resources are applied to reduce user fees, while leveraging the private sector to expand TB diagnostic and treatment coverage.

1.4.2 Catalyzing progress and new opportunities to engage private providers

Although private provider engagement in TB is far from adequate, considerable experience has accrued regarding how to successfully engage private providers for TB care.[180] Many small, externally supported pilot projects to engage private providers have been implemented over the years. A study in 2006 reviewed data from 15 projects in 8 countries,[181] a systematic review in 2011 considered 45 studies from 22 projects in 12 countries[182], and another in 2016 found 78 studies documenting 48 programs in 16 countries.[183] Although, most projects have failed to reach significant scale or to be sustained over long periods. Nevertheless, these projects have generated abundant evidence that engaging private providers can significantly increase TB case detection and achieve treatment success rates that are at least as good as those in the public sector. Data on cost-effectiveness, financial protections, delays to treatment, and reaching the poor is less robust but also available.[184] New research continues to add to our understanding of the functioning of private healthcare markets with respect to TB.[31,185,186]
More recently, sustained scale-up of private provider engagement has taken place in several key countries (Figure 5). Bangladesh has sustained a moderate level of private provider engagement for the past five years, with private notifications reaching 18% of incident cases, while notifications in Myanmar have declined recently from similar levels. Recently, India, Pakistan, and the Philippines all increased their engagement of private providers, with private notifications increasing to 9%-13% of incident cases in 2016. Unfortunately, Indonesia and Nigeria–two countries with substantial numbers of “missing” TB cases–have made little progress, with private notifications averaging just 4% and 1% of estimated incidence, respectively.

In Bangladesh, Myanmar, and Pakistan, engagement of large numbers of private primary care providers has been led by strong non-governmental organizations (NGOs) acting as intermediaries between providers and the NTPs. These mission-driven NGOs have identified enhancing private provider

engagement for TB as part of their long-term role and have succeeded in attracting resources from multiple donors to sustain their work. Some are generalist NGOs, such as BRAC in Bangladesh and Mercy Corps in Pakistan; others are more focused on TB, such as Damien Foundation in Bangladesh and more recently Interactive Research and Development in Pakistan; Greenstar in Pakistan and Population Services International in Myanmar are social marketing organizations that have long engaged private markets for family planning and other health issues. All these organizations have in common an understanding of private providers, the ability to operate at scale, strong management systems (for human resources, information, and logistics), dynamic leadership, an aptitude for adaptation and innovation, and success in fundraising.

Efforts in Indonesia and the Philippines have focused on private specialists and hospitals rather than primary care providers. The NTPs have partnered with specialist-led associations (such as the Indonesia Pulmonologist Society and the Philippines Tuberculosis Society). However, much of the initial care-seeking and TB treatment in these countries are among private primary care providers, and therefore more effort to engage these providers will be needed. Social health insurance schemes, approaching full population coverage in both countries, are contracting with an increasing number of private providers for primary care services. Yet collaboration between the NTP and social health insurance remains quite limited.[15]

One of the most exciting developments is the recent political commitment in India to scale-up private provider engagement nationwide, building on the success of several large demonstration projects (Appendix Panel xx).[16] India's National Strategic Plan for TB (2017-2020) commits to a massive expansion of private provider engagement and calls for a six-fold increase in private notifications to two million patients per year by 2020, which would represent 75% of estimated TB incidence. If India's plan succeeds, it will be the first major high-burden country with a dominant private healthcare sector to align its TB program with the care-seeking patterns of its population. Private notification targets for Bangladesh, Pakistan, Indonesia, and the Philippines are much more modest: 18-24% of estimated TB incidence by 2020 (Figure 5). Overall, at least 10 countries have recently prepared PPM Action Plans,[17] and the latest round of GFATM funding (2018-2020) includes substantial components for private provider engagement in several countries.

As successful experiences on private provider engagement accumulate, defined packages of interventions could be disseminated as templates that could be adapted for rapid scale-up.[18] The core

interventions in such templates include defined activities to engage private providers (including stakeholder consultation, provider mapping and prioritization, relationship management, facilitating reporting of TB cases and data, and patient support for adherence); addressing financial and non-financial incentives for private providers, and ensuring private patients have access to quality drugs and diagnostics according to national protocols. While intervention packages can and have been summarized in general terms, continued innovation and adaptation should be encouraged.

In addition, legal and regulatory frameworks should be in place to ensure TB notification and quality services by private providers. Several countries have re-issued laws and regulations requiring providers to report cases, sometimes conditioning re-licensing and accreditation to TB notification.[19] While regulatory penalties may have a role to play, countries most successful in engaging private providers have invested more in enablers (such as call centers to facilitate notification) and incentives (such as easy access to drugs and diagnostics) while respecting private providers' interests. Professional societies can be and have been successfully engaged to help define best practices for TB among private providers.

Looking ahead, new opportunities and developments could enhance private provider engagement for TB in the coming years. First, success in a country like India could set an example that inspires other countries. Second, the digital revolution is finally reaching TB. The use of information and communication technology (ICT) systems, coupled with call centers, can facilitate the engagement of private providers and provide digital, case-based information on private TB patients. Third, such ICT systems can enable additional innovations that further facilitate private provider engagement at scale, such as digital vouchers for drugs and diagnostics, adherence monitoring technologies, and digital payment of incentives and enablers to both patients and providers. Fourth, access to new and improved diagnostic and treatment tools, such as digital chest x-rays and Xpert MTB/RIF®, increased the value to private providers of engaging with the public sector. Finally, the emergence of social health insurance schemes for UHC offers an unprecedented platform to engage private providers at scale across all health conditions and provides an opportunity to improve quality and access of both curative and preventive TB services in the private primary sector in countries like Indonesia and Philippines.[20,21]

The challenges of optimizing private sector to deliver high TB quality care, while protecting patients from excessive out-of-pocket expendiure, are considerable. To be successful these models must minimize fee-for-service payments that reward quantity over quality and do not promote high value, low cost interventions, such as TB preventive therapy. Nonetheless, as part of a broader UHC agenda,

leveraging private sector services to provide public-financed services may enable extended capability while aso accommodating the preferences of those most at risk for, or suffering from TB.[187]

1.4.3 Modeling the impact of optimal private sector engagement

Because of the large burden of TB that is managed in the private sector globally, it is essential to assess the impact of improving private sector engagement. Modeling commissioned for this report assessed how greater private sector engagement in a high-burden country like India, where private providers offer extended capability, could influence TB incidence and mortality. In such a setting, strategies to improve quality of private sector care, such as subsidized TB diagnostics, and NTP-funded adherence support mechanisms for patients accessing care privately, would avert 28% of TB deaths over the next 30 years, saving an additional eight million lives from TB, beyond those lives saved by full implementation of other evidence-based interventions (Figure 4). The additional cost of optimized private sector engagement would involve an annual increase of US$290 million in NTP costs. While this strategy alone would not be enough to end the epidemic in India, it has the potential to substantially reduce the public health threat posed by TB. Further, enhanced private sector engagement in concert with other strategies to close gaps in the care cascade, such as targeted ACF interventions, optimization of diagnostic networks, and improved adherence support strategies, could lead to significant reductions in TB mortality over the next 30 years.[188]

1.5 Tackling drug resistance

Over the next decade, at least six million people are projected to develop drug-resistant tuberculosis (DR TB). At current levels of treatment provision and success, most of these people will die from TB, with many transmitting their DR infections to others before they succumb. By 2050, one-fourth of the predicted 10 million annual deaths attributable to antimicrobial resistance (AMR) globally are expected to be due to DR -TB, which will make it the leading cause of AMR-related death and *Mtb* the most significant airborne pathogen that is drug-resistant.[189]

Given these projections, addressing TB drug resistance is essential both for curtailing the global AMR crisis and ending TB. Although providing universal drug resistance testing and scaling up access to high-quality, tailored treatment for DR -TB will require substantial funding and commitment, the consequences of not doing so would be enormous, including massive loss of life and trillions of dollars spent as multidrug-resistant TB (MDR -TB) increases dramatically.[189] Furthermore, addressing DR -TB cannot be divorced from scaling up access to diagnosis and treatment of drug-susceptible TB; if we improve case detection for drug-susceptible TB without a meaningful change in quality and identification of DR -TB, we will only increase the selection pressure for DR -TB.

A modelling analysis commissioned for this report demonstrates the impact of ensuring universal access to DST and second-line therapy in a high DR -TB country such as Moldova. As highlighted in Figure 4, optimizing access to DST and increasing treatment success rates would lead to a 43% reduction in TB mortality and a 73% reduction in incidence over the next 30 years. With adequate investment in tools, the prospect of definitively addressing the threat of DR -TB within a generation is credible.

Encouragingly, the rapidly evolving field of DR -TB diagnostics and the increasing availability of new and repurposed drugs and regimens for treating patients with multidrug-resistant/rifampicine-resistant (MDR/RR) TB present opportunities to dramatically improve the epidemic response (Appendix Table xx). Emerging data suggest that in high-burden settings, more than 90% of incident MDR/RR-TB disease results from direct transmission of already resistant TB bacteria from one person to another.[61,62] As a result, failure to diagnose and effectively treat a significant proportion of individuals with active TB disease is a major driver of the epidemic. Barriers to diagnosis and treatment scale-up vary across countries but include 1) the high cost of providing treatment (although data show such costs can decrease dramatically when more individuals are offered access[190]); 2) perceived complexity of

treatment regimens; 3) poor programmatic treatment outcomes in most part due to lengthy and toxic drug regimens that impose enormous burdens on individuals;; 4) reliance on centralized and specialized treatment; and 5) lack of political will and commitment.[191-194]

Because most DR-TB is caused by direct transmission, early diagnosis and initiation of effective therapy, combined with effective preventive therapy for close contacts should be key priorities in preventing DR-TB[195].[189] While, reducing the risk of further resistance development, particularly to new TB drugs, is also of concern, with data suggesting that when TB drugs are used as "last resort options," resistance is more likely to emerge[196] , policies that 'protect' the drugs rather than prioritising improving patient care through expanded use are neither scientifically sound nor patient-centred. Rather, strategies for implementing new TB regimens need to take into account the factors that led key first-line drugs to acquire resistance in the past. Such factors include varying individual pharmacokinetics, comorbidities (particularly those that may affect drug absorption, e.g., HIV), poor drug quality, inadequate dosing, weak supply chains and inadequate prescribing, and selective treatment adherence.[197-202] Weak health systems that offer limited support for patients and their families contribute to many of these factors, emphasizing the importance of strengthening health systems to help respond to the DR TB epidemic and provide more patient-centred care.[203-205] Because TB drug resistance emerges spontaneously and can be selected for during treatment,[206] using standard combination regimens in patients with undiagnosed drug resistance likely will contribute to further resistance acquisition, in addition to poor patient outcomes.[207-212] Robust stewardship mechanisms, especially in the private sector, such as that recently described for a large private hospital in India, are crucial in this regard.[213]

1.5.1 Increasing universal access to drug susceptibility testing

Given the clear requirements to find and treat all individuals with DR -TB, and to prevent the emergence of further resistance, universal drug sensitivity testing (DST) (to rifampicin as a minimum) with access to second-line treatment is a key recommendation of this Commission. Prompt use of molecular DST for patients failing first line therapy should also be implemented to obviate the practice of standardized re-treatment with a regimen that only includes one additional drug and is highly likely to contribute to resistance amplification, in addition to poor patient outcomes.

Until relatively recently, diagnosis of DR -TB relied on TB culture, with consequent long delays and the need for specialised laboratories.[214] Because DR -TB results from the presence of resistance-conferring

mutations in the bacterial genome, newer tests, such as the Xpert MTB/RIF test[215] and line probe assays[216], rely on identifying mutations known to infer drug resistance. These more rapid tests have shortened the time required to receive results from months to hours,[215,217] consequently reducing how long it takes to initiate treatment across a range of settings,[218,219] and they are being used at scale in some countries (Appendix Panel xx). Newer versions of these and related tests, including whole genome sequencing, are expected to expand the range of drugs that can be tested and reduce reliance on specialised laboratories.[220-222] A pipeline of candidate point-of-care diagnostics, implemented at the same time as an initial health care visit, have the potential to dramatically improve case detection and reduce losses along complicated diagnostic and care cascades.[5,223,224]

1.5.2 Improving DR -TB treatment

The high MDR/RR-TB burden and poor patient outcomes highlight the dire need for safe and effective, less toxic, shorter, and less costly treatment regimens for MDR/RR-TB.[55,225-228] Encouragingly, two new TB drugs (bedaquiline and delamanid) are now available for use in MDR/RR TB treatment.[229-231] These drugs, along with drugs repurposed for TB (including linezolid and clofazimine) and pretomanid (a similar drug to delamanid), are included in a range of new, shorter, all-oral regimens currently being tested in clinical trials for MDR/RR TB treatment.[232] Results from most of these trials, however, are not expected for several years.[233] In the meantime, these new and repurposed drugs have been increasingly used programmatically. Data from South Africa suggest dramatic improvements in mortality and reductions in treatment failure among more than 3,000 patients treated with bedaquiline to date (Appendix Panel xx).[234] As a direct result, South Africa recently announced the implementation of an injectable-free, bedaquiline-containing treatment for all RR-TB pateints.[235]

The South African data, complemented by a large individual MDR-TB patient-level meta-analysis, have contributed to new WHO guidance prioritising the use of bedaquiline and linezolid for MDR-TB treatment.[236] To date, there is insufficient data to support similar prioritisation for delamanid. Increasing the use of these new and repurposed drugs would remove reliance on some of the more toxic and less effective drugs, including the second-line injectable agents, which are associated with irreversible hearing loss in up to 50% of individuals who receive them.[237] It also would help relieve the burden on the health care system to deliver the daily injections.[238] However, to date, uptake of new drugs based on previous WHO guidance has been disappointingly limited, despite a US Agency for International Development (USAID)/ Janssen Pharmaceuticals (Beerse, Belgium) donation program in

many countries.[239] Barriers include drug costs, difficulties in individual country regulatory approval and drug procurement, and lack of high level national government support.[240] Overcoming these barriers is essential moving forward. As highlighted earlier, TB programs also need to be continuously evolving, to ensure that national guidelines and clinical practice reflects the best available evidence. Civil society organizations have a vital role to play ensuring that this is the case.

Additionally, a more individualized approach to DR- TB treatment—one that encompasses access to all second-line drugs and is guided by more extensive DST through whole genome sequencing—would enable individuals with DR -TB to receive the best chance of cure, while limiting both the unnecessary use of toxic drugs and resistance amplification.[241] Such an approach would need to be supported by implementation research to guide its integration into existing TB programmes and the health system as a whole, in addition to pharmacovigilance systems.[233,242,243] While full treatment individualisation may not be feasible in all settings, more stratified approaches that takes into account local drug resistance profiles are potentially feasible.[244]

Given the arduous nature of current TB treatment regimens as well as socioeconomic challenges, many patients withdraw from treatment before completing the full course: globally reported as 15% in the 2014 cohort, and ranging between 1% and 56% in individual studies, with a tendency to increase as more patients are treated in a particular setting.[55,245] These data emphasize the need for more patient- and household-centered approaches that ensure health systems are optimally aligned with the needs of the populations affected by DR -TB. While the emphasis has been on improving adherence and reducing catastrophic costs, a person-centered model of care also includes ensuring that people with possible DR -TB (and those supporting them) are fully informed about, and included in, therapeutic decisions. At their heart, such models must tackle active discrimination within the health system as well as in other sectors. Person-centered care also includes providing treatment closer to where patients live and initially seek care, i.e., community-based and decentralised as much as possible.[246] Full implementation of such a decentralized approach requires considerable upgrading of the capacity of peripheral facilities to manage complex patients. Such facilities should be supported by easy, routine communication with treatment initiation centers and expert providers. While a country or region may often have many DR -TB cases in the aggregate, peripheral facilities may have very few if any MDR -TB patients at any given

time. Thus, experience is lacking, and decentralized needs to occur in tandem with close support from experts, even those experts are accessed remotely.

1.5.3 Preventing resistance acquisition

While diagnosis and prompt treatment are central to tackling the TB epidemic, minimizing the risk of further resistance acquisition, both to existing first- and second-line drugs and new drugs, is also paramount. This includes addressing the drivers of TB drug resistance listed above through programmatic quality improvement (Section 1.1), but also avoiding the use of standardized regimens in the absence of DST wherever possible. Finally, antibiotic stewardship entails ensuring that new drugs are used in tailored, effective multidrug regimens for all patients with DR- TB, not just those with limited therapeutic options. Such use also needs to be supported by expanded TB drug-resistance surveillance (to replace intermittent, expensive DR -TB surveys).

As with drug-susceptible TB, treatment of latent DR- TB may significantly impact the epidemic in the long term. Currently at least two trials are evaluating different prevention regimens for individuals in close contact with MDR/RR TB patients.[232] In addition, WHO released a conditional recommendation in 2018 supporting the use of individualized preventive treatment for contacts of MDR/RR TB patients who are at high risk of progressing to disease.[247] Given the high morbidity and mortality associated with DR-TB, preventive treatment of these high-risk contacts, including children and people living with HIV, is a priority.

1.5.4 Increasing DR- TB as global health security threat – implications for donor financing

The cost of treatment for MDR/RR TB, ranges from estimates of US$1,218 in low-income countries to US$83,365 in high-income countries[248]. The high cost has been a significant barrier to scaling up treatment to date. The Stop TB Partnership estimated that in 2017, US$2 billion was required to fund DR- TB care; it is expected to increase to US$3.6 billion by 2020.[55] Funding at this level is unlikely to be sustainable for many high MDR/RR TB burden countries; the BRICS countries (Brazil, the Russian Federation, India, China, and South Africa) are notable exceptions. As a result, funding to support DR- TB programme implementation will likely be required from international sources, even in countries with the capacity to fund their own DR- TB programmes. The current and future projected economic costs associated with DR-TB, provides a compelling rationale to justify increased donor financing, even in

middle-income countries transitioning out of donor eligibility[249,250]. We discuss the implications of this further in Section 3.

Section 2: Investing in TB Research and development

Despite causing more than one billion deaths during the last two centuries,[251] TB remains poorly understood. Although we can and must do more to broadly implement currently available TB control tools and strategies, achieving an end to the epidemic will require answering fundamental questions about TB and developing new biomedical tools to accelerate our progress toward that goal.[252] The urgency of boosting our investment in TB R&D to enable these transformative advances demands that governments and their partners in high- and middle-income countries commit now to sustained, increased funding of these efforts. The UNHLM underscored the crucial role accelerating TB R&D plays and will continue to play in achieving an end to the TB epidemic. Building on that call to action, here we highlight R&D priorities and provide an economic rationale for why investment in these R&D priorities is critical to success.

2.1 Biomedical research priorities

Future successes in developing new diagnostics, therapeutics, and vaccines for TB fundamentally will require a better understanding of the pathogenesis of TB disease. In this regard, a key basic science priority is identifying the correlates of risk for progression to disease. An intensified search for biomarkers associated with protection from disease,[253] as well as the development of better animal models, are among other priorities. Large gaps also exist in understanding TB pathogenesis and the host immune response, especially in children[254] [Panel 4] and in individuals co-infected with HIV.[255] Nonetheless, promising preclinical efforts exist that must be significantly expanded. These include using computational modelling to better understand complex biological interactions between pathogen and host,[256] high-throughput host genomic screening to identify RNA signatures[257] associated with the risk for disease, and improved animal models of TB latency[258].

To accelerate the development pipelines for diagnostics, therapeutics and chemopreventive strategies and vaccines, it is imperative to develop an integrated research strategy and agenda to close cross-cutting gaps in TB R&D (Figure 6, Appendix Figure xx). Outlined below are key research priorities, including those outlined recently in the US National Institute of Allergy and Infectious Diseases (NIAID), Strategic Plan for TB. This Plan and similar multi-pronged, multi-disciplinary efforts are essential to significantly advance TB R&D and end TB.[259,260]

2.1.1 Diagnostics

With nearly four million people estimated to have undiagnosed or unreported TB, including an estimated 558,000 people with undiagnosed, drug-resistant TB,[5] the importance of having rapid and accurate diagnostics at entry into TB care cannot be overstated. Early, accurate diagnosis together with drug susceptibility testing at the time of diagnosis is key to breaking the cycle of transmission, enabling patients to be quickly started on an effective TB regimen. Investments in R&D for TB diagnostics have led to the progressive introduction of six new diagnostic tools since 2005. These have helped overcome major barriers in identifying drug-sensitive and drug-resistant forms of *M. tuberculosis*, including cost, complexity, slow time-to-result, and low accuracy.[261] An additional 45 candidates are in the TB diagnostic pipeline.[262] Unfortunately, many of these are molecular technologies that are unlikely to meet the three most important needs of high-burden low- and middle-income countries (LMICs) as described below.

For high-burden, low-resource settings, the first priority is an easy-to-use, low-cost, non-sputum-based[263] rapid diagnostic test that can identify individuals with active TB and can be incorporated into active case-finding strategies or used in primary care facilities (Appendix Panel xx). Modelling has shown that a triage test, implemented at the community level and used in combination with a confirmatory test (e.g., GeneXpert), could close case detection gaps and reduce incidence by 19% and mortality by 37% over ten years.[264] The second priority, highlighted in Section 1.5, is rapid tests for drug-resistance that would help direct patients to appropriate treatments and safeguard medicines against antimicrobial resistance.[265,266] Priority three is an incipient TB *in vitro* diagnostic to identify individuals at high risk of progression from latent TB infection to active disease. This *in vitro* diagnostic would enable targeted preventative treatment in communities as a prerequisite to TB elimination in the absence of an effective vaccine.

Achieving priority one requires identifying a suitable host and microbial biomarkers and biosignatures (primarily antigen, antibody, or a volatile organic compound). Several promising diagnostic biomarker combinations have been identified that are undergoing validation or being transferred to point-of-care platforms.[267,268] If successful, a triage test could be introduced by 2020; however, given high candidate failure rates and few priority one candidates in the biomarker pipeline, additional funding is needed to enrich the pipeline. Expansion of the drug susceptibility testing menu is underway for existing molecular platforms, and next-generation sequencing tools show promise; however, further translational work is required to make them affordable and deployable in high TB burden countries.[269,270] Similar to the triage test, a breakthrough in biomarker discovery is necessary to diversify the incipient test pipeline, which is currently is sparsely populated.[271]

2.1.2 Therapeutics

Development of markedly improved therapeutics could rapidly accelerate efforts towards ending TB. The principal desired characteristics are shorter, non-toxic, patient-friendly treatment regimens that can be implemented widely.[272] Preferably, the individual components of improved therapies should focus on either novel targets or targets that do not have cross resistance with available drugs. Since approximately one million new TB cases occur in the pediatric population each year, it is also critical that new TB therapeutics be formulated to be appropriate for and effective in children as well as in adults.[273]

Developing novel, safer, shorter, and simpler regimens will have to overcome many challenges. The existing drug regimens to treat drug susceptible TB are remarkably effective, largely non-toxic and extraordinarily inexpensive. New drugs are unlikely to be tested individually but added to existing regimens and tested for non-inferiority and safety rather than superiority. As a consequence many of the newer drugs are being tested on drug-resistant TB, where the effectiveness of current regiments are limited and smaller trials in a defined targed population are feasible. In addition to the research costs of preclinical development and Phase I and II clinical trials, the lack of reliable, validated biomarkers that can be used to predict the duration of therapy necessary to cure virtually all patients treated with a given therapy.[274] The findings of three recent Phase III trials[275-277], which failed to shorten TB therapy for drug-sensitive TB despite promising Phase II data, clearly demonstrate how the lack of predictive biomarkers constrains clinical research. The lack of predictive biomarkers is particularly problematic because, due to their complexity and long duration, the cost of late-stage clinical trials of novel TB regimens is so high.

During the past decade, remarkable progress has been made in the search for new TB drugs and therapeutic regimens. In the early 2000's, there were no new drug candidates to treat latent TB; the pipeline has more than 30 compounds (although few are new chemical entities), including several drugs in late-stage product development (Appendix Table xx). Two novel drugs have received conditional regulatory approval.[5] Because of the pipeline growth, it is now feasible to investigate novel combinations of drugs and new therapeutic regimens. New regimens currently in Phase 2 and 3 clinical trials show considerable promise and may enable much shorter durations of treatment —even for the most resistant forms of extensively drug-resistant TB—than what is currently recommended.[278] Furthermore, a two-month universal regimen, active against all forms of TB, may be possible within the next decade. This would offer the potential to shorten and simplify treatment strategies and drug-susceptibility testing needs,[279] and should be a high funding priority in the next decade The potential utility of a pan-TB regimen must be considered together with person-centered approaches to treatment, tailored to pharmacogenetics, co-morbidities, and drug co-administration, as well as the risk of new forms of resistance.[280] A diversified portfolio of therapeutic products offers the best hope for long-term success; however, substantial investment in the short-to-medium term is needed to guarantee those products make it to market.

2.1.3 Vaccines and Chemopreventive Strategies

Prior to the antibiotic era, evidence existed to indicate that remarkable protection against TB could be produced by latent TB infection, and that BCG was protective in some populations but not others.[281] Yet today, as highlighted in section 0, BCG remains the only available vaccine—one that is more than 100 years old, has variable effectiveness in preventing adult pulmonary TB, and is not recommended for children who are infected with HIV. Despite compelling evidence from models demonstrating that a vaccine with 60% efficacy could avert 70 million TB cases within 25 years if given to only 20% of at-risk adults, [282] progress towards developing viable vaccines has been hindered by numerous scientific and funding challenges. In constrast to drugs, vaccines are given to healthy people to prevent illness. Thus, the stringency in being certain that candidate TB vaccines are as safe as possible represents a high bar. Also, because many individuals who will never be infected have to be vaccinated to demonstrate protection in a smaller group infected with *Mtb,* trials require large populations and access to sophisticated laboratories.

Currently, 14 candidate vaccines in the pipeline that have shown some degree of protection against TB in animal models are now in human clinical trials.[274] Some are live recombinant vaccines (for example, BCG with added antigens and genes to elicit strong immune responses, or genetically attenuated *M. tuberculosis*); others are live virus vectors expressing multiple antigens of TB to provide long-lasting immunity (e.g., recombinant cytomegalovirus [CMV] vectors expressing TB antigens). [282] To date, only two Phase III preventive TB vaccine studies have been published, one using an inactivated whole-cell mycobacterial vaccine (*M. obteneuse*) reporting <40% protection in adults with [283] and the other evaluating the modified vaccinia Ankara virus expressing antigen 85A (MVA85A) to boost the effectiveness of the BCG vaccine in infants, which failed to show protection.[284,285]

However, two new Phase IIb trials offer new promise for vaccines against TB.[286] Revaccination with BCG of South African adolescents, who received BCG as infants but were not exposed to Mtb (Quantiferon-negative), provided 45% protection against TB.[287] In high burden countries, a high percentage of individuals have been previously exposed to or latently infected with *M. tuberculosis,* and no vaccine has previously been reported to provide protection to tuberculin-positive individuals. A new subunit TB vaccine, with two Mtb antigens in an adjuvant that has been effective in vaccines against zoster and malaria, M72AS01$_{E,}$ tested in several thousand adolescents in 3 sub-Saharan countries, showed 54% protection overall, and notably 87% protection in those under 25 years.[288] These results emphasize the

importance of clinical trials and suggest that targeting vaccines to adolescents may provide optimal protection. It is only from searching for correlates of protection in human trials that necessary and sufficient mechanisms of protection can be discerned, which could shorten the time and expense of future trials.

Clearly these encouraging results need to be validated and extended, particularly in different geographical situations. But they make clear that, despite challenges, the scientific prospects for developing a safe and effective vaccine to prevent TB are more promising than ever before; an increased focus on early-stage research has led to a robust pipeline, and new technologies, which are providing unprecedented scientific opportunities.[289] Vaccines represent the most cost-effective intervention to prevent disease and death. In the case of TB, long-term and sustained investments will be necessary to build on these promising results, but the returns even from a partially effective vaccine would be vey great[318].

2.1.4 Population, policy, and implementation research priorities

Progress towards ending TB has been limited because existing tools have been ineffectively implemented and the currently used control strategies used are outdated. Greater national and global investments in population, policy, and implementation research capacity will be required to enable the scaling of effective approaches.[97] In particular, implementation research is needed to understand how to improve care cascades, i.e., find patients earlier, evaluate them quickly, and provide effective treatment resulting in a cure. Population research to characterize the factors that drive TB transmission within families and communities , particularly in high TB burden settings, is also critical for developing strategies to interrupt Mtb transmission[26] While research on sensitive, inexpensive point-of-care diagnostic tests continue, active screening strategies could be implemented with existing technologies, including automated X-radiography in contacts and high risk groups in high burden countries, followed by culture or Xpert testing diagnosis, in view of the strong evidence from surveys showing that 20-30% of TB cases globally are asymptomatic.[5,148, 174.]

To optimize treatment outcomes, differentiated strategies for providing patient-centred care and supporting treatment adherence must be developed in concert with the creation of new therapeutic regimens.[290-292] Likewise, research is necessary to determine the most efficient and cost-effective TB

prevention therapies. The potential of digital technology to overcome weak health system infrastructures, enhance TB program quality, and improve disease surveillance, remains largely untapped. While numerous disparate pilot studies have been conducted evaluating IT, e-Health, and connectivity solutions, [290,293-296] future studies should be guided by a comprehensive research agenda underpinned by a commitment from countries and funders to translate evidence to action at scale.

Cross-cutting all of this, mechanisms must be identified and implemented to strengthen the infrastructure and capacity of countries to absorb--in terms of both speed and scale-- innovations, as well as to rapidly translate research findings into policy.[297] For instance, the Initiative for Providing Affordable & Quality TB Tests (IPAQT)[298] provides a proven model for incentivizing the uptake of new diagnostics among private sector providers in India; however, it has yet to be translated into a replicable model and implemented in other countries. In part, this reflects the need for improved implementation research capacity in LMICs to realize the benefits of investment in TB R&D.[4] The role of trans-national research networks to build such infrastructure and capacity is essential.

2.2 The cost of inaction in R&D

The human costs of failure to develop and implement new and improved interventions is unacceptably high. Even in the WHO best case scenario where treatment coverage was extended to 90% of persons with TB and 90% were successfully cured (substantially higher than what global estimates indicate, e.g. notification is 65% for Ethiopia, 72% for india; few high burden countries have data on cure rates),[5] we estimate that there would be nearly one million unaverted deaths with current technologies (Figure 8). To achieve these goals would require unprecedented case finding, treatment completion and prevention, underscoring the important need to close gaps with scientific discovery and programmatic innovation.

The potential economic value of new tools is illustrated by modeling analysis in three different country-settings –India, Kenya and Moldova, illustrated in Figure 9, leveraging an approach where the value of lives lost prematurely was derived using value of statistical life estimates (See Appendix for methodology).[94,299,300] Optimal implementation of existing evidence-based strategies to improve the care continuum for active TB in each of those countries will still leave millions of deaths unaverted over the next 30 years. The value of the loss associated with TB mortality is, on average, $32bn per year in India; $2.7bn in Kenya; and $35mn in Moldova. However, these estimates are likely to be

underestimates since: (i) they arise from an arguably ambitious scenario, of reducing losses in the care cascade to 10% and delays by 25%, and (ii) they do not account for opportunity costs associated with underaverted disease that does not lead to deaths, nor the financial burden placed on the health system associated with this underaverted disease burden.

It is fair to ask why there is such a gap in investments in TB R&D. There are many reasons: The most obvious is that the burden of disease falls on low and middle income countries which are least able to afford new expensive tests and drugs. As a relatively low prevalence disease and a high latently infected population, efficacy testing of new tools will require large and lengthy trials. Finally, new tools are only as effective in controlling the disease as are health systems able to implement them, and hence improvements in health systems are critical. Nonetheless our analysis clearly demonstrates that further tools, particularly tools for primary prevention will have a profound return on investment, insofar as they prevent these needless TB deaths. Furthermore, it validates the argument that greater spending in TB research is likely to bring important economic benefits and have a disproportionately beneficial impact on health outcomes in LMICs.[93.] It also underscores how proposed investments in R&D- estimated to be US$8.7 billion over the next 4 years[134] represents an excellent ROI. If new tools were developed that would enable reaching WHO's targets, it is estimated that the ROI of each dollar, depending on the value per DALY and the assumed discount rate, would be $16-82[318].

2.3 Reaching global TB R&D goals

Despite powerful public health and economic rationales for investing in TB R&D—essential for producing breakthrough technologies and strategies to end TB, as outlined above—a significant gap in financing remains. There are many reasons for this, including the lack of financial incentives to produce new tools, the cost and duration of clinical trials, and the lack of compelling demand by affected countries. It is a slow and quiet killer compared to malaria and HIV, and few new interventions have been demonstrated to be successful. Global funding for TB product development was US$726 million in 2016,[262] a mere one-third of the annual funding called for by the Stop TB partnership, and far less than is desireable to achieve the kinds of R&D breakthroughs that have characterized HIV research over the last two decades.[134] Modelling analyses have suggested that current funding levels may be sufficient to realize some key, near-term successes, e.g., a triage test and regimens for DR- TB based on repurposed drugs, but that a multiple of current levels funding – but perhaps a substantial multiple - is needed to enable the development of truly transformative treatments and prevention tools (e.g., an incipient TB test, new

vaccines).[301,302] Closing the funding gap of at least US$1.3 billion per year will require high-income countries to sharply increase their investments in TB R&D, in tandem with increased efforts from LMICs, particularly BRICS, as well as the development of creative funding models that enhance industry commitments.

Currently, 89% of investment in TB R&D comes from non-commercial sources — that is, governments and philanthropies. US public agencies alone support 44% of all TB-related research globally.[262] Only a small fraction of the public funding for TB R&D comes from LMICs.[303] Increasing contributions from LMIC governments so that their total share of TB R&D matches their share of the global economy (i.e., 36.5%), as has been proposed by a WHO expert group, would generate an additional US$146 million per year, a 26% increase in total global R&D financing. Given that late-stage clinical trials represent a critical funding bottleneck, a self-funded BRICS/LMIC clinical trials network, which is focused on bringing innovative tools through the regulatory pipelines, would be another way for high-burden countries to carry a greater share of the TB R&D costs. It would be possible to increase public contributions further if some HICs (or philanthropies) were willing to *match* increased contributions from LMICs, as Switzerland offered to do in order to stimulate LMICs to contribute financing for several WHO-selected R&D projects in 2014.[304] This type of "matching grant" could increase total R&D to US$861 million per year, a 52% increase over the status quo (Appendix Table xx). Matching funding from international donors and high-burden countries could also ensure TB R&D is more 'needs driven' and address the problem of 'free-riding', whereby countries withhold resources as long as others cover the costs.[305]

Meanwhile, industry investment in TB R&D has stagnated, while R&D for other infectious diseases have seen meaningful funding increases.[262] UNITAID, through small taxes on international air travel is is an increasingly important source of funding for TB R&D, providing US$215 million in 2018 for a variety of innovative research projects. However, more creative models to secure private investment, collaboration and partnership are needed to close the funding gap. Examples include the TB Drug Accelerator, a collaboration between pharmaceutical companies and research institutions, which has had several early successes in addressing the shortage of new TB drugs by funding early-stage TB drug discovery,[306]and the Global Health Innovative Technology Fund (GHIT) model, a Japanese government funding mechanism that leverages matched funding from industry.[307 308] Other funding mechanisms including 'downstream investments or 'pull' strategies (that promise reward for successful product development) have been successful in the pneumococcal vaccine development, and have potential

role in funding TB R&D.[309] The Life Prize (Appendix Panel xx) offers a novel model to stimulate drug development, rewarding researchers and developers fully and upfront for their investments, thereby de-linking the financing of R&D from product prices and sales and promoting access and affordability as well as appropriate use of resulting products.

While these various options could represent an important increase, funding will still be far short of the US$2 billion annual target. This shortage highlights the inescapable conclusion that HICs must contribute more. To ensure the necessary increased investment from HICs, TB R&D must be understood as an important global public good that will yield substantial economic dividends, as we highlight in Section 3. Greater investment is also essential to address negative cross-border externalities that TB, particularly DR -TB, poses and as central focus of the broader antimicrobial resistance research agenda. Hence, strong advocacy for increased R&D funding to science ministries and research-oriented pharmaceutical companies must occur in tandem with advocacy to international donor agencies.

Section 3: Sustainable financing for TB

Everyone dedicated to achieving an end to TB – impacted countries, donor nations, the private sector, foundations – must redouble their efforts to finance strategies that are working now and, more importantly, strategies that have the real potential to make a significant impact in the coming years. To end TB, this Commission advocates for substantially more investment in all aspects of TB programming. Increased domestic resource mobilization will be especially important, but new models of donor financing that can catalyze domestic investment must also be a priority. Evidence on the cost-effectiveness and benefits of expanded financing for tuberculosis control suggests that such investments will yield a high return.[310]

3.1 Economic evaluation of TB control interventions

3.1.1 The basics of TB economics

In this section we will distill a highly heterogeneous literature[311] into indicative values of key economic parameters. The section will focus on two such parameters: the cost required to avert a TB death and estimates of benefit to cost ratios for TB control efforts. An additional important question is that of the cost required to meet goals and we provide an approximation that is broadly consistent with this Report's goal of reducing the global TB death rate by 90% compared to 2015 levels, estimated to be 2 per 100,000. Such estimates of cost are intimately bound with questions of revenue generation or finance and are dealt with in the finance section of this report. Benefit to cost and cost effectiveness ratios in this section will be generated under the same sets of assumptions as are the total cost estimates of the domestic finance section (section 3.2).

3.1.2 Costs per death averted

The literature[312] contains multiple estimates of different indicators of program effectiveness for different interventions in different environments and with different assumptions about how much in the way of health system strengthening costs should be included in the cost estimates. The literature is far less well developed in assessing to whom costs and benefits accrue, distributional questions. The diversity of the literature poses problems for the high-level message objective of a report like this, but at the same time it provides multiple valuable starting points for analysts with different objectives and interests. Such estimates meet the objective of positioning our thinking even though the numbers themselves make no claim to portray any particular set of conditions.

3.1.3 The ratio of benefits to costs for TB control

Benefits are estimated using methods that are standard in many governments' (and the OECD's) guidelines for economic evaluation of projects.[311] Within the OECD structure, this Report uses the conservative (low) value of 0.7% of per capita income as the value of reducing mortality risk for an individual by 1/10,000 for one year. Although these results have been generated for this report using conservative assumptions, the estimates here suggest that recent economic analyses undertaken by the consulting firm KPMG,[313] estimating cost of failing to respond to the TB epidemic, did not fully capture the value gained from successful TB interventions. Rather than convey a highly heterogenous range of estimates, we chose instead to rely on recent efforts to aggregate the literature.[5,94,252] These efforts provide estimates of cost per death averted that are typically stated implicitly rather than explicitly (Table 6). Acknowledging major heterogeneity and uncertainty, it is reasonable to think that the cost per death averted from drug sensitive TB would be in the range of US$5,000-10,000 and for DR-TB, US$15000-20,000.

Using US$7000 as an approximation of the cost per TB death averted and the 0.7% of GDP approach to valuation, we arrive at a benefit-to-cost ratio for TB interventions of 7:1. This figure reflects the Stop TB estimate[314] in Table 6 for multi-intervention programs required to sharply reduce TB mortality and hence can be viewed as an average across the range of required interventions. Other estimates have been higher.[312,315] And as noted, KPMG found much lower (although still attractive) values using a very different methodology. Uncertainty concerning a specific value abounds. But no serious uncertainty attaches to the conclusion that the value of benefits exceeds the value of costs by more than a factor of 2 or 3.

3.1.4 Costs of ending TB in a generation

As TB incidence declines over time, both because of expanded control efforts and (probably) favourable trends in poverty and other risk factor reduction, it is reasonable to project declines in needed expenditure to keep TB deaths at very low levels. Initially, if TB deaths were to be reduced by 90% from the current level of 1.7 million per year to under 200,000 per year the additional expenditure required would be on the order of:

1.5 million deaths per year averted x US$7,000 per death averted ≈ US$ 10 billion per year

Obviously, it would be impossible to scale up within a few years and early investments will yield reduction in cases and costs. However, a plausible cost trajectory for ending TB in our generation would be a rise from current expenditure by, perhaps US$5 billion per year, followed by a reduction to a long-term level of US$1 to 2 billion per year by the early 2040s. This number reflects a reduction in incidence and hence treatment costs that ending TB mortality will require. This Commission makes no attempt at precision concerning this number in the belief that our basic understanding of the relevant determinants of cost remain highly imperfect: expressing precise numbers is more likely to mislead than inform. That said, these numbers provide a reasonable approximation of the magnitude involved.

3.2 Domestic Financing for TB

Section 3.0 makes the case for the economic benefits of investing in TB. In this section, we examine the extent to which TB programmes currently rely on domestic sources of finance in high- burden countries; and the influence of domestic financing on the sustainability, efficiency, and equity of TB funding. In addition, we explore the potential for rapidly increasing domestic financing for TB in the coming five years. Finally, we highlight the importance of investing in NTPs, and other domestic funding agencies of TB services, to allocate, distribute, and manage domestic TB resources; recognizing that it is essential to develop the capacity to ensure increased financing is spent effectively to end the epidemic.

3.2.1 The pivotal role of sustained domestic financing for TB

Improved domestic financing for TB is one of the success stories in global health over the past two decades. By 2017, 84% of funding for TB came from domestic sources. This high proportion reflects a consistent pattern of increased commitment to TB from high-burden countries. From 2007 to 2017, global funding for TB doubled, with much of the increase coming from Brazil, Russia, India, China, and

South Africa (BRICS). On average, the BRICS have domestically financed 95% of their public TB expenditures over the past decade [316].

Outside of the BRICS, the picture of domestic funding for TB is complex, reflecting a general scarcity in health sector resourcing and capacity. In 2017, less than half of public funding for TB in low-income countries came from domestic sources. Nonetheless, the trend over time is promising; on average, low-income countries doubled their domestic financing of TB between 2007 and 2017, with a rate of increase similar to that of international TB funding to their countries[317]. Not all low-income countries are following this trend, and there is room for improvement: the current proportion of the domestic contribution to public TB expenditure ranges from under 1% to 24%[317]. Likewise, in lower-middle income countries, the proportion of domestic public funding ranges from 7% to 88%[317], with the average growth in domestic TB financing stable until 2013, but doubling since then.

3.2.2 Who provides domestic finance, and how does it flow to TB?

TB expenditures can be divided into those that flow through general health service provision and those that flow through National Tuberculosis Programmes (NTPs). While the proportional domestic contribution to overall TB expenditure is generally are high, NTP specific expenditure and TB-specific commodities are more reliant on international finance. In 23 of the 30 high-burden countries, NTPs receive more than 80% of their funding externally[317], with the Global Fund being a substantial payer for TB commodities. This apparent dependency of NTPs on international finance has most likely arisen due to disease specific allocation of international funds, rather than reflecting an overall lack of domestic commitment. Ministries of Finance inevitably reduce domestic resource allocation to TB to the extent that they perceive international finance to be available.

Domestic financing for TB within countries can come from a range of sources. Ultimately it is populations and corporate taxes who pay, but TB patients still face much of the burden in some countries. Despite the policy of free or reimbursed TB care in most countries, patients with TB can still incur substantial out-of-pocket payments for public TB services [248]. Moreover, in several high-burden countries, large proportions of patients seek and receive TB care in the private sector, paying for their own care and treatment. Subsidizing and pooling these private domestic expenditures, an important goal of broader UHC agenda, will have beneficial consequences in terms of financial risk protection[318,319] and possibly health outcomes[320] for those with TB.

3.2.3 Is the allocation of domestic finance to TB efficient?

Although many countries have increased their allocation of public monies to TB, a mismatch remains between funding levels and need, the latter defined in terms of the resources required to reach global End TB targets [317]. From a domestic public finance perspective however, need is not a sufficient criterion to increase investment. Ministries of Finance will have requests to fund many other development and health interventions that have potentially high returns. Hence, those advocating for increased investment in TB, both within and external to governments, need to demonstrate that investment in TB performs well, at the very least compared to other health sector investments. Investments in TB hence need to be efficient, defined as maximimising population health for any given level of funding.

Increasingly countries are developing public finance processes that formally assess the return on investment of different health sector interventions, rather than relying on global evidence. These processes are being supported by improved data and understanding of the costs, effectiveness, and long-term impacts of investment in TB on both health and economic outcomes.[321] In the main, supporting these efforts often work in favor of TB. In Malawi for example, a recent assessment to determine the essential package of health care found that seven of the top 10 'best buys' for health sector budget prioritization were TB interventions.[322] This mirrors systematic reviews of return to investment of TB expenditures across several countries.[146] supporting the assertion that increasing domestic allocation to TB can improve the efficiency of the entire health sector.

There is, however, room to improve the efficiency of TB expenditures, through improvements in the delivery and implementation of TB services, as highlighted in Section 1. In some countries the split of TB expenditures on TB commodities versus general service provision may not be optimal. Improvements in health system strengthening are critical to ensuring that health staff at the front end of TB service delivery receive the right mix of resources to provide high-quality patient-centered TB services [323]. Some countries also have higher than average TB treatment costs, due to the over hospitalization of TB patients, in particular those with DR-TB. Nonetheless, the decentralization of DR -TB care in South Africa illustrates the substantial additional funding that may be generated by reducing hospitalization for patients, including those requiring intensive treatment for DR-TB [324] . Improved integration of TB services may also support patient-centered care and reduce costs [325]. Several new TB technologies, such as shortened regimens, may reduce the costs substantially. More analyses on the efficiency of these

different approaches to scaling up TB services is necessary to help guide how countries can spend funding effectively.[326]

3.2.4 Can domestic funding for TB be substantially increased in the next five years?

Generating additional domestic financing for TB depends on: governments' commitment to allocate more funding to TB; the future potential for efficiency gains; and increases in the overall level of available public finance. Increases in domestic financing for TB in the past two decades demonstrate that countries experiencing GDP growth may be able to expand their funding of TB rapidly, and at the same time reduce TB incidence[327]. In addition, the ability to raise domestic finance for TB from private individuals and firms depends on the system of revenue generation and taxation structures. In recent years, a range of innovative mechanisms, including earmarked taxation of alcohol and cigarettes, government loan buy downs, in which a third party contributes to loan payment to open up social spending and the expansion of health insurance coverage, have been explored to improve the financial sustainability of the health sector, with positive consequences for population health [328]. These mechanisms have yet though to provide substantial funding for HIV,[328] and there are considerable questions as to their feasibility to raise high levels of funding for TB.

Conducted in collaboration with the Lancet Commission, a team at the London School of Hygiene & Tropical Medicine (LSHTM) and UCSF conducted an analysis examining the potential fiscal space for TB for 28 of the 30 high-burden countries over the next five years (two countries excluded due to data scarcity). Fiscal space analyses apply international public financing norms to current fiscal performance to determine the extent to which funding can grow in a way that does not damage overall fiscal stability. The financing sources examined included GDP growth, increasing public revenues, improving allocation to the health sector, improving allocations to TB, and increasing the efficiency of public TB service delivery. The researchers found that most high-burden TB countries can substantially increase public domestic financing of TB. By 2023, countries such as Bangladesh, Zambia, China, and Indonesia can potentially increase their annual TB expenditures more than five-fold, through a combination of optimized resource allocation, revenue generation and improved resourcing of the health sector (Figure 10). In countries like Zambia, increased prioritization and efficiency of TB services would enable the greatest resource mobilization for TB. In countries like Bangladesh, China and Indonesia, governments will need to commit to substantial policy action around revenue raising, such as increasing tobacco taxation and the increased pooling of health sector funds. Despite the potential impact of tobacco

taxation highlighted in this analysis, we acknowledge the limitations of raising tax in the short term and advocate for optimized resource allocation and improved resourcing of the health sector as the most sustainable means of increasing financing for TB.

3.2.5 Policy Implications

In summary, mobilizing domestic resources for TB will take policy action and commitment across government, including Ministries of Finance and Ministries of Health. Increasing tobacco taxation and allocating those revenues to health is a clear policy action that can support financing TB elimination and have positive benefits for persons with TB, but is a long term public health objective. Increasing domestic public financing for TB in a manner that protects TB patients from catastrophic expenditures is particularly important, and also serves a broader UHC agenda.

However, it should not be assumed that high level commitment to this broad policy agenda is sufficient. Rapid increases in domestic financing for TB will require enhanced capacity to allocate and spend resources effectively and transparently to demonstrate results. A clearly defined accountability framework to ensure commitments made at the high level meeting will be critical. In addition, NTPs need to strengthen their 'absorption' capacity, otherwise the the rate at which additional financing is disbursed in practice may be slow. The experience of HIV demonstrates it is possible to rapidly strengthen progammes, but that strong systems are required to ensure efficiency and maximise health outcomes. Effective, rapid disbursement will depend on the capacity of NTPS to mobilize expertise, infrastructure, and sufficient human resources in a timely manner. Upfront support to NTPs to build the mechanisms to absorb new funding, and fully participate in resource allocation and management systems and processes within the health sector, will therefore be critical to ensure additional resources are used. The commitment of many HBCs over the past two decades is commendable, and many have the space and willingness to do more, but achieving real increases in expenditures, beyond the current rate will require concerted attention by all those working to end TB to absorb additional resources effectively.

3.3 Donor Financing for TB

3.3.1 Donor investments in TB

The potential for increased domestic health spending, economic growth, as mentioned in Section 3.1, along with the recent rise of populism and protectionism,[329] will inevitably shape external financing for TB programs over the coming decade. Nearly all high-burden countries can substantially increase domestic resources allocated to TB. While many low-income countries still require donor financing for TB, new opportunities exist to re-think how and where donor financing is allocated such that its impact is maximal. In this section of the report, we discuss the role of donor financing to catalyze domestic efforts and invest in global public goods, especially in those countries transitioning out of donor finance eligibility. In addition, we highlight the potential benefits to donor partners of investing in TB, economically and in terms of addressing the negative cross-border externalities that TB, especially DR-TB poses. Finally, we underscore the importance of sustained financing for the poorest countries and advocate for continued investment to end the epidemic in those countries.

3.3.1 Who is investing in TB programs?

According to the OECD's Creditor Reporting System, international donors provided US$871 million for TB prevention, diagnosis, and treatment in 2016 (the latest year for which data are available), 69% of this was expended by the Global Fund, of which the United States (US) was the major contributor.[5] In addition, the US disbursed US$179 million channeled via its own agencies and other institutions. Between 2006 and 2016, approximately 46% of international donor expenditure for TB originated in the US.[5] The next largest contributors were France (10%), the United Kingdom (9%) and Germany (6.2%).[5] According to the Institute for Health Metrics and Evaluation (IHME), The Bill and Melinda Gates Foundation was the largest non-state funder of TB activities, responsible for US$204 million of disbursements in 2016, including $68 million allocated to the Global Fund, while other sources private philanthropy spent $70 million, of which 14% was allocated to the Global Fund.[330]

Development assistance for health (D.A.H) for TB has increased from US$30 million in 1990 to well over US$1 billion in 2016, underscoring the substantial increases in international financing that have occurred over that period, as well as the relative contribution of foundations, development banks, the Global Fund and traditional bilateral funding. Nonetheless, current levels of funding for TB still fall very far short of the annual US$2.6 billion proposed in the Global Plan to End TB, outlined by the Stop TB Partnership.[134]

3.3.2 How is donor finance being used?

Analyses of donor financing for health have traditionally tracked flows by funding source, channel, recipient, and disease. For this Commission, a team at UCSF and Duke University conducted an analysis of development assistance for health (DAH) for TB broken- down into functions (Annex xx and yy).[331] Global functions refers to transnational topics, including supporting global public goods such as R&D, managing cross-border disease spread and fostering leadership and stewardship. The researchers analyzed DAH for TB in the year 2015, using the OECD Creditor Reporting System, which provides detailed information on aid expenditure.[332] They found that in 2015, US$932 million in DAH was directed towards TB-related activities. Half of DAH for TB was disbursed to to lower MICs, 22% to LICs, 4% to upper MICs, 23% to bilateral unspecified activities, and a small portion (0.4%) to regional efforts. Only about one-quarter (24%) of DAH for TB was for global functions, supporting product development (17%), population, policy and implementation research (PPIR) (3%), advocacy and priority setting (2%), and other global public goods (Figure 11). Around three-quarters (76%) of DAH for TB supported country-specific functions, including TB programs for care delivery (52%) and health system strengthening (24%). Almost all (96%) of the health system strengthening support was TB specific, with only 4% directed at system-wide, cross-cutting health system strengthening. These allocations highlight that donor funds are being primarily targeted to support country-specific activities, especially those countries with the highest burden, rather than focused on global public goods. The policy implications of these findings are discussed below.

3.3.3 Policy implications

To our knowledge the analysis outlined above is the first to determine how much TB-specific DAH is devoted to supporting global functions versus country-specific functions. Notably, this analysis does not shed any light on trends in TB funding or how country-specific TB program funding is disaggregated between DR-TB and DS-TB control efforts or provide granularity with DAH differs by disease burden or country income group. Nonetheless, the findings highlight the need to increase investment to support Global TB functions, in addition to country-specific functions. Although our baseline analysis cannot prove that global functions are being neglected, prioritizing funds to these global functions should be considered, especially as domestic resource allocation for TB increases. In particular, this Commission asserts that donor financing should increasingly be focused on the following functions (Appendix Table xx):

Global Functions

Supplying global public goods (GPG) - Greater investment in global public goods, in particular TB R&D for new drugs and technologies, are likely to bring important economic benefits and have a disproportionately beneficial impact on health outcomes in low- and middle-income countries.[93] New tools deriving from TB R&D are also likely to provide financial protection and be most beneficial to the poorest-members of society, as shown by "extended" cost-effective analyses.[319] The investment in HIV R&D over the last two decades, leading to over thirty new drugs and numerous diagnostic and preventive technologies, provides compelling evidence for greater investment in TB R&D.[256]

Market-shaping activities The Global Drug Facility (GDF), an arm of the Stop TB Partnership, serves an important function in this capacity, using donor financing to consolidate demand from different countries to negotiate lower prices for TB drugs, attract additional suppliers, and incentivize innovation, in particular for more expensive second-line agents and pediatric medicines.[333-335] These kinds of activities will remain important as countries increasingly assume co-financing and/or transition out of donor eligibility, as they may have difficulty negotiating lowest possible prices or accessing concessional prices for diagnostics. As countries move away from donor funding, the global market for TB medicines and diagnostics will surely become much more fragmented and the need for a global TB market steward, such as GDF, will become more important. In addition, the importance of GDF to facilitate uptake of new diagnostic and therapeutic tools will also be essential as investment in R&D yield greater successes in the coming years. [336]

Exercising leadership and advocacy - An important, albeit often neglected global function of aid relates to investment in health advocacy and priority setting. This includes but is not limited to donor financing to support civil society organizations (CSOs) as important catalysts for change. While donor partners have increasingly committed to supporting community engagement efforts over the last decade,[337] CSOs continue to lack recognition as legitimate partners at national levels, their impact undermined by lack of resources for community initiatives.[338] Recognizing that funding for HIV advocates and activists has been crucial to global HIV efforts,[339,340] this Commission affirms the importance of increased funding for TB advocates as a global public good, deserving investment commensurate with the part they plays in improving health outcomes.

Consideration should be given to increased investment in WHO's Global TB Program, given its important role in facilitating uptake of new policies, strengthening surveillance systems and providing technical assistance. A better-funded WHO would enable it to fulfill those functions more effectively.[329] Independent regional initiatives such as those established to tackle malaria,[341] that can provide locally-relevant, agile and responsive support to high burden countries may also be worthy of donor investment.

Country specific functions

Targeted investment is needed for countries graduating from DAH. Presently, 54% of country-specific aid in our analysis is directed towards high burden, middle-income countries, many of which will soon be ineligible for donor financing; based on their national GDP per capita, they are becoming 'too rich' to qualify for DAH. Unfortunately, many of these countries are likely to have large pockets of poverty and avertable mortality from TB. Here we propose targeted investments directed to social insurance schemes that protect those at highest risk for TB. Furthermore, we argue that sustained funding in many of these countries, especially those with a significant DR- TB burden, is warranted given the global security implications of failing to ensure TB control in these settings:

DR-TB and management of cross-border externalities – As highlighted in Section 1, the high cost of treatment for DR -TB, especially in middle-income countries[248], has been a significant barrier to scaling up treatment provision to date, and the cost will continue to rise over the coming years.[55] Donor partners, especially the Global Fund, are already investing disproportionately in DR- TB control activities. Nonetheless, given the substantial weight of data demonstrating extensive cross-border spread of DR-TB, [342-352] DR- TB poses perplexing economic and health security issues for donor countries. It is important that sustained funding for DR -TB control efforts, even in countries that will be soon 'graduating' out of ODA eligibility, be sustained to mitigate the cross-border threat that DR- TB poses. Aligning DR- TB control efforts with the broader AMR agenda is also essential to maximize investment; unchecked TB will be the single biggest cause of antimicrobial resistance related deaths by 2050.[353] Funding for multisectoral, regional

Protecting risk pools – Prisoners, people living with TB/HIV coinfection, migrants, refugees and indigenous populations are all highly vulnerable to TB, and experience significant marginalization, decreased access to quality services, and human rights violations. These communities will continue to

benefit from donor support, for example, through support for social health insurance schemes that include TB services,[319] even as domestic resources for health are increasing.

Co-financing and catalytic funding - In addition to *where* DAH is spent, *how* it is spent is also crucial to guaranteeing the impact of donor support. Catalytic investments, such as those supported by the Global Fund, offer examples of how new models of financing, through use of matching funds to incentivize country allocation for priority areas, or multicounty funding mechanisms that address specific priority areas such as developing innovative approaches to accelerate active case finding and scale up new tools or facilitating re-tooling initiatives as new drugs and diagnostics because available.[354]

Notwithstanding the need for better data assessing the impact of these funding mechanisms, co-financing solutions provide an important pathway to ensure greater country ownership while also ensuring sustained funding for TB activities even during the transition process.

Ongoing support is needed to help the poorest countries. By 2035, there are still likely to be around two dozen low-income countries that will require direct country assistance for years to come.[4] Donor financing for these countries needs to increase substantially to make up for funding shortfalls over the last few years. Despite a small increase in funding between 2016 and 2017, it still fell *very far* short of the annual $2.6B in DAH that is needed for TB according to the Global Plan.[5] The moral imperative of sustained donor investment in these countries should be highlighted – millions of individuals will potentially die from TB in these countries without external assistance. In addition, the scale of the impact of those avoidable deaths on the global economy is substantial, as our analysis in section 3.0, highlights. Investing in TB control will reap economic dividends that will likely benefit both donor and recipient nations. Underscoring the importance of investing in TB as an important tracer for progress towards UHC[64] should also inform how and where donor funds are allocated. As global momentum builds towards achieving UHC, investment in TB as a disease of poverty is imperative to that progress.

3.3.4 A new era of shared responsibility

The UN HLM declaration, and the stated commitment to shared responsibility highlighted how priorities and approaches to TB financing are evolving. We are entering a new era of increased country ownership and global cooperation.[329,355] In addition, the architecture of donor financing for TB is changing as high-burden countries mobilize additional resources for TB control. Leveraging concessionary loans from development banks[356] and innovative financing mechanisms (e.g. social impact

bonds, loan guarantees)[134,329] should have an increased role. Such financing solutions have great potential, but they are no panacea.[357] Strategies that can help increase domestic investment are crucial. Even in low-income countries still reliant on donor support, the nature of donor-recipient financing must evolve. Partnership agreements between donors and recipients, as a tool to ensure ownership, accountability, and transparency, should be encouraged. By this mechanism, donors could also help unlock domestic resources, by commiting funds that pair global and national resources for shared priorities.[358] New models of donor financing that focus on results, encourage innovation and strengthen government accountability to citizens rather than donors are also necessary. One promising example of a new financing strategy, is the USAID's Global Accelerator to End TB which was launched in Septemer 2018. The Accelerator will seek to link financial support with performance-based measurements in order to maximize resources, while also leveraging additional resources from countries, private sector partners and other local organizations.[359] In addition to new funding mechanisms, new funding partners, such as multinational business and corporate philanthropists, should be encouraged to close TB funding gaps. The opportunity for legacy impacts at national and global level, an oft-cited motivator of such funders, will increase as TB elimination efforts become tangible.

Section 4: Creating the enabling environment to end TB

In Section 4 we highlight the importance of an enabling environment to each country's success in responding to TB. Figure 12 provides a framework for operationalizing country-owned responses to drive progress towards ending TB and to leverage good practices in the TB response to advance other Sustainable Development Goals. This framework represents an idealized response and illustrates mutually reinforcing functions performed by state and global actors. These functions are person-centered, rights-based, and data-informed. The priority is ensuring high quality care for persons with TB who present followed closely by a focus on active case-finding strategies and TB prevention interventions targeted at high-risk groups. A strong TB response needs to be guided by country-owned, multisector and multi-stakeholder coordination, accountability and good governance at all levels to achieve sustained long-term efforts. Civil society is a vital constituency to ensure that TB programs and stakeholders are held accountable at global, national and subnational levels. In addition, the framework underscores the importance of addressing TB as a core component in achieving UHC. While countries are in varying stages of progress towards UHC, for high TB burden countries, prioritizing investments in TB to realize UHC will be critical. UHC, backed by donor assistance when needed, also offers an opportunity to tackle TB with multisectoral initiatives that are consistent with the principles of the Sustainable Development Goals.

4.1 Ending TB is important on the pathway to achieving UHC

As this report highlights, progress towards ending TB ideally will occur together with achieving UHC. UHC means all people have access to high-quality health services—at a minimum, health promotion and primary care—at no or little cost at the point of service. This Commission asserts that ending the TB epidemic must involve strong national TB programs that can prioritize specific TB care and prevention functions within a progressive universalist pathway to UHC. This pathway is a publicly financed approach covering those core health-care services that directly benefit the poor, who are disproportionally affected by TB.[360] To this end, TB care and prevention functions should be addressed specifically and included within essential service packages.[361,362] Social insurance models that prioritize diseases that disproportionately affect low-income and other vulnerable populations will automatically incorporate TB. To realize the End TB targets, this Commission proposes to reach populations at highest risk for TB early in the roll-out of such schemes. In countries with high TB burdens, maintaining a separate TB budget and program within a broader UHC framework typically will prove efficient. Even as

the TB burden declines, ensuring that TB programs maintain a very visible position within primary care budgets and Ministry of Health activities is advocated

Several other system-wide frameworks are integral to a TB-inclusive UHC agenda. These include ensuring the uninterrupted availability of and access to appropriately regulated TB medications and diagnostic tests, strong information and performance systems and new or merged risk financing pools.[363] Regulation should address how medical products are subsidized as well as the types of medical professionals authorized to prescribe or dispense TB medicines. High-burden countries will also need to establish an optimal mix of skilled health workers to deliver services, and to design appropriate pay incentives for health professionals to support scaling up the TB response as well as a broader UHC agenda.[364] Robust information systems that are sensitive to TB indicators[365] and infection control measures in health facilities are important.[154] In addition, technical solutions applied to TB programs, such as network optimization and quality management, as highlighted in Section 1, are necessary to that UHC agenda, and underscore how success in ending TB is tied to each country's success in ensuring high quality health for all.[366]

4.2 Social protection

The adverse financial consequences of TB on households resulting from lost income during long periods of illness can be profound and long-lasting, as illustrated in Panel 3 To reduce the risk of impoverishment from TB requires policies that protect patients and their households against ruinous financial costs associated with TB.[34] Especially in those settings where private sector care predominates, strategies must be adopted that ensure financial protection and adequate quality of care, in both public and private sectors. This Commission argues that, as part of the UHC agenda, public finance should be extended to private providers for TB care, and that private finance in public facilities (user fees) should be minimized. Beyond public financing of treatment and case-finding, many TB patients also may need economic and social support. These measures, particularly, social support, can enhance treatment adherence and positively affect clinical outcomes.[142]

Social protection interventions—policies and programs designed to protect individuals from social and economic risk[367]—are a promising approach to improving TB outcomes[368,369] and achieving these larger policy goals. Examples include cash transfers and nutrition programs offered as part of national policies. Such interventions can contribute to successful TB outcomes indirectly by addressing social, biological,

and structural determinants or directly by enabling access to care.[66,370,371] Such interventions can significantly affect tuberculosis trends by enhancing access to TB care and by mitigating the effect of TB-related catastrophic costs.[372]

4.3 Sustaining top-level political support and leadership

Strong national and local political leadership creates an environment conducive to sustained attention and funding. To end TB, governments of high-burden countries will need to propose bold plans to end TB rather than be content with modest incremental gains. Encouragingly, there is growing political recognition that countries need to act now to address the TB epidemic. Since its establishment in 2014, the Global TB Caucus,[373] which supports 2,300 parliamentarians in 130 countries, has become a driving force to mobilize political capital to address TB. TB legislation in the Philippines[374] and Peru[375] that mobilized national finances to drive improvements in TB care and prevention, highlights successes that can be achieved because political leaders in these countries championed the cause. In South Africa, key political leaders from Ministries of Health and Finance have been instrumental in formulating a TB investment case, to marshal additional resources to find new cases and treat more drug-resistant TB (Figure 5). Progress as dramatic as that envisioned in the End TB strategy can be achieved only when each country's leadership outlines a long-term strategy to combat TB within its borders, similar to longstanding strategies established to fight HIV/AIDS.

Effective leadership at the National Tuberculosis Programme (NTP) level is also a critical element of a successful TB response and evidence of high-level commitment to addressing TB. The size and capacity of the NTP's central coordination team and the level of decentralization and integration of specific services depend on many factors, including the country's size, governance, administrative structure, and TB epidemiology. However, chronic underinvestment in TB control efforts can undermine all aspects of TB programming, including the caliber of NTP key personnel, human resource planning, capacity strengthening, and supervision and monitoring of service quality. Empowering NTP managers to take the necessary steps to institute effective strategies will require increased financing and recognition that NTP leaders must play an inter-sectoral, convening role with stakeholders of other government ministries, including finance, justice, labor, social welfare, housing, mining, and agriculture. Furthermore, a high priority must be placed on ensuring that these leaders have access to senior government leadership (Heads of Government and Ministers of Finance) who can authorize mobilization of funds to realize the goals identified. To ensure the high-caliber NTP leadership needed to fulfill these expanded roles

demands that these managers receive adequate pay, reasonable autonomy, and opportunities to maintain up-to-date technical knowledge.

4.4 Maintaining multisectoral engagement

In the SDG era, addressing TB must occur as part of a broader multisectoral framework that addresses key social determinants– especially poverty and overcrowding,[376] malnutrition[8], smoking,[377] and air pollution[378] –clearly linked with TB and TB mortality. Success will require collaboration among multiple ministries, agencies, and civil society. The health sector, particularly the NTP, can play a key role in identifying and communicating the potential health impact of policies on food security, improved housing, poverty reduction, employment safeguards, and human rights protections for migrant, prisoners, and other marginalized groups.[364] Numerous policy tools, including taxes and subsidies, laws and regulations, information and communication and improvements in urban planning, should be employed to address these issues. As highlighted below, accountability to address these determinants, at both a national and subnational level may be valuable, especially in addressing issues such as tobacco control and under-nutrition.

While not disavowing the critical importance of a multisectoral agenda to address determinants of TB disease, this Commission recommends that improving access to diagnostic, treatment, and preventive services, especially for high-risk populations, should be the primary means of ending TB as a disease of global public health significance, in most high burden countries. Over the next generation, substantial progress can be made by ensuring that individuals with TB can access curative treatment, and those at highest risk for TB disease can access preventive therapy, especially since so many currently lack that access. Continued improvements in TB control tools and the systems for delivering TB programs coupled with greater financial resource mobilization for health offer the most concrete likelihood of ending the epidemic.[94]

4.5 Strengthen civil society involvement in all aspects of the TB response

A critical lesson learned from HIV/AIDS response is that engaging stakeholders from the civil, public, and private sectors requires national leadership to bring disparate actors together, overcome communication barriers, enable policies, and scale up access to effective medical tools. Civil society dramatically changed the global response to HIV/AIDS, making it a top priority at all levels and driving unprecedented growth of donor support for lifesaving interventions.[379] [339]

Until recently, few TB survivors or other people affected by the disease have served as public advocates, in part because of TB's curable nature, the top-down orientation of TB control efforts, and the persistent stigma of TB worldwide, the lack of funding to support community involvement in TB programming.[380,381] Fortunately, this is changing. A growing cadre of healthcare workers and students who are TB survivors are using their dual perspectives and professional networks as platforms to call for rights-based services and accelerated access to diagnostics, new treatment regimens, and vaccines.[380] National and transnational TB activism is emerging as a vital force advocating for services in hard-to-reach populations, mobilizing communities and strengthening community systems. TB survivors can play an essential role in creating incentives for political leaders to make difficult and risky decisions, by generating public support for those decisions, and in holding leaders and service providers accountable for how resources, commitments, and services are delivered.

In the post UNHLM-era, the continued input of TB-affected civil actors is essential to ensure the accountability of politicians and program planners. Recognizing their contribution as a global public good, governments and international organizations must create conditions for civil society actors to play an expanded role in the fight against TB, supporting their contribution through direct investments and assembly to raise inconvenient truths. This should include involving such advocates in national TB strategic planning processes, national TB research-agenda setting activities, and national and regional accountability mechanisms.

4.6 Strategies to reduce TB-stigma and ensure a human rights-based approach to TB

An important lesson from the HIV epidemic (and for global health generally) is that only by committing to universal human rights for everyone can the highest available standard of physical and mental health care be fulfilled.[339] To uphold and defend the human rights of people with TB or those at most risk of TB can bring down rates of infection and death. Practical solutions are needed to expedite changes in the laws, policies and public attitudes that violate human rights of vulnerable populations who might be at particular risk of developing TB disease, including people living with HIV, prisoners, refugees and migrants, miners, and health care workers. Furthermore, human rights must be an intergral part of the design, implementation and evaluation of an integrated and multisectoral response to TB.[138] A human rights approach to TB research is required to ensure that legislative and policy frameworks exist to enable the widespread application of encouraging new scientific discoveries, provide accountability for

R&D investments[382] and remove barriers that preclude new TB research technologies being broadly available for public benefit.[383]

In addition to addressing legal frameworks that undermine TB control efforts, action must be taken to address TB stigma, which is pervasive throughout health care systems. Burdensome legal and social practices that systematically infantilize, impoverish, and expose people with or at risk for TB must be removed to end TB stigma.[384,385] Public awareness campaigns that dispel fears and promote positive messages about TB, drawing on patient testimonials, can aslso help reduce stigmatizing attitudes.[386-388] [388,389] Furthermore, campaigns that highlight the unfairness of obstacles faced by people who are sick can evoke public support for greater investment in the welfare of stigmatized groups.[390] Social protection interventions, such as as conditional cash transfer programs also can build resiliency to stigma,[76,391-393] especially among patients whose self-identity and social capital are linked to their ability to sustain their families and themselves.[394] It may also be useful to learn from and model successful campaigns from HIV/AIDS, where community engagement, advocacy, and political buy-in have aligned to ensure that policymaking and program planning mitigate stigma.

4.7 WHO – a new role for a new era

With greater emphasis on sustainable domestic resources and the centrality of national health systems, the SDG era also offers an opportunity to better define the role of WHO in ending the TB epidemic. This Commission has identified several priorities for which WHO can be a leading catalyst for change. First, technical assistance to countries and strategic leadership may not be unique to WHO, it must ensure that critical technical assistance is available to member states.[329] Second, the WHO global TB program must catalyze a rethinking of TB surveillance systems and the use of data platforms. In particular, WHO has a crucial role to play in modernizing and expanding health information systems relevant to TB. Incorporating routine reporting of social protection indices and non-health SDGs into global TB reports is one key responsibility WHO has already embraced.[365] However, by advocating for the better use of, subnational, real-time data and dashboard technologies, including performance data, the WHO can encourage countries to use these systems to improve the quality and efficiency of their TB programs, enable greater accountability, and facilitate more responsive and targeted technical assistance.

WHO's Director-General has repeatedly asserted the importance of UHC to his tenure,[395] committing to 'making universal health coverage happen in our lifetime.'[396] Accordingly, WHO must continue to

support robust TB programs as a central component of UHC. To end TB, both a focused commitment to TB activities and a progressive, inclusive vision of health care are essential. WHO must wok to support countries to hold these two complementary priorities in tension is critical.

4.8 Establishing local, national, and global accountability

Turning written commitments into substantive actions requires an accountability framework that tracks all elements of the TB response occurring at local, national and global levels. This framework must measure progress towards ending TB worldwide and include timely reviews of results through government and civil society accountability mechanisms, both national and global. It also must incorporate a means for taking appropriate corrective actions.[86]

At a national level, this Commission proposes a framework to ensure that accountability extends beyond national TB programs and reports directly to Heads of State. TB accountability should, as an exception, be reported to Heads of State because of the health security risk that TB poses, and its adverse impact on national economies and health systems. Consistent with national strategic plans, such a framework should include specific targets for reducing mortality and detecting more cases, screening populations at high risk and scaling up access to preventive therapy, and addressing inequities in TB risk across populations. As highlighted earlier in this report, country-specific targets deriving from the global targets agreed upon at the UNHLM have been developed and provide benchmarks that all countries should achieve between 2018 and 2022.[397] In addition the framework also needs to ensure that financial resources are matched to achieving these targets. Furthermore, it should engage ministers across government to ensure multisectoral accountability on issues such as tobacco taxation and the regulation of air pollution, as well as progress towards addressing relevant SDGs. National TB Commissions or cabinets that can monitor progress across sectors and/or ensure implementation of TB specific national strategic plans may be appropriate in high-burden countries. Enabling subnational accountability, using regional data to highlight gaps in services and opportunities for allocative efficiency, is also likely to be effective. Linking accountability mechanisms to financial resources that are allocated separately from health budgets can enable responsive, targeted responses. Such approaches have proven effective in addressing the HIV/AIDS epidemic in several countries; [339] given the health security risks and adverse economic impact of TB, similar approaches are justified to address the TB epidemic in many high-burden countries.

Separate mechanisms must also include accountability for nation states at a global level. We propose that Heads of State should be accountable for their countries progress at the United Nations General Assembly on a biannual basis. Unfortunately, the political declaration arising from the UNHLM did not include any specific accountability framework, but rather a commitment to support WHO to develop such a framework at the level of the World Health Assembly. As such, it is unclear that Heads of State would be held to account for inaction to end this disease. This Commission asserts that accountability at the level of the UN, and independent of the WHO, offers the the best chance of driving global political action and recommends that a report card be established to hold nations accountable for their commitments and determine where additional assistance is needed. This approach has been an important political component of the global fight to end HIV/AIDS, as it has maintained global recognition and financial investment to address this disease. While the details of any national report card would need to be drafted and approved to ensure stakeholder consensus, commitments on accountability should include progress towards key End TB milestones and other relevant SDGs; adoption and implementation of WHO recommended policies; registration of and access to the newest and best medical tools; and TB financing. [86] Table 7, gives an example of a report card, highlighting the current performance of ten high TB burden countries on several epidemiologic, programmatic, financial and multisectoral indicators.

Finally, OECD donor countries; international multilateral funding agencies such as the Global Fund and UNITAID; non-governmental funders, like the Bill and Melinda Gates Foundation; and the agencies of the United Nations, including WHO, UNICEF and UNAIDS all play vital roles in global efforts to end TB, for which they also must be held to account. Leveraging the Quality of ODA metrics already published by the Center for Global Development Appendix Table xx provides a report card that highlights strengths and weaknesses of major bilateral TB donors. Its purpose is to illustrate metrics on which these donors can be evaluated. Donor accountability to address DR-TB and TB R&D must be a focus in these report cards, including the allocation of funds to address DR-TB related activities and/or the investment in TB R&D. Similar report cards for multilateral funders and major non-state actors are also necessary to ensure that these institutions also are held accountable for their efforts towards ending the epidemic, and to ensure that investments are syngergistic with domestic investments. Enhanced accountability of these institutions, not just to their board members or citizenry, but to TB survivors and their advocates in recipient countries, represents a global public good. While the indicators and governance for these proposed report cards will need to be drafted and agreed to by consensus, dimensions should

include performance monitoring and assessment, efficiency and effectiveness, sustainability, transparency and responsiveness to corrective feedback.

4.9 The Lancet TB Observatory

To spur political action and monitor progress towards ending TB after the United Nations High-Level Meeting) on Tuberculosis, *The Lancet* Commission and experts participating in this Commission will launch *The Lancet TB Observatory*. The idea for this *Observatory* was first proposed in 2010[16] to promote urgent global action to control the TB epidemic. It is needed now more than ever. *The Observatory* will be composed of global experts and stakeholders from high-burden countries and will meet annually between now and 2022, to critically evaluate progress towards targets made at the UN High-Level Meeting. Leveraging the TB report card, it also will monitor domestic and global financing for efforts to End TB and identify corrective actions and investments necessary to achieve targets. By providing an independent perspective on the the activities of key global stakeholders, including WHO, the Stop TB Partnership and the Global Fund, *The Lancet TB Observatory* can also help optimize alignment of these different bodies towards ending the epidemic.

Section 5: Conclusions

We can build a TB-free world. Many countries – even many low- and middle-income countries – have demonstrated that that it is achievable, despite the limitations of existing tools. The prospect of a TB-free world is not a distant aspiration. It is a realistic objective that can be achieved with the right commitment of leadership and resources. It will be a difficult task, with potential setbacks including the challenge of drug-resistance, funding obstacles and uncertainties about the correct prioritization of tools and implementation approaches. However, the Commission hopes that the recommendations and supporting evidence provided in this Report gives countries a roadmap to end their TB epidemics. With targeted, proven strategies, smart investments based on sound science, accelerated research and development, and a shared responsibility, we can defeat TB within a generation.

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