

**THE LANCET COMMISSION ON TUBERCULOSIS**

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**Lancet Commission on TB:  
Building a TB-free world**

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### 21 **Introduction: Tuberculosis in the 21st Century**

22

23 *‘Knowing is not enough; we must apply. Willing is not enough; we must do.’*

24 Goethe

25

### 26 **Progress against tuberculosis: moving forward, but not fast enough**

27 In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a public health emergency.<sup>1</sup>

28 WHO urged governments worldwide to significantly scale up their TB control efforts and within a year

29 unveiled ‘directly observed treatment, short course,’ or DOTS, as its solution to the problem. DOTS,

30 which used direct observation to improve adherence to a rifampicin-based standardized treatment

31 regimen of 6-9 months, also required diagnosing TB by sputum smear and reporting cases and

32 treatment outcomes to public health authorities. Unfortunately, the original DOTS framework largely

33 ignored smear-negative TB, extrapulmonary TB, latent tuberculosis infection (LTBI), childhood TB, and

34 drug-resistant TB (DR-TB). The DOTS approach, while perhaps fit to budget constraints, was neither

35 comprehensive enough nor sufficient to curtail ongoing TB transmission. The emphasis on directly

36 observed treatment was also inimical to delivery of person-centered care. The expanding HIV epidemic

37 and the growth of DR TB further undermined the DOTS strategy, which was hampered by imprecise

38 diagnostic tools and passive case detection.

39

40 Despite gains made against the TB epidemic since the introduction of DOTS—and subsequently, an

41 enhanced strategy by WHO to intensify TB control efforts<sup>2</sup>—the potential to dramatically reduce the

42 rates of TB incidence and mortality worldwide as first proposed 25 years ago has not been realized.

43 Dismayed by this lack of progress, in 2014, the global TB community outlined The End TB strategy, that has

44 been incorporated into the UN Sustainable Development Goals (SDGs). By 2035, the strategy aims to

45 reduce TB deaths to 95% of 2015 levels by 2035 and cut TB incidence to 90% of 2015 levels by 2035, and

46 to ensure that no families face catastrophic costs due to tuberculosis.<sup>3,4</sup> Tragically, the global burden

47 of TB in 2019 remains substantial and, for reasons outlined below, those targets will not be attained

48 without urgent corrective action.

49

### 50 **TB-related mortality and the persistent burden of TB infection and disease**

51 *TB-related mortality:* TB remains a global public health emergency, responsible for more deaths than

52 any other infectious disease. While globally, the TB mortality rate has declined approximately 3 percent

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

64  
65 *TB incidence:* An estimated 10 million people (90 percent adults, 58 percent male) became ill with TB in  
66 2017. Eight countries in Southeast Asia and Africa (India, Indonesia, China, the Philippines, Pakistan,  
67 South Africa, Bangladesh and Nigeria) accounted for two-thirds of all new cases worldwide. Overall, TB  
68 incidence has fallen approximately 1.4% per year since 2000 and 2% per year since 2015 – far less than  
69 the rate needed to achieve WHO End TB targets<sup>5</sup> (an annual incidence rate decline of 4-5% by 2020 and  
70 10% by 2025 to achieve the milestone case reductions) and less than declining trends in mortality. The  
71 overall slow decline in TB burden suggests that TB programs, while reducing deaths, are insufficient to  
72 overcome poverty-related drivers that substantially impact the epidemic.<sup>8</sup> Modeling suggests that to  
73 avert transmission, individuals at risk must be identified and provided effective preventive therapy, *and*  
74 individuals with less infectious, early TB must be diagnosed and provided immediate treatment.<sup>9,10</sup>

75  
76 *TB Prevalence:* Between 2000 and 2016, 32 national TB prevalence surveys were performed in 26  
77 countries.<sup>5</sup> These studies consistently found a higher prevalence of TB than previous estimates based on  
78 less precise information such as case notifications. The upwardly revised incidence estimates highlighted  
79 large numbers of undiagnosed or unreported TB cases in many countries. Prevalence surveys also  
80 revealed that people with TB often sought care for TB symptoms that health care workers failed to  
81 identify. Other individuals did not recognize the seriousness of their symptoms and had not sought care.  
82 All prevalence surveys in the last decade have found a higher burden of TB among men, with  
83 male:female ratios ranging from 1.2 (in Ethiopia) to 4.6 (in Viet Nam).<sup>5</sup> The higher global disease burden  
84 in men—estimated to be 1.8 times higher than in women<sup>5</sup>—combined with larger detection and

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

88

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

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

97

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

107

108 *Under-investment in TB research and development* – Funding for TB R&D has been stagnant for many  
109 years, despite that TB remains a major global health threat.<sup>3</sup> A reflection of this under-investment is the  
110 continued reliance upon tools such as smear microscopy and the BCG vaccine developed nearly a  
111 century ago.<sup>14</sup> While global funding for TB research received more funding in 2018 than ever before  
112 (\$772 million), the pace at which scientific discovery progresses has been greatly hindered by lack of  
113 sufficient funding dedicated to research priorities that have been defined ad nauseam. <sup>15-17</sup>

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

127

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

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

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

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145 poor clinical and financial implications<sup>34</sup> for patients, are self-evident. Substantially reducing TB  
146 mortality and incidence will require significantly increasing both the coverage and the quality of TB  
147 services across the entire care continuum.

148 *Failures to optimize private sector engagement* Of the 3.6 million unrecognized or “missing” TB patients  
149 in 2017, 63% of them are in six countries where primary care is dominated by private providers and  
150 >67% of initial care-seeking is in the private sector (Table 3). However, in these countries, private  
151 provider notifications are just 18% of total TB notifications and 9% of estimated TB incidence. Based on  
152 data from TB prevalence surveys and private sector drug sales,<sup>35</sup> a considerable proportion of TB  
153 patients are treated in the private sector, with largely unknown levels of quality and patient outcomes. .  
154 Given the dominance of private health care in countries with the largest share of “missing” TB patients,  
155 to meet national and indeed global TB goals, private providers must be engaged to provide high-quality,  
156 patient-centered care on a scale equal to their role in primary care.

157

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

165

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

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176 case finding alone. Unfortunately, active case finding strategies, even in the highest risk populations,  
177 are not widely implemented because of cost concerns and lack of research consensus on what best  
178 practices should include.<sup>44</sup>

179  
180 *Neglecting to implement TB prevention strategies* - Ending TB as a disease of public health significance  
181 must entail a comprehensive, cogent prevention agenda. Because the human reservoir of M.  
182 tuberculosis infection is enormous,<sup>45</sup> overwhelmingly asymptomatic, and long-lived, identifying  
183 individuals who are at highest risk of progression to disease, who would thus benefit the most from  
184 preventive therapy, is crucial. The benefits of preventive TB therapy have been known for more than 60  
185 years. Pioneering studies in the 1950s–1960s provided overwhelming evidence of the efficacy of  
186 isoniazid in preventing active TB in children,<sup>46</sup> Alaskan Native populations, residents of congregate  
187 living facilities such as mental hospitals, and household contacts of TB patients.<sup>47</sup> Subsequent work has  
188 further documented the benefits of preventive therapy for individuals with evidence of recent infection,  
189 those with radiographic evidence of prior untreated TB,<sup>48</sup> people with HIV infection,<sup>49</sup> recipients of  
190 immunosuppressive therapy such as TNF-alpha inhibitors,<sup>50</sup> and other immunocompromised  
191 individuals.<sup>51</sup>

192  
193 Large population-based studies of TB preventive therapy and mathematical models both suggest that  
194 preventive treatment of TB infection—as part of a comprehensive approach that includes active case-  
195 finding and prompt, effective treatment—can sufficiently reduce population-level transmission to  
196 interrupt the cycle of infection, illness, and death.<sup>52,53</sup> Unfortunately, despite abundant evidence of its  
197 efficacy, the use of preventive therapy globally has been limited,<sup>54</sup> as TB control programs in LMICs have  
198 focused almost exclusively on detection and treatment of individuals with active TB disease.

199



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

217

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

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

250

251

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

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

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

267

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

281

282

### 283 **Report Roadmap**

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

290

291 The challenge TB now presents also has in part resulted from neglecting to identify TB research as an  
292 integral, critical priority during the last quarter century.<sup>92</sup> While ending TB with existing tools is possible,  
293 new products are essential to reduce cost, simplify implementation and accelerate progress. In Section  
294 2, we describe why current funding for TB research and development (R&D) must increase to expedite  
295 transformative innovations in point-of-care diagnostics; safer, less toxic, shorter treatment regimens;

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296 chemoprevention; and a more effective TB vaccine. The economic rates of return on greater TB R&D  
297 investment are both substantial and invariably beneficial to poor and marginalized communities.<sup>93</sup>

298

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

309

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

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### 318 **Section 1: Scaling up proven strategies**

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

333

334

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### 335 **1.1 Ensuring delivery of high quality, person-centred services**

#### 336 **1.1.1 Defining person-centered care**

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

346  
347 Unfortunately, in many high-burden settings, health system frailties are inimical to delivery of person-  
348 centered TB services: first, individuals with TB often are neither identified nor appropriately evaluated in  
349 a timely manner;<sup>98,99</sup> second, once a diagnosis is established, they are not started or supported to  
350 complete treatment that ensures a durable cure. TB services must align with care-seeking behavior to  
351 bring about person-centred care and prevention. Optimizing alignment of services, both in national TB  
352 programmes (NTPs) and in the non-state sector (private providers, nongovernmental organizations,  
353 etc.), can help ensure higher TB cure rates and improve the efficiency of care delivery to ensure greater  
354 equity and control costs. By redressing inequities in access, improving efficiencies in delivery, and  
355 protecting patients from physical and financial hardships, these interventions are also integral to robust  
356 health systems and to the broader UN Sustainable Development Goal (SDG) agenda.<sup>100</sup>

357

#### 358 **1.1.1. Re-thinking TB service delivery**

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

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366 (inpatient, day hospital or at home). After the intervention, adherence improved from 52% to 81% and  
367 treatment success of 71% was achieved.<sup>101</sup>

368

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

379

### 380 **1.1.1 Aligning TB services with care seeking patterns**

381 To realize the vision of sustainable health for all, we must ensure that health systems are fully resourced  
382 so all of those at risk for TB care can access TB diagnostic, curative and preventive services. Immediate  
383 and incremental steps are needed to strategically required to ensure that available resources are  
384 appropriately allocated, with a longer-term goal of creating optimally integrated, patient-centered  
385 health systems. To do this requires that TB programs pivot resources so that they align with how and  
386 where people with TB, and those at risk of developing TB, seek care. Patient pathway analysis (PPAs)  
387 mapping the continuum of care for people with TB, using existing population-based surveys and routine  
388 programmatic data, can enable programs to better understand how well patient care-seeking and TB  
389 service availability align, highlighting system-level obstacles to patients accessing care. This is an  
390 essential step to prioritizing efforts and planning the placement of services to meet patient needs and  
391 preferences. This methodology is well characterized,<sup>102</sup> and in 2017, results from five countries  
392 implementing PPAs and two countries implementing care cascades were published.<sup>18</sup> These analyses  
393 revealed marked mismatches between diagnostic capability and TB care-seeking behavior, with less than  
394 30% of facilities where TB patients initiate care able to perform sputum smear microscopy and even  
395 fewer having the capacity to conduct a GeneXpert test or refer a sample for GeneXpert testing<sup>19</sup>.  
396 These results also highlighted the need to prioritize deployment of rapid molecular tests in certain  
397 places and strengthen specimen referral mechanisms in others. In addition, these PPAs demonstrated

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

400

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

405

### 406 **Person-centred care requires evidence-based priority-setting**

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

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

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



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

434

### 435 **1.1.2 Utilize network optimization and big data analytics to ensure all patients have access to services**

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

447

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

458

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

476

### 477 **1.1.3 Improving quality management to ensure high quality service delivery**

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

486

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

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490 management (QM) tools can help front-line providers and NTP managers address those gaps to improve  
491 care quality as well as address the drivers of ongoing TB transmission.<sup>109</sup>

492

### 493 **Implementing quality improvement: lessons learned from tackling HIV**

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

506

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

511

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

518

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

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

524

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

526 Quality management programs must become part of NTPs and ideally integrated into existing national  
527 quality management programs. Ensuring that NTP managers and their teams have access to this  
528 expertise will facilitate the development of ways to measure and improve quality in their NTP.

529 Nonetheless, a culture change in how TB data are used to improve care must occur at every level of the  
530 health system, including greater accountability of local TB clinics to patients they serve. Globally, a  
531 quality management program that embraces improvement methodologies can be a powerful lever to  
532 improve donor-recipient accountability and enhance donor efficiency. WHO plays a crucial role in  
533 supporting a quality management agenda and creating a global culture that supports QI and accelerates  
534 dissemination of learning through peer exchange. Linking donor support to quality indicators could also  
535 improve efficiencies in donor financing and enhance transparency.

536

### 537 **1.1.4 Assessing the impact of strategies to deliver high-quality, person-centered services**

538 Together, the strategies described in this section share the common objective of accurately diagnosing  
539 TB as early as possible: they reflect ways of realising the maximum potential impact of a system of TB  
540 services that is contingent on cases presenting for care. What are the potential epidemiological  
541 implications of these measures? Modelling analysis, commissioned for this report, casts some light on  
542 the potential value of these and other measures in three different country settings, each with distinct  
543 challenges in TB control: India (with a large private sector); Kenya (with HIV confection); and Moldova  
544 (with a high burden of MDR TB). The full analysis is provided in (Vesga Gaviria et al, in press, 2018).

545 Figure 3 illustrates the example of Kenya: in this setting, patient pathway analysis has already identified  
546 the lack of diagnostic facilities as a key challenge.<sup>20</sup> The figure shows the potential impact of measures  
547 that could increase the probability of diagnosis per provider visit to 90%: the impact is to reduce  
548 cumulative TB cases from 2018 – 2045 by 25% (95% credible intervals 11-39%), and cumulative TB  
549 mortality over this time by 38% (95% CrI 17 – 50%). As described in this section, such measures are not  
550 limited to diagnostic tools: they also involve network optimisation, correcting misalignments of TB  
551 services; and other such measures to maximise the effective uptake of rapid, accurate diagnostics. As  
552 the modelling illustrates, these measures are necessary but insufficient to end TB. However, in concert

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

555

### 556 **1.2 Prioritized active case finding**

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

#### 566 **1.2.1 ACF: Closing the ‘know-do’ gap**

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

577

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

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

586

### 587 **1.2.2 Prioritizing high risk groups**

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

594

595 Other risk groups may warrant targeted screening programs based on epidemiology, health system  
596 capacity, availability of resources, and feasibility. Given higher rates of TB in men compared to women in  
597 almost all high-risk groups,<sup>12</sup> male-friendly strategies, such as workplace interventions should be  
598 employed where feasible. In preparing ACF scale-up strategies, the risk of discrimination and  
599 stigmatization should be carefully addressed. In addition, the legal status of migrants, with regard to  
600 both access to health services and risk of expatriation in case of TB diagnosis, needs to be considered.<sup>138</sup>

601 Engaging with civil society groups to better understand the expectations and concerns of high-risk  
602 groups when planning and implementing TB screening activities is critical to their success.

603

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

610

### 611 **1. 2.3 Anticipating costs and using planning tools**

612 Scaling up ACF strategies will require substantial additional resources. The cost of screening can be high  
613 per case identified,<sup>143-145</sup> especially when compared with other health promotion interventions.<sup>146</sup>

614 Nonetheless, as highlighted in Section 3, evidence on the cost-effectiveness and benefits of expanded  
615 financing for ACF suggests that such investments will yield a high return. Modelling performed as part of

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

621  
622 Planning tools, such as the WHO’s online ScreenTB tool,<sup>147</sup> can help NTPs plan their case-finding  
623 activities and prioritize risk groups for screening by modeling the potential case yields and costs of  
624 different screening approaches. The ScreenTB tool allows the user to select risk groups of interest and  
625 compare estimates of the yield of screening (including true-positive and false-positive cases found), the  
626 total costs, and the cost per case detected across the selected risk groups and across different screening  
627 algorithms.

628

### 629 **1.2.4 Leveraging technology to improve the efficiency of case-finding strategies**

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

640

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

648

649 **1.2.6 Finding cases in lower-risk populations**

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

660

661 **1.2.5 Recognizing that ACF in high-risk populations will not be enough**

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

669

670



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### 671 **1.3 Prioritizing TB prevention**

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

684

#### 685 **1.3.1 Targeting preventive therapy**

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

699

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

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703 therapy, not least because of compelling evidence of its efficacy as TB prevention intervention.<sup>158,159</sup>  
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.<sup>160-162</sup> 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<sup>162</sup>, 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.<sup>163</sup> 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).<sup>153</sup> 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,<sup>164</sup> 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,<sup>165-167</sup> reduce the risk of resistance emergence, while also  
726 saving money and lives.<sup>165,168,169</sup> 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.<sup>160,170</sup> Global

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735 efforts to provide antiretroviral therapy have now reached 20 million individuals with HIV, but another  
736 17-19 million remain untreated. Fewer than four million people with HIV have ever received TB PT,  
737 highlighting the opportunity to substantially scale-up this intervention. Failure to scale up TB PT in  
738 people living with HIV has likely caused several million deaths over the past decade.<sup>170</sup>

739

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

756

### 757 **1.4 Importance of private provider engagement: from acknowledgment to prioritization**

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

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767 strategies to enable high quality TB care in the private sector, opportunities for greater synergy  
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.<sup>174</sup> 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.”<sup>175</sup> 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.<sup>176</sup>

783 Failure to engage private providers is often blamed on NTP staff shortages, but clearly the constraints  
784 are much more profound.<sup>177</sup> 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

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

804

### 805 **1.4.2 Catalyzing progress and new opportunities to engage private providers**

806 Although private provider engagement in TB is far from adequate, considerable experience has accrued  
807 regarding how to successfully engage private providers for TB care.<sup>180</sup> Many small, externally supported  
808 pilot projects to engage private providers have been implemented over the years. A study in 2006  
809 reviewed data from 15 projects in 8 countries,<sup>181</sup> a systematic review in 2011 considered 45 studies from  
810 22 projects in 12 countries<sup>182</sup>, and another in 2016 found 78 studies documenting 48 programs in 16  
811 countries.<sup>183</sup> Although, most projects have failed to reach significant scale or to be sustained over long  
812 periods. Nevertheless, these projects have generated abundant evidence that engaging private  
813 providers can significantly increase TB case detection and achieve treatment success rates that are at  
814 least as good as those in the public sector. Data on cost-effectiveness, financial protections, delays to  
815 treatment, and reaching the poor is less robust but also available.<sup>184</sup> New research continues to add to  
816 our understanding of the functioning of private healthcare markets with respect to TB.<sup>31,185,186</sup>  
817 More recently, sustained scale-up of private provider engagement has taken place in several key  
818 countries (Figure 5). Bangladesh has sustained a moderate level of private provider engagement for the  
819 past five years, with private notifications reaching 18% of incident cases, while notifications in Myanmar  
820 have declined recently from similar levels. Recently, India, Pakistan, and the Philippines all increased  
821 their engagement of private providers, with private notifications increasing to 9%-13% of incident cases  
822 in 2016. Unfortunately, Indonesia and Nigeria—two countries with substantial numbers of “missing” TB  
823 cases—have made little progress, with private notifications averaging just 4% and 1% of estimated  
824 incidence, respectively.

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

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

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

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

856 As successful experiences on private provider engagement accumulate, defined packages of  
857 interventions could be disseminated as templates that could be adapted for rapid scale-up.<sup>18</sup> The core

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

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

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

884

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

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889 leveraging private sector services to provide public-financed services may enable extended capability  
890 while also accommodating the preferences of those most at risk for, or suffering from TB.<sup>187</sup>

891

### 892 **1.4.3 Modeling the impact of optimal private sector engagement**

893 Because of the large burden of TB that is managed in the private sector globally, it is essential to assess  
894 the impact of improving private sector engagement. Modeling commissioned for this report assessed  
895 how greater private sector engagement in a high-burden country like India, where private providers  
896 offer extended capability, could influence TB incidence and mortality. In such a setting, strategies to  
897 improve quality of private sector care, such as subsidized TB diagnostics, and NTP-funded adherence  
898 support mechanisms for patients accessing care privately, would avert 28% of TB deaths over the next  
899 30 years, saving an additional eight million lives from TB, beyond those lives saved by full  
900 implementation of other evidence-based interventions (Figure 4). The additional cost of optimized  
901 private sector engagement would involve an annual increase of US\$290 million in NTP costs. While this  
902 strategy alone would not be enough to end the epidemic in India, it has the potential to substantially  
903 reduce the public health threat posed by TB. Further, enhanced private sector engagement in concert  
904 with other strategies to close gaps in the care cascade, such as targeted ACF interventions, optimization  
905 of diagnostic networks, and improved adherence support strategies, could lead to significant reductions  
906 in TB mortality over the next 30 years.<sup>188</sup>

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### 911 **1.5 Tackling drug resistance**

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

918

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

927

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

933

934 Encouragingly, the rapidly evolving field of DR -TB diagnostics and the increasing availability of new and  
935 repurposed drugs and regimens for treating patients with multidrug-resistant/rifampicine-resistant  
936 (MDR/RR) TB present opportunities to dramatically improve the epidemic response (Appendix Table xx).

937 Emerging data suggest that in high-burden settings, more than 90% of incident MDR/RR-TB disease  
938 results from direct transmission of already resistant TB bacteria from one person to another.<sup>61,62</sup> As a  
939 result, failure to diagnose and effectively treat a significant proportion of individuals with active TB  
940 disease is a major driver of the epidemic. Barriers to diagnosis and treatment scale-up vary across  
941 countries but include 1) the high cost of providing treatment (although data show such costs can  
942 decrease dramatically when more individuals are offered access<sup>190</sup>); 2) perceived complexity of

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

946

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

964

### 965 **1.5.1 Increasing universal access to drug susceptibility testing**

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

972

973 Until relatively recently, diagnosis of DR -TB relied on TB culture, with consequent long delays and the  
974 need for specialised laboratories.<sup>214</sup> Because DR -TB results from the presence of resistance-conferring

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

984

### 985 **1.5.2 Improving DR -TB treatment**

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

997

998 The South African data, complemented by a large individual MDR-TB patient-level meta-analysis, have  
999 contributed to new WHO guidance prioritising the use of bedaquiline and linezolid for MDR-TB  
1000 treatment.<sup>236</sup> To date, there is insufficient data to support similar prioritisation for delamanid.  
1001 Increasing the use of these new and repurposed drugs would remove reliance on some of the more toxic  
1002 and less effective drugs, including the second-line injectable agents, which are associated with  
1003 irreversible hearing loss in up to 50% of individuals who receive them.<sup>237</sup> It also would help relieve the  
1004 burden on the health care system to deliver the daily injections.<sup>238</sup> However, to date, uptake of new  
1005 drugs based on previous WHO guidance has been disappointingly limited, despite a US Agency for  
1006 International Development (USAID)/ Janssen Pharmaceuticals (Beerse, Belgium) donation program in

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1007 many countries.<sup>239</sup> Barriers include drug costs, difficulties in individual country regulatory approval and  
1008 drug procurement, and lack of high level national government support.<sup>240</sup> Overcoming these barriers is  
1009 essential moving forward. As highlighted earlier, TB programs also need to be continuously evolving, to  
1010 ensure that national guidelines and clinical practice reflects the best available evidence. Civil society  
1011 organizations have a vital role to play ensuring that this is the case.

1012

1013 Additionally, a more individualized approach to DR- TB treatment—one that encompasses access to all  
1014 second-line drugs and is guided by more extensive DST through whole genome sequencing—would  
1015 enable individuals with DR -TB to receive the best chance of cure, while limiting both the unnecessary  
1016 use of toxic drugs and resistance amplification.<sup>241</sup> Such an approach would need to be supported by  
1017 implementation research to guide its integration into existing TB programmes and the health system as  
1018 a whole, in addition to pharmacovigilance systems.<sup>233,242,243</sup> While full treatment individualisation may  
1019 not be feasible in all settings, more stratified approaches that takes into account local drug resistance  
1020 profiles are potentially feasible.<sup>244</sup>

1021

1022

1023 Given the arduous nature of current TB treatment regimens as well as socioeconomic challenges, many  
1024 patients withdraw from treatment before completing the full course: globally reported as 15% in the  
1025 2014 cohort, and ranging between 1% and 56% in individual studies, with a tendency to increase as  
1026 more patients are treated in a particular setting.<sup>55,245</sup> These data emphasize the need for more patient-  
1027 and household-centered approaches that ensure health systems are optimally aligned with the needs of  
1028 the populations affected by DR -TB. While the emphasis has been on improving adherence and reducing  
1029 catastrophic costs, a person-centered model of care also includes ensuring that people with possible DR  
1030 -TB (and those supporting them) are fully informed about, and included in, therapeutic decisions. At  
1031 their heart, such models must tackle active discrimination within the health system as well as in other  
1032 sectors. Person-centered care also includes providing treatment closer to where patients live and  
1033 initially seek care, i.e., community-based and decentralised as much as possible.<sup>246</sup> Full implementation  
1034 of such a decentralized approach requires considerable upgrading of the capacity of peripheral facilities  
1035 to manage complex patients. Such facilities should be supported by easy, routine communication with  
1036 treatment initiation centers and expert providers. While a country or region may often have many DR -  
1037 TB cases in the aggregate, peripheral facilities may have very few if any MDR -TB patients at any given

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1038 time. Thus, experience is lacking, and decentralized needs to occur in tandem with close support from  
1039 experts, even those experts are accessed remotely.

1040

### 1041 **1.5.3 Preventing resistance acquisition**

1042 While diagnosis and prompt treatment are central to tackling the TB epidemic, minimizing the risk of  
1043 further resistance acquisition, both to existing first- and second-line drugs and new drugs, is also  
1044 paramount. This includes addressing the drivers of TB drug resistance listed above through  
1045 programmatic quality improvement (Section 1.1), but also avoiding the use of standardized regimens in  
1046 the absence of DST wherever possible. Finally, antibiotic stewardship entails ensuring that new drugs  
1047 are used in tailored, effective multidrug regimens for all patients with DR- TB, not just those with limited  
1048 therapeutic options. Such use also needs to be supported by expanded TB drug-resistance surveillance  
1049 (to replace intermittent, expensive DR -TB surveys).

1050

1051 As with drug-susceptible TB, treatment of latent DR- TB may significantly impact the epidemic in the  
1052 long term. Currently at least two trials are evaluating different prevention regimens for individuals in  
1053 close contact with MDR/RR TB patients.<sup>232</sup> In addition, WHO released a conditional recommendation in  
1054 2018 supporting the use of individualized preventive treatment for contacts of MDR/RR TB patients who  
1055 are at high risk of progressing to disease.<sup>247</sup> Given the high morbidity and mortality associated with DR-  
1056 TB, preventive treatment of these high-risk contacts, including children and people living with HIV, is a  
1057 priority.

1058

### 1059 **1.5.4 Increasing DR- TB as global health security threat – implications for donor financing**

1060 The cost of treatment for MDR/RR TB, ranges from estimates of US\$1,218 in low-income countries to  
1061 US\$83,365 in high-income countries<sup>248</sup>. The high cost has been a significant barrier to scaling up  
1062 treatment to date. The Stop TB Partnership estimated that in 2017, US\$2 billion was required to fund  
1063 DR- TB care; it is expected to increase to US\$3.6 billion by 2020.<sup>55</sup> Funding at this level is unlikely to be  
1064 sustainable for many high MDR/RR TB burden countries; the BRICS countries (Brazil, the Russian  
1065 Federation, India, China, and South Africa) are notable exceptions. As a result, funding to support DR- TB  
1066 programme implementation will likely be required from international sources, even in countries with  
1067 the capacity to fund their own DR- TB programmes. The current and future projected economic costs  
1068 associated with DR-TB, provides a compelling rationale to justify increased donor financing, even in

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1069 middle-income countries transitioning out of donor eligibility<sup>249,250</sup>. We discuss the implications of this  
1070 further in Section 3.  
1071

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### 1072 **Section 2: Investing in TB Research and development**

1073 Despite causing more than one billion deaths during the last two centuries,<sup>251</sup> TB remains poorly  
1074 understood. Although we can and must do more to broadly implement currently available TB control  
1075 tools and strategies, achieving an end to the epidemic will require answering fundamental questions  
1076 about TB and developing new biomedical tools to accelerate our progress toward that goal.<sup>252</sup> The  
1077 urgency of boosting our investment in TB R&D to enable these transformative advances demands that  
1078 governments and their partners in high- and middle-income countries commit now to sustained,  
1079 increased funding of these efforts. The UNHLM underscored the crucial role accelerating TB R&D plays  
1080 and will continue to play in achieving an end to the TB epidemic. Building on that call to action, here we  
1081 highlight R&D priorities and provide an economic rationale for why investment in these R&D priorities is  
1082 critical to success.

1083

1084

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### 1085 **2.1 Biomedical research priorities**

1086 Future successes in developing new diagnostics, therapeutics, and vaccines for TB fundamentally will  
1087 require a better understanding of the pathogenesis of TB disease. In this regard, a key basic science  
1088 priority is identifying the correlates of risk for progression to disease. An intensified search for  
1089 biomarkers associated with protection from disease,<sup>253</sup> as well as the development of better animal  
1090 models, are among other priorities. Large gaps also exist in understanding TB pathogenesis and the host  
1091 immune response, especially in children<sup>254</sup> [Panel 4] and in individuals co-infected with HIV.<sup>255</sup>  
1092 Nonetheless, promising preclinical efforts exist that must be significantly expanded. These include using  
1093 computational modelling to better understand complex biological interactions between pathogen and  
1094 host,<sup>256</sup> high-throughput host genomic screening to identify RNA signatures<sup>257</sup> associated with the risk  
1095 for disease, and improved animal models of TB latency<sup>258</sup>.

1096

1097 To accelerate the development pipelines for diagnostics, therapeutics and chemopreventive strategies  
1098 and vaccines, it is imperative to develop an integrated research strategy and agenda to close cross-  
1099 cutting gaps in TB R&D (Figure 6, Appendix Figure xx). Outlined below are key research priorities,  
1100 including those outlined recently in the US National Institute of Allergy and Infectious Diseases (NIAID),  
1101 Strategic Plan for TB. This Plan and similar multi-pronged, multi-disciplinary efforts are essential to  
1102 significantly advance TB R&D and end TB.<sup>259,260</sup>

1103

#### 1104 **2.1.1 Diagnostics**

1105 With nearly four million people estimated to have undiagnosed or unreported TB, including an  
1106 estimated 558,000 people with undiagnosed, drug-resistant TB,<sup>5</sup> the importance of having rapid and  
1107 accurate diagnostics at entry into TB care cannot be overstated. Early, accurate diagnosis together with  
1108 drug susceptibility testing at the time of diagnosis is key to breaking the cycle of transmission, enabling  
1109 patients to be quickly started on an effective TB regimen. Investments in R&D for TB diagnostics have  
1110 led to the progressive introduction of six new diagnostic tools since 2005. These have helped overcome  
1111 major barriers in identifying drug-sensitive and drug-resistant forms of *M. tuberculosis*, including cost,  
1112 complexity, slow time-to-result, and low accuracy.<sup>261</sup> An additional 45 candidates are in the TB  
1113 diagnostic pipeline.<sup>262</sup> Unfortunately, many of these are molecular technologies that are unlikely to  
1114 meet the three most important needs of high-burden low- and middle-income countries (LMICs) as  
1115 described below.



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1116 For high-burden, low-resource settings, the first priority is an easy-to-use, low-cost, non-sputum-  
1117 based<sup>263</sup> rapid diagnostic test that can identify individuals with active TB and can be incorporated into  
1118 active case-finding strategies or used in primary care facilities (Appendix Panel xx). Modelling has shown  
1119 that a triage test, implemented at the community level and used in combination with a confirmatory  
1120 test (e.g., GeneXpert), could close case detection gaps and reduce incidence by 19% and mortality by  
1121 37% over ten years.<sup>264</sup> The second priority, highlighted in Section 1.5, is rapid tests for drug-resistance  
1122 that would help direct patients to appropriate treatments and safeguard medicines against antimicrobial  
1123 resistance.<sup>265,266</sup> Priority three is an incipient TB *in vitro* diagnostic to identify individuals at high risk of  
1124 progression from latent TB infection to active disease. This *in vitro* diagnostic would enable targeted  
1125 preventative treatment in communities as a prerequisite to TB elimination in the absence of an effective  
1126 vaccine.

1127  
1128 Achieving priority one requires identifying a suitable host and microbial biomarkers and biosignatures  
1129 (primarily antigen, antibody, or a volatile organic compound). Several promising diagnostic biomarker  
1130 combinations have been identified that are undergoing validation or being transferred to point-of-care  
1131 platforms.<sup>267,268</sup> If successful, a triage test could be introduced by 2020; however, given high candidate  
1132 failure rates and few priority one candidates in the biomarker pipeline, additional funding is needed to  
1133 enrich the pipeline. Expansion of the drug susceptibility testing menu is underway for existing molecular  
1134 platforms, and next-generation sequencing tools show promise; however, further translational work is  
1135 required to make them affordable and deployable in high TB burden countries.<sup>269,270</sup> Similar to the triage  
1136 test, a breakthrough in biomarker discovery is necessary to diversify the incipient test pipeline, which is  
1137 currently is sparsely populated.<sup>271</sup>

1138

### 1139 **2.1.2 Therapeutics**

1140 Development of markedly improved therapeutics could rapidly accelerate efforts towards ending TB.  
1141 The principal desired characteristics are shorter, non-toxic, patient-friendly treatment regimens that can  
1142 be implemented widely.<sup>272</sup> Preferably, the individual components of improved therapies should focus on  
1143 either novel targets or targets that do not have cross resistance with available drugs. Since  
1144 approximately one million new TB cases occur in the pediatric population each year, it is also critical that  
1145 new TB therapeutics be formulated to be appropriate for and effective in children as well as in adults.<sup>273</sup>

1146

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1147 Developing novel, safer, shorter, and simpler regimens will have to overcome many challenges. The  
1148 existing drug regimens to treat drug susceptible TB are remarkably effective, largely non-toxic and  
1149 extraordinarily inexpensive. New drugs are unlikely to be tested individually but added to existing  
1150 regimens and tested for non-inferiority and safety rather than superiority. As a consequence many of  
1151 the newer drugs are being tested on drug-resistant TB, where the effectiveness of current regimens are  
1152 limited and smaller trials in a defined targeted population are feasible. In addition to the research costs of  
1153 preclinical development and Phase I and II clinical trials, the lack of reliable, validated biomarkers that  
1154 can be used to predict the duration of therapy necessary to cure virtually all patients treated with a  
1155 given therapy.<sup>274</sup> The findings of three recent Phase III trials<sup>275-277</sup>, which failed to shorten TB therapy for  
1156 drug-sensitive TB despite promising Phase II data, clearly demonstrate how the lack of predictive  
1157 biomarkers constrains clinical research. The lack of predictive biomarkers is particularly problematic  
1158 because, due to their complexity and long duration, the cost of late-stage clinical trials of novel TB  
1159 regimens is so high.

1160

1161 During the past decade, remarkable progress has been made in the search for new TB drugs and  
1162 therapeutic regimens. In the early 2000's, there were no new drug candidates to treat latent TB; the  
1163 pipeline has more than 30 compounds (although few are new chemical entities), including several drugs  
1164 in late-stage product development (Appendix Table xx). Two novel drugs have received conditional  
1165 regulatory approval.<sup>5</sup> Because of the pipeline growth, it is now feasible to investigate novel  
1166 combinations of drugs and new therapeutic regimens. New regimens currently in Phase 2 and 3 clinical  
1167 trials show considerable promise and may enable much shorter durations of treatment—even for the  
1168 most resistant forms of extensively drug-resistant TB—than what is currently recommended.<sup>278</sup>  
1169 Furthermore, a two-month universal regimen, active against all forms of TB, may be possible within the  
1170 next decade. This would offer the potential to shorten and simplify treatment strategies and drug-  
1171 susceptibility testing needs,<sup>279</sup> and should be a high funding priority in the next decade. The potential  
1172 utility of a pan-TB regimen must be considered together with person-centered approaches to treatment,  
1173 tailored to pharmacogenetics, co-morbidities, and drug co-administration, as well as the risk of new  
1174 forms of resistance.<sup>280</sup> A diversified portfolio of therapeutic products offers the best hope for long-  
1175 term success; however, substantial investment in the short-to-medium term is needed to guarantee  
1176 those products make it to market.

1177

1178

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### 1179 **2.1.3 Vaccines and Chemopreventive Strategies**

1180 Prior to the antibiotic era, evidence existed to indicate that remarkable protection against TB could be  
1181 produced by latent TB infection, and that BCG was protective in some populations but not others.<sup>281</sup> Yet  
1182 today, as highlighted in section 0, BCG remains the only available vaccine—one that is more than 100  
1183 years old, has variable effectiveness in preventing adult pulmonary TB, and is not recommended for  
1184 children who are infected with HIV. Despite compelling evidence from models demonstrating that a  
1185 vaccine with 60% efficacy could avert 70 million TB cases within 25 years if given to only 20% of at-risk  
1186 adults,<sup>282</sup> progress towards developing viable vaccines has been hindered by numerous scientific and  
1187 funding challenges. In contrast to drugs, vaccines are given to healthy people to prevent illness. Thus,  
1188 the stringency in being certain that candidate TB vaccines are as safe as possible represents a high bar.  
1189 Also, because many individuals who will never be infected have to be vaccinated to demonstrate  
1190 protection in a smaller group infected with *Mtb*, trials require large populations and access to  
1191 sophisticated laboratories.

1192

1193 Currently, 14 candidate vaccines in the pipeline that have shown some degree of protection against TB  
1194 in animal models are now in human clinical trials.<sup>274</sup> Some are live recombinant vaccines (for example,  
1195 BCG with added antigens and genes to elicit strong immune responses, or genetically attenuated *M.*  
1196 *tuberculosis*); others are live virus vectors expressing multiple antigens of TB to provide long-lasting  
1197 immunity (e.g., recombinant cytomegalovirus [CMV] vectors expressing TB antigens).<sup>282</sup> To date, only  
1198 two Phase III preventive TB vaccine studies have been published, one using an inactivated whole-cell  
1199 mycobacterial vaccine (*M. obteneuse*) reporting <40% protection in adults with<sup>283</sup> and the other  
1200 evaluating the modified vaccinia Ankara virus expressing antigen 85A (MVA85A) to boost the  
1201 effectiveness of the BCG vaccine in infants, which failed to show protection.<sup>284,285</sup>

1202

1203 However, two new Phase IIb trials offer new promise for vaccines against TB.<sup>286</sup> Revaccination with BCG  
1204 of South African adolescents, who received BCG as infants but were not exposed to *Mtb* (Quantiferon-  
1205 negative), provided 45% protection against TB.<sup>287</sup> In high burden countries, a high percentage of  
1206 individuals have been previously exposed to or latently infected with *M. tuberculosis*, and no vaccine has  
1207 previously been reported to provide protection to tuberculin-positive individuals. A new subunit TB  
1208 vaccine, with two *Mtb* antigens in an adjuvant that has been effective in vaccines against zoster and  
1209 malaria, M72AS01<sub>E</sub>, tested in several thousand adolescents in 3 sub-Saharan countries, showed 54%  
1210 protection overall, and notably 87% protection in those under 25 years.<sup>288</sup> These results emphasize the

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1211 importance of clinical trials and suggest that targeting vaccines to adolescents may provide optimal  
1212 protection. It is only from searching for correlates of protection in human trials that necessary and  
1213 sufficient mechanisms of protection can be discerned, which could shorten the time and expense of  
1214 future trials.

1215

1216 Clearly these encouraging results need to be validated and extended, particularly in different  
1217 geographical situations. But they make clear that, despite challenges, the scientific prospects for  
1218 developing a safe and effective vaccine to prevent TB are more promising than ever before; an increased  
1219 focus on early-stage research has led to a robust pipeline, and new technologies, which are providing  
1220 unprecedented scientific opportunities.<sup>289</sup> Vaccines represent the most cost-effective intervention to  
1221 prevent disease and death. In the case of TB, long-term and sustained investments will be necessary to  
1222 build on these promising results, but the returns even from a partially effective vaccine would be very  
1223 great<sup>318</sup>.

1224

1225

### 1226 **2.1.4 Population, policy, and implementation research priorities**

1227 Progress towards ending TB has been limited because existing tools have been ineffectively  
1228 implemented and the currently used control strategies used are outdated. Greater national and global  
1229 investments in population, policy, and implementation research capacity will be required to enable the  
1230 scaling of effective approaches.<sup>97</sup> In particular, implementation research is needed to understand how to  
1231 improve care cascades, i.e., find patients earlier, evaluate them quickly, and provide effective treatment  
1232 resulting in a cure. Population research to characterize the factors that drive TB transmission within  
1233 families and communities, particularly in high TB burden settings, is also critical for developing  
1234 strategies to interrupt Mtb transmission<sup>26</sup> While research on sensitive, inexpensive point-of-care  
1235 diagnostic tests continue, active screening strategies could be implemented with existing technologies,  
1236 including automated X-radiography in contacts and high risk groups in high burden countries, followed  
1237 by culture or Xpert testing diagnosis, in view of the strong evidence from surveys showing that 20-30%  
1238 of TB cases globally are asymptomatic.<sup>5,148, 174.</sup>

1239 To optimize treatment outcomes, differentiated strategies for providing patient-centred care and  
1240 supporting treatment adherence must be developed in concert with the creation of new therapeutic  
1241 regimens.<sup>290-292</sup> Likewise, research is necessary to determine the most efficient and cost-effective TB

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1242 prevention therapies. The potential of digital technology to overcome weak health system  
1243 infrastructures, enhance TB program quality, and improve disease surveillance, remains largely  
1244 untapped. While numerous disparate pilot studies have been conducted evaluating IT, e-Health, and  
1245 connectivity solutions,<sup>290,293-296</sup> future studies should be guided by a comprehensive research agenda  
1246 underpinned by a commitment from countries and funders to translate evidence to action at scale.

1247 Cross-cutting all of this, mechanisms must be identified and implemented to strengthen the  
1248 infrastructure and capacity of countries to absorb--in terms of both speed and scale-- innovations, as  
1249 well as to rapidly translate research findings into policy.<sup>297</sup> For instance, the Initiative for Providing  
1250 Affordable & Quality TB Tests (IPAQT)<sup>298</sup> provides a proven model for incentivizing the uptake of new  
1251 diagnostics among private sector providers in India; however, it has yet to be translated into a replicable  
1252 model and implemented in other countries. In part, this reflects the need for improved implementation  
1253 research capacity in LMICs to realize the benefits of investment in TB R&D.<sup>4</sup> The role of trans-national  
1254 research networks to build such infrastructure and capacity is essential.

1255

### 1256 **2.2 The cost of inaction in R&D**

1257 The human costs of failure to develop and implement new and improved interventions is unacceptably  
1258 high. Even in the WHO best case scenario where treatment coverage was extended to 90% of persons  
1259 with TB and 90% were successfully cured (substantially higher than what global estimates indicate, e.g.  
1260 notification is 65% for Ethiopia, 72% for India; few high burden countries have data on cure rates),<sup>5</sup> we  
1261 estimate that there would be nearly one million unaverted deaths with current technologies (Figure 8).  
1262 To achieve these goals would require unprecedented case finding, treatment completion and  
1263 prevention, underscoring the important need to close gaps with scientific discovery and programmatic  
1264 innovation.

1265

1266 The potential economic value of new tools is illustrated by modeling analysis in three different country-  
1267 settings –India, Kenya and Moldova, illustrated in Figure 9, leveraging an approach where the value of  
1268 lives lost prematurely was derived using value of statistical life estimates (See Appendix for  
1269 methodology).<sup>94,299,300</sup> Optimal implementation of existing evidence-based strategies to improve the  
1270 care continuum for active TB in each of those countries will still leave millions of deaths unaverted over  
1271 the next 30 years. The value of the loss associated with TB mortality is, on average, \$32bn per year in  
1272 India; \$2.7bn in Kenya; and \$35mn in Moldova. However, these estimates are likely to be

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1273 underestimates since: (i) they arise from an arguably ambitious scenario, of reducing losses in the care  
1274 cascade to 10% and delays by 25%, and (ii) they do not account for opportunity costs associated with  
1275 underaverted disease that does not lead to deaths, nor the financial burden placed on the health system  
1276 associated with this underaverted disease burden.

1277

1278 It is fair to ask why there is such a gap in investments in TB R&D. There are many reasons: The most  
1279 obvious is that the burden of disease falls on low and middle income countries which are least able to  
1280 afford new expensive tests and drugs. As a relatively low prevalence disease and a high latently infected  
1281 population, efficacy testing of new tools will require large and lengthy trials. Finally, new tools are only  
1282 as effective in controlling the disease as are health systems able to implement them, and hence  
1283 improvements in health systems are critical. Nonetheless our analysis clearly demonstrates that further  
1284 tools, particularly tools for primary prevention will have a profound return on investment, insofar as  
1285 they prevent these needless TB deaths. Furthermore, it validates the argument that greater spending in  
1286 TB research is likely to bring important economic benefits and have a disproportionately beneficial  
1287 impact on health outcomes in LMICs.<sup>93</sup> It also underscores how proposed investments in R&D-  
1288 estimated to be US\$8.7 billion over the next 4 years<sup>134</sup> represents an excellent ROI. If new tools were  
1289 developed that would enable reaching WHO's targets, it is estimated that the ROI of each dollar,  
1290 depending on the value per DALY and the assumed discount rate, would be \$16-82<sup>318</sup>.

1291

### 1292 **2.3 Reaching global TB R&D goals**

1293 Despite powerful public health and economic rationales for investing in TB R&D—essential for producing  
1294 breakthrough technologies and strategies to end TB, as outlined above—a significant gap in financing  
1295 remains. There are many reasons for this, including the lack of financial incentives to produce new tools,  
1296 the cost and duration of clinical trials, and the lack of compelling demand by affected countries. It is a  
1297 slow and quiet killer compared to malaria and HIV, and few new interventions have been demonstrated  
1298 to be successful. Global funding for TB product development was US\$726 million in 2016,<sup>262</sup> a mere  
1299 one-third of the annual funding called for by the Stop TB partnership, and far less than is desirable to  
1300 achieve the kinds of R&D breakthroughs that have characterized HIV research over the last two  
1301 decades.<sup>134</sup> Modelling analyses have suggested that current funding levels may be sufficient to realize  
1302 some key, near-term successes, e.g., a triage test and regimens for DR- TB based on repurposed drugs,  
1303 but that a multiple of current levels funding – but perhaps a substantial multiple - is needed to enable  
1304 the development of truly transformative treatments and prevention tools (e.g., an incipient TB test, new

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1305 vaccines).<sup>301,302</sup> Closing the funding gap of at least US\$1.3 billion per year will require high-income  
1306 countries to sharply increase their investments in TB R&D, in tandem with increased efforts from LMICs,  
1307 particularly BRICS, as well as the development of creative funding models that enhance industry  
1308 commitments.

1309

1310 Currently, 89% of investment in TB R&D comes from non-commercial sources — that is, governments  
1311 and philanthropies. US public agencies alone support 44% of all TB-related research globally.<sup>262</sup> Only a  
1312 small fraction of the public funding for TB R&D comes from LMICs.<sup>303</sup> Increasing contributions from LMIC  
1313 governments so that their total share of TB R&D matches their share of the global economy (i.e., 36.5%),  
1314 as has been proposed by a WHO expert group, would generate an additional US\$146 million per year, a  
1315 26% increase in total global R&D financing. Given that late-stage clinical trials represent a critical funding  
1316 bottleneck, a self-funded BRICS/LMIC clinical trials network, which is focused on bringing innovative  
1317 tools through the regulatory pipelines, would be another way for high-burden countries to carry a  
1318 greater share of the TB R&D costs. It would be possible to increase public contributions further if some  
1319 HICs (or philanthropies) were willing to *match* increased contributions from LMICs, as Switzerland  
1320 offered to do in order to stimulate LMICs to contribute financing for several WHO-selected R&D projects  
1321 in 2014.<sup>304</sup> This type of “matching grant” could increase total R&D to US\$861 million per year, a 52%  
1322 increase over the status quo (Appendix Table xx). Matching funding from international donors and high-  
1323 burden countries could also ensure TB R&D is more ‘needs driven’ and address the problem of ‘free-  
1324 riding’, whereby countries withhold resources as long as others cover the costs.<sup>305</sup>

1325

1326 Meanwhile, industry investment in TB R&D has stagnated, while R&D for other infectious diseases have  
1327 seen meaningful funding increases.<sup>262</sup> UNITAID, through small taxes on international air travel is an  
1328 increasingly important source of funding for TB R&D, providing US\$215 million in 2018 for a variety of  
1329 innovative research projects. However, more creative models to secure private investment,  
1330 collaboration and partnership are needed to close the funding gap. Examples include the TB Drug  
1331 Accelerator, a collaboration between pharmaceutical companies and research institutions, which has  
1332 had several early successes in addressing the shortage of new TB drugs by funding early-stage TB drug  
1333 discovery,<sup>306</sup> and the Global Health Innovative Technology Fund (GHIT) model, a Japanese government  
1334 funding mechanism that leverages matched funding from industry.<sup>307 308</sup> Other funding mechanisms  
1335 including ‘downstream investments or ‘pull’ strategies (that promise reward for successful product  
1336 development) have been successful in the pneumococcal vaccine development, and have potential

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1337 role in funding TB R&D.<sup>309</sup> The Life Prize (Appendix Panel xx) offers a novel model to stimulate drug  
1338 development, rewarding researchers and developers fully and upfront for their investments, thereby de-  
1339 linking the financing of R&D from product prices and sales and promoting access and affordability as  
1340 well as appropriate use of resulting products.

1341  
1342 While these various options could represent an important increase, funding will still be far short of the  
1343 US\$2 billion annual target. This shortage highlights the inescapable conclusion that HICs must contribute  
1344 more. To ensure the necessary increased investment from HICs, TB R&D must be understood as an  
1345 important global public good that will yield substantial economic dividends, as we highlight in Section 3.  
1346 Greater investment is also essential to address negative cross-border externalities that TB, particularly  
1347 DR -TB, poses and as central focus of the broader antimicrobial resistance research agenda. Hence,  
1348 strong advocacy for increased R&D funding to science ministries and research-oriented pharmaceutical  
1349 companies must occur in tandem with advocacy to international donor agencies.

1350



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### 1351 **Section 3: Sustainable financing for TB**

1352 Everyone dedicated to achieving an end to TB – impacted countries, donor nations, the private sector,  
1353 foundations – must redouble their efforts to finance strategies that are working now and, more  
1354 importantly, strategies that have the real potential to make a significant impact in the coming years. To  
1355 end TB, this Commission advocates for substantially more investment in all aspects of TB programming.  
1356 Increased domestic resource mobilization will be especially important, but new models of donor  
1357 financing that can catalyze domestic investment must also be a priority. Evidence on the cost-  
1358 effectiveness and benefits of expanded financing for tuberculosis control suggests that such investments  
1359 will yield a high return.<sup>310</sup>

1360

### 1361 **3.1 Economic evaluation of TB control interventions**

#### 1362 **3.1.1 The basics of TB economics**

1363 In this section we will distill a highly heterogeneous literature<sup>311</sup> into indicative values of key economic  
1364 parameters. The section will focus on two such parameters: the cost required to avert a TB death and  
1365 estimates of benefit to cost ratios for TB control efforts. An additional important question is that of the  
1366 cost required to meet goals and we provide an approximation that is broadly consistent with this  
1367 Report's goal of reducing the global TB death rate by 90% compared to 2015 levels, estimated to be 2  
1368 per 100,000. Such estimates of cost are intimately bound with questions of revenue generation or  
1369 finance and are dealt with in the finance section of this report. Benefit to cost and cost effectiveness  
1370 ratios in this section will be generated under the same sets of assumptions as are the total cost  
1371 estimates of the domestic finance section (section 3.2).

1372

#### 1373 **3.1.2 Costs per death averted**

1374 The literature<sup>312</sup> contains multiple estimates of different indicators of program effectiveness for  
1375 different interventions in different environments and with different assumptions about how much in the  
1376 way of health system strengthening costs should be included in the cost estimates. The literature is far  
1377 less well developed in assessing to whom costs and benefits accrue, distributional questions. The  
1378 diversity of the literature poses problems for the high-level message objective of a report like this, but at  
1379 the same time it provides multiple valuable starting points for analysts with different objectives and  
1380 interests. Such estimates meet the objective of positioning our thinking even though the numbers  
1381 themselves make no claim to portray any particular set of conditions.

1382

1383 **3.1.3 The ratio of benefits to costs for TB control**

1384 Benefits are estimated using methods that are standard in many governments' (and the OECD's)  
1385 guidelines for economic evaluation of projects.<sup>311</sup> Within the OECD structure, this Report uses the  
1386 conservative (low) value of 0.7% of per capita income as the value of reducing mortality risk for an  
1387 individual by 1/10,000 for one year. Although these results have been generated for this report using  
1388 conservative assumptions, the estimates here suggest that recent economic analyses undertaken by the  
1389 consulting firm KPMG,<sup>313</sup> estimating cost of failing to respond to the TB epidemic, did not fully capture  
1390 the value gained from successful TB interventions. Rather than convey a highly heterogenous range of  
1391 estimates, we chose instead to rely on recent efforts to aggregate the literature.<sup>5,94,252</sup> These efforts  
1392 provide estimates of cost per death averted that are typically stated implicitly rather than explicitly  
1393 (Table 6). Acknowledging major heterogeneity and uncertainty, it is reasonable to think that the cost  
1394 per death averted from drug sensitive TB would be in the range of US\$5,000-10,000 and for DR-TB,  
1395 US\$15000-20,000.

1396

1397 Using US\$7000 as an approximation of the cost per TB death averted and the 0.7% of GDP approach to  
1398 valuation, we arrive at a benefit-to-cost ratio for TB interventions of 7:1. This figure reflects the Stop TB  
1399 estimate<sup>314</sup> in Table 6 for multi-intervention programs required to sharply reduce TB mortality and  
1400 hence can be viewed as an average across the range of required interventions. Other estimates have  
1401 been higher.<sup>312,315</sup> And as noted, KPMG found much lower (although still attractive) values using a very  
1402 different methodology. Uncertainty concerning a specific value abounds. But no serious uncertainty  
1403 attaches to the conclusion that the value of benefits exceeds the value of costs by more than a factor of  
1404 2 or 3.

1405

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### 1406 **3.1.4 Costs of ending TB in a generation**

1407 As TB incidence declines over time, both because of expanded control efforts and (probably) favourable  
1408 trends in poverty and other risk factor reduction, it is reasonable to project declines in needed  
1409 expenditure to keep TB deaths at very low levels. Initially, if TB deaths were to be reduced by 90% from  
1410 the current level of 1.7 million per year to under 200,000 per year the additional expenditure required  
1411 would be on the order of:

1412

1413 1.5 million deaths per year averted x US\$7,000 per death averted  $\approx$  US\$ 10 billion per year

1414 Obviously, it would be impossible to scale up within a few years and early investments will yield  
1415 reduction in cases and costs. However, a plausible cost trajectory for ending TB in our generation would  
1416 be a rise from current expenditure by, perhaps US\$5 billion per year, followed by a reduction to a long-  
1417 term level of US\$1 to 2 billion per year by the early 2040s. This number reflects a reduction in incidence  
1418 and hence treatment costs that ending TB mortality will require. This Commission makes no attempt at  
1419 precision concerning this number in the belief that our basic understanding of the relevant determinants  
1420 of cost remain highly imperfect: expressing precise numbers is more likely to mislead than inform. That  
1421 said, these numbers provide a reasonable approximation of the magnitude involved.

1422

### 1423 **3.2 Domestic Financing for TB**

1424 Section 3.0 makes the case for the economic benefits of investing in TB. In this section, we examine the  
1425 extent to which TB programmes currently rely on domestic sources of finance in high- burden countries;  
1426 and the influence of domestic financing on the sustainability, efficiency, and equity of TB funding. In  
1427 addition, we explore the potential for rapidly increasing domestic financing for TB in the coming five  
1428 years. Finally, we highlight the importance of investing in NTPs, and other domestic funding agencies of  
1429 TB services, to allocate, distribute, and manage domestic TB resources; recognizing that it is essential to  
1430 develop the capacity to ensure increased financing is spent effectively to end the epidemic.

1431

#### 1432 **3.2.1 The pivotal role of sustained domestic financing for TB**

1433 Improved domestic financing for TB is one of the success stories in global health over the past two  
1434 decades. By 2017, 84% of funding for TB came from domestic sources. This high proportion reflects a  
1435 consistent pattern of increased commitment to TB from high-burden countries. From 2007 to 2017,  
1436 global funding for TB doubled, with much of the increase coming from Brazil, Russia, India, China, and

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1437 South Africa (BRICS). On average, the BRICS have domestically financed 95% of their public TB  
1438 expenditures over the past decade <sup>316</sup>.

1439  
1440 Outside of the BRICS, the picture of domestic funding for TB is complex, reflecting a general scarcity in  
1441 health sector resourcing and capacity. In 2017, less than half of public funding for TB in low-income  
1442 countries came from domestic sources. Nonetheless, the trend over time is promising; on average, low-  
1443 income countries doubled their domestic financing of TB between 2007 and 2017, with a rate of  
1444 increase similar to that of international TB funding to their countries<sup>317</sup>. Not all low-income countries are  
1445 following this trend, and there is room for improvement: the current proportion of the domestic  
1446 contribution to public TB expenditure ranges from under 1% to 24%<sup>317</sup>. Likewise, in lower-middle income  
1447 countries, the proportion of domestic public funding ranges from 7% to 88%<sup>317</sup>, with the average  
1448 growth in domestic TB financing stable until 2013, but doubling since then.

1449

### 1450 **3.2.2 Who provides domestic finance, and how does it flow to TB?**

1451 TB expenditures can be divided into those that flow through general health service provision and those  
1452 that flow through National Tuberculosis Programmes (NTPs). While the proportional domestic  
1453 contribution to overall TB expenditure is generally high, NTP specific expenditure and TB-specific  
1454 commodities are more reliant on international finance. In 23 of the 30 high-burden countries, NTPs  
1455 receive more than 80% of their funding externally<sup>317</sup>, with the Global Fund being a substantial payer for  
1456 TB commodities. This apparent dependency of NTPs on international finance has most likely arisen due  
1457 to disease specific allocation of international funds, rather than reflecting an overall lack of domestic  
1458 commitment. Ministries of Finance inevitably reduce domestic resource allocation to TB to the extent  
1459 that they perceive international finance to be available.

1460

1461 Domestic financing for TB within countries can come from a range of sources. Ultimately it is  
1462 populations and corporate taxes who pay, but TB patients still face much of the burden in some  
1463 countries. Despite the policy of free or reimbursed TB care in most countries, patients with TB can still  
1464 incur substantial out-of-pocket payments for public TB services <sup>248</sup>. Moreover, in several high-burden  
1465 countries, large proportions of patients seek and receive TB care in the private sector, paying for their  
1466 own care and treatment. Subsidizing and pooling these private domestic expenditures, an important  
1467 goal of broader UHC agenda, will have beneficial consequences in terms of financial risk protection<sup>318,319</sup>  
1468 and possibly health outcomes<sup>320</sup> for those with TB.

1469

1470 **3.2.3 Is the allocation of domestic finance to TB efficient?**

1471 Although many countries have increased their allocation of public monies to TB, a mismatch remains  
1472 between funding levels and need, the latter defined in terms of the resources required to reach global  
1473 End TB targets<sup>317</sup>. From a domestic public finance perspective however, need is not a sufficient criterion  
1474 to increase investment. Ministries of Finance will have requests to fund many other development and  
1475 health interventions that have potentially high returns. Hence, those advocating for increased  
1476 investment in TB, both within and external to governments, need to demonstrate that investment in TB  
1477 performs well, at the very least compared to other health sector investments. Investments in TB hence  
1478 need to be efficient, defined as maximising population health for any given level of funding.

1479

1480 Increasingly countries are developing public finance processes that formally assess the return on  
1481 investment of different health sector interventions, rather than relying on global evidence. These  
1482 processes are being supported by improved data and understanding of the costs, effectiveness, and  
1483 long-term impacts of investment in TB on both health and economic outcomes.<sup>321</sup> In the main,  
1484 supporting these efforts often work in favor of TB. In Malawi for example, a recent assessment to  
1485 determine the essential package of health care found that seven of the top 10 ‘best buys’ for health  
1486 sector budget prioritization were TB interventions.<sup>322</sup> This mirrors systematic reviews of return to  
1487 investment of TB expenditures across several countries.<sup>146</sup> supporting the assertion that increasing  
1488 domestic allocation to TB can improve the efficiency of the entire health sector.

1489

1490 There is, however, room to improve the efficiency of TB expenditures, through improvements in the  
1491 delivery and implementation of TB services, as highlighted in Section 1. In some countries the split of TB  
1492 expenditures on TB commodities versus general service provision may not be optimal. Improvements in  
1493 health system strengthening are critical to ensuring that health staff at the front end of TB service  
1494 delivery receive the right mix of resources to provide high-quality patient-centered TB services<sup>323</sup>. Some  
1495 countries also have higher than average TB treatment costs, due to the over hospitalization of TB  
1496 patients, in particular those with DR-TB. Nonetheless, the decentralization of DR -TB care in South Africa  
1497 illustrates the substantial additional funding that may be generated by reducing hospitalization for  
1498 patients, including those requiring intensive treatment for DR-TB<sup>324</sup>. Improved integration of TB  
1499 services may also support patient-centered care and reduce costs<sup>325</sup>. Several new TB technologies, such  
1500 as shortened regimens, may reduce the costs substantially. More analyses on the efficiency of these

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1501 different approaches to scaling up TB services is necessary to help guide how countries can spend  
1502 funding effectively.<sup>326</sup>

1503

### 1504 **3.2.4 Can domestic funding for TB be substantially increased in the next five years?**

1505 Generating additional domestic financing for TB depends on: governments' commitment to allocate  
1506 more funding to TB; the future potential for efficiency gains; and increases in the overall level of  
1507 available public finance. Increases in domestic financing for TB in the past two decades demonstrate  
1508 that countries experiencing GDP growth may be able to expand their funding of TB rapidly, and at the  
1509 same time reduce TB incidence<sup>327</sup>. In addition, the ability to raise domestic finance for TB from private  
1510 individuals and firms depends on the system of revenue generation and taxation structures. In recent  
1511 years, a range of innovative mechanisms, including earmarked taxation of alcohol and cigarettes,  
1512 government loan buy downs, in which a third party contributes to loan payment to open up social  
1513 spending and the expansion of health insurance coverage, have been explored to improve the financial  
1514 sustainability of the health sector, with positive consequences for population health <sup>328</sup>. These  
1515 mechanisms have yet though to provide substantial funding for HIV,<sup>328</sup> and there are considerable  
1516 questions as to their feasibility to raise high levels of funding for TB.

1517

1518 Conducted in collaboration with the Lancet Commission, a team at the London School of Hygiene &  
1519 Tropical Medicine (LSHTM) and UCSF conducted an analysis examining the potential fiscal space for TB  
1520 for 28 of the 30 high-burden countries over the next five years (two countries excluded due to data  
1521 scarcity). Fiscal space analyses apply international public financing norms to current fiscal performance  
1522 to determine the extent to which funding can grow in a way that does not damage overall fiscal stability.  
1523 The financing sources examined included GDP growth, increasing public revenues, improving allocation  
1524 to the health sector, improving allocations to TB, and increasing the efficiency of public TB service  
1525 delivery. The researchers found that most high-burden TB countries can substantially increase public  
1526 domestic financing of TB. By 2023, countries such as Bangladesh, Zambia, China, and Indonesia can  
1527 potentially increase their annual TB expenditures more than five-fold, through a combination of  
1528 optimized resource allocation, revenue generation and improved resourcing of the health sector (Figure  
1529 10). In countries like Zambia, increased prioritization and efficiency of TB services would enable the  
1530 greatest resource mobilization for TB. In countries like Bangladesh, China and Indonesia, governments  
1531 will need to commit to substantial policy action around revenue raising, such as increasing tobacco  
1532 taxation and the increased pooling of health sector funds. Despite the potential impact of tobacco

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1533 taxation highlighted in this analysis, we acknowledge the limitations of raising tax in the short term and  
1534 advocate for optimized resource allocation and improved resourcing of the health sector as the most  
1535 sustainable means of increasing financing for TB.

1536

### 1537 **3.2.5 Policy Implications**

1538 In summary, mobilizing domestic resources for TB will take policy action and commitment across  
1539 government, including Ministries of Finance and Ministries of Health. Increasing tobacco taxation and  
1540 allocating those revenues to health is a clear policy action that can support financing TB elimination and  
1541 have positive benefits for persons with TB, but is a long term public health objective. Increasing  
1542 domestic public financing for TB in a manner that protects TB patients from catastrophic expenditures is  
1543 particularly important, and also serves a broader UHC agenda.

1544

1545 However, it should not be assumed that high level commitment to this broad policy agenda is sufficient.  
1546 Rapid increases in domestic financing for TB will require enhanced capacity to allocate and spend  
1547 resources effectively and transparently to demonstrate results. A clearly defined accountability  
1548 framework to ensure commitments made at the high level meeting will be critical. In addition, NTPs  
1549 need to strengthen their 'absorption' capacity, otherwise the the rate at which additional financing is  
1550 disbursed in practice may be slow. The experience of HIV demonstrates it is possible to rapidly  
1551 strengthen programmes, but that strong systems are required to ensure efficiency and maximise health  
1552 outcomes. Effective, rapid disbursement will depend on the capacity of NTPS to mobilize expertise,  
1553 infrastructure, and sufficient human resources in a timely manner. Upfront support to NTPs to build the  
1554 mechanisms to absorb new funding, and fully participate in resource allocation and management  
1555 systems and processes within the health sector, will therefore be critical to ensure additional resources  
1556 are used. The commitment of many HBCs over the past two decades is commendable, and many have  
1557 the space and willingness to do more, but achieving real increases in expenditures, beyond the current  
1558 rate will require concerted attention by all those working to end TB to absorb additional resources  
1559 effectively.

1560

1561

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### 1562 **3.3 Donor Financing for TB**

#### 1563 **3.3.1 Donor investments in TB**

1564 The potential for increased domestic health spending, economic growth, as mentioned in Section 3.1,  
1565 along with the recent rise of populism and protectionism,<sup>329</sup> will inevitably shape external financing for  
1566 TB programs over the coming decade. Nearly all high-burden countries can substantially increase  
1567 domestic resources allocated to TB. While many low-income countries still require donor financing for  
1568 TB, new opportunities exist to re-think how and where donor financing is allocated such that its impact  
1569 is maximal. In this section of the report, we discuss the role of donor financing to catalyze domestic  
1570 efforts and invest in global public goods, especially in those countries transitioning out of donor finance  
1571 eligibility. In addition, we highlight the potential benefits to donor partners of investing in TB,  
1572 economically and in terms of addressing the negative cross-border externalities that TB, especially DR-  
1573 TB poses. Finally, we underscore the importance of sustained financing for the poorest countries and  
1574 advocate for continued investment to end the epidemic in those countries.

1575

#### 1576 **3.3.1 Who is investing in TB programs?**

1577 According to the OECD's Creditor Reporting System, international donors provided US\$871 million for TB  
1578 prevention, diagnosis, and treatment in 2016 (the latest year for which data are available), 69% of this  
1579 was expended by the Global Fund, of which the United States (US) was the major contributor.<sup>5</sup> In  
1580 addition, the US disbursed US\$179 million channeled via its own agencies and other institutions.  
1581 Between 2006 and 2016, approximately 46% of international donor expenditure for TB originated in the  
1582 US.<sup>5</sup> The next largest contributors were France (10%), the United Kingdom (9%) and Germany (6.2%).<sup>5</sup>  
1583 According to the Institute for Health Metrics and Evaluation (IHME), The Bill and Melinda Gates  
1584 Foundation was the largest non-state funder of TB activities, responsible for US\$204 million of  
1585 disbursements in 2016, including \$68 million allocated to the Global Fund, while other sources private  
1586 philanthropy spent \$70 million, of which 14% was allocated to the Global Fund.<sup>330</sup>

1587

1588 Development assistance for health (D.A.H) for TB has increased from US\$30 million in 1990 to well over  
1589 US\$1 billion in 2016, underscoring the substantial increases in international financing that have  
1590 occurred over that period, as well as the relative contribution of foundations, development banks, the  
1591 Global Fund and traditional bilateral funding. Nonetheless, current levels of funding for TB still fall very  
1592 far short of the annual US\$2.6 billion proposed in the Global Plan to End TB, outlined by the Stop TB  
1593 Partnership.<sup>134</sup>



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1594

### 1595 **3.3.2 How is donor finance being used?**

1596 Analyses of donor financing for health have traditionally tracked flows by funding source, channel,  
1597 recipient, and disease. For this Commission, a team at UCSF and Duke University conducted an analysis  
1598 of development assistance for health (DAH) for TB broken- down into functions (Annex xx and yy).<sup>331</sup>  
1599 Global functions refers to transnational topics, including supporting global public goods such as R&D,  
1600 managing cross-border disease spread and fostering leadership and stewardship. The researchers  
1601 analyzed DAH for TB in the year 2015, using the OECD Creditor Reporting System, which provides  
1602 detailed information on aid expenditure.<sup>332</sup> They found that in 2015, US\$932 million in DAH was directed  
1603 towards TB-related activities. Half of DAH for TB was disbursed to to lower MICs, 22% to LICs, 4% to  
1604 upper MICs, 23% to bilateral unspecified activities, and a small portion (0.4%) to regional efforts. Only  
1605 about one-quarter (24%) of DAH for TB was for global functions, supporting product development (17%),  
1606 population, policy and implementation research (PIIR) (3%), advocacy and priority setting (2%), and  
1607 other global public goods (Figure 11). Around three-quarters (76%) of DAH for TB supported country-  
1608 specific functions, including TB programs for care delivery (52%) and health system strengthening  
1609 (24%). Almost all (96%) of the health system strengthening support was TB specific, with only 4%  
1610 directed at system-wide, cross-cutting health system strengthening. These allocations highlight that  
1611 donor funds are being primarily targeted to support country-specific activities, especially those countries  
1612 with the highest burden, rather than focused on global public goods. The policy implications of these  
1613 findings are discussed below.

1614

### 1615 **3.3.3 Policy implications**

1616 To our knowledge the analysis outlined above is the first to determine how much TB-specific DAH is  
1617 devoted to supporting global functions versus country-specific functions. Notably, this analysis does  
1618 not shed any light on trends in TB funding or how country-specific TB program funding is disaggregated  
1619 between DR-TB and DS-TB control efforts or provide granularity with DAH differs by disease burden or  
1620 country income group. Nonetheless, the findings highlight the need to increase investment to support  
1621 Global TB functions, in addition to country-specific functions. Although our baseline analysis cannot  
1622 prove that global functions are being neglected, prioritizing funds to these global functions should be  
1623 considered, especially as domestic resource allocation for TB increases. In particular, this Commission  
1624 asserts that donor financing should increasingly be focused on the following functions (Appendix Table  
1625 xx):

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1626

### 1627 **Global Functions**

1628 *Supplying global public goods (GPG)* - Greater investment in global public goods, in particular TB R&D  
1629 for new drugs and technologies, are likely to bring important economic benefits and have a  
1630 disproportionately beneficial impact on health outcomes in low- and middle-income countries.<sup>93</sup> New  
1631 tools deriving from TB R&D are also likely to provide financial protection and be most beneficial to the  
1632 poorest-members of society, as shown by “extended” cost-effective analyses.<sup>319</sup> The investment in HIV  
1633 R&D over the last two decades, leading to over thirty new drugs and numerous diagnostic and  
1634 preventive technologies, provides compelling evidence for greater investment in TB R&D.<sup>256</sup>

1635

1636 *Market-shaping activities* The Global Drug Facility (GDF), an arm of the Stop TB Partnership, serves an  
1637 important function in this capacity, using donor financing to consolidate demand from different  
1638 countries to negotiate lower prices for TB drugs, attract additional suppliers, and incentivize innovation,  
1639 in particular for more expensive second-line agents and pediatric medicines.<sup>333-335</sup> These kinds of  
1640 activities will remain important as countries increasingly assume co-financing and/or transition out of  
1641 donor eligibility, as they may have difficulty negotiating lowest possible prices or accessing concessional  
1642 prices for diagnostics. As countries move away from donor funding, the global market for TB medicines  
1643 and diagnostics will surely become much more fragmented and the need for a global TB market  
1644 steward, such as GDF, will become more important. In addition, the importance of GDF to facilitate  
1645 uptake of new diagnostic and therapeutic tools will also be essential as investment in R&D yield greater  
1646 successes in the coming years.<sup>336</sup>

1647

1648 *Exercising leadership and advocacy* - An important, albeit often neglected global function of aid relates  
1649 to investment in health advocacy and priority setting. This includes but is not limited to donor financing  
1650 to support civil society organizations (CSOs) as important catalysts for change. While donor partners  
1651 have increasingly committed to supporting community engagement efforts over the last decade,<sup>337</sup> CSOs  
1652 continue to lack recognition as legitimate partners at national levels, their impact undermined by lack of  
1653 resources for community initiatives.<sup>338</sup> Recognizing that funding for HIV advocates and activists has been  
1654 crucial to global HIV efforts,<sup>339,340</sup> this Commission affirms the importance of increased funding for TB  
1655 advocates as a global public good, deserving investment commensurate with the part they plays in  
1656 improving health outcomes.

1657

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1658 Consideration should be given to increased investment in WHO’s Global TB Program, given its important  
1659 role in facilitating uptake of new policies, strengthening surveillance systems and providing technical  
1660 assistance. A better-funded WHO would enable it to fulfill those functions more effectively.<sup>329</sup>  
1661 Independent regional initiatives such as those established to tackle malaria,<sup>341</sup> that can provide locally-  
1662 relevant, agile and responsive support to high burden countries may also be worthy of donor  
1663 investment.

1664

### 1665 **Country specific functions**

1666 Targeted investment is needed for countries graduating from DAH. Presently, 54% of country-specific  
1667 aid in our analysis is directed towards high burden, middle-income countries, many of which will soon be  
1668 ineligible for donor financing; based on their national GDP per capita, they are becoming ‘too rich’ to  
1669 qualify for DAH. Unfortunately, many of these countries are likely to have large pockets of poverty and  
1670 avertable mortality from TB. Here we propose targeted investments directed to social insurance  
1671 schemes that protect those at highest risk for TB. Furthermore, we argue that sustained funding in  
1672 many of these countries, especially those with a significant DR- TB burden, is warranted given the global  
1673 security implications of failing to ensure TB control in these settings:

1674

1675 *DR-TB and management of cross-border externalities* – As highlighted in Section 1, the high cost of  
1676 treatment for DR -TB, especially in middle-income countries<sup>248</sup>, has been a significant barrier to scaling  
1677 up treatment provision to date, and the cost will continue to rise over the coming years.<sup>55</sup> Donor  
1678 partners, especially the Global Fund, are already investing disproportionately in DR- TB control activities.  
1679 Nonetheless, given the substantial weight of data demonstrating extensive cross-border spread of DR-  
1680 TB, <sup>342-352</sup> DR- TB poses perplexing economic and health security issues for donor countries. It is  
1681 important that sustained funding for DR -TB control efforts, even in countries that will be soon  
1682 ‘graduating’ out of ODA eligibility, be sustained to mitigate the cross-border threat that DR- TB poses.  
1683 Aligning DR- TB control efforts with the broader AMR agenda is also essential to maximize investment;  
1684 unchecked TB will be the single biggest cause of antimicrobial resistance related deaths by 2050.<sup>353</sup>

1685 Funding for multisectoral, regional

1686

1687 *Protecting risk pools* – Prisoners, people living with TB/HIV coinfection, migrants, refugees and  
1688 indigenous populations are all highly vulnerable to TB, and experience significant marginalization,  
1689 decreased access to quality services, and human rights violations. These communities will continue to

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1690 benefit from donor support, for example, through support for social health insurance schemes that  
1691 include TB services,<sup>319</sup> even as domestic resources for health are increasing.

1692

1693 *Co-financing and catalytic funding* - In addition to *where* DAH is spent, *how* it is spent is also crucial to  
1694 guaranteeing the impact of donor support. Catalytic investments, such as those supported by the Global  
1695 Fund, offer examples of how new models of financing, through use of matching funds to incentivize  
1696 country allocation for priority areas, or multicounty funding mechanisms that address specific priority  
1697 areas such as developing innovative approaches to accelerate active case finding and scale up new tools  
1698 or facilitating re-tooling initiatives as new drugs and diagnostics become available.<sup>354</sup>

1699 Notwithstanding the need for better data assessing the impact of these funding mechanisms, co-  
1700 financing solutions provide an important pathway to ensure greater country ownership while also  
1701 ensuring sustained funding for TB activities even during the transition process.

1702

1703 Ongoing support is needed to help the poorest countries. By 2035, there are still likely to be around two  
1704 dozen low-income countries that will require direct country assistance for years to come.<sup>4</sup> Donor  
1705 financing for these countries needs to increase substantially to make up for funding shortfalls over the  
1706 last few years. Despite a small increase in funding between 2016 and 2017, it still fell *very far* short of  
1707 the annual \$2.6B in DAH that is needed for TB according to the Global Plan.<sup>5</sup> The moral imperative of  
1708 sustained donor investment in these countries should be highlighted – millions of individuals will  
1709 potentially die from TB in these countries without external assistance. In addition, the scale of the  
1710 impact of those avoidable deaths on the global economy is substantial, as our analysis in section 3.0,  
1711 highlights. Investing in TB control will reap economic dividends that will likely benefit both donor and  
1712 recipient nations. Underscoring the importance of investing in TB as an important tracer for progress  
1713 towards UHC<sup>64</sup> should also inform how and where donor funds are allocated. As global momentum  
1714 builds towards achieving UHC, investment in TB as a disease of poverty is imperative to that progress.

1715

### 1716 **3.3.4 A new era of shared responsibility**

1717 The UN HLM declaration, and the stated commitment to shared responsibility highlighted how  
1718 priorities and approaches to TB financing are evolving. We are entering a new era of increased country  
1719 ownership and global cooperation.<sup>329,355</sup> In addition, the architecture of donor financing for TB is  
1720 changing as high-burden countries mobilize additional resources for TB control. Leveraging  
1721 concessional loans from development banks<sup>356</sup> and innovative financing mechanisms (e.g. social impact

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1722 bonds, loan guarantees)<sup>134,329</sup> should have an increased role. Such financing solutions have great  
1723 potential, but they are no panacea.<sup>357</sup> Strategies that can help increase domestic investment are crucial.  
1724 Even in low-income countries still reliant on donor support, the nature of donor-recipient financing must  
1725 evolve. Partnership agreements between donors and recipients, as a tool to ensure ownership,  
1726 accountability, and transparency, should be encouraged. By this mechanism, donors could also help  
1727 unlock domestic resources, by committing funds that pair global and national resources for shared  
1728 priorities.<sup>358</sup> New models of donor financing that focus on results, encourage innovation and strengthen  
1729 government accountability to citizens rather than donors are also necessary. One promising example of  
1730 a new financing strategy, is the USAID's Global Accelerator to End TB which was launched in September  
1731 2018. The Accelerator will seek to link financial support with performance-based measurements in  
1732 order to maximize resources, while also leveraging additional resources from countries, private sector  
1733 partners and other local organizations.<sup>359</sup> In addition to new funding mechanisms, new funding  
1734 partners, such as multinational business and corporate philanthropists, should be encouraged to close  
1735 TB funding gaps. The opportunity for legacy impacts at national and global level, an oft-cited motivator  
1736 of such funders, will increase as TB elimination efforts become tangible.  
1737

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### 1738 **Section 4: Creating the enabling environment to end TB**

1739 In Section 4 we highlight the importance of an enabling environment to each country's success in  
1740 responding to TB. Figure 12 provides a framework for operationalizing country-owned responses to  
1741 drive progress towards ending TB and to leverage good practices in the TB response to advance other  
1742 Sustainable Development Goals. This framework represents an idealized response and illustrates  
1743 mutually reinforcing functions performed by state and global actors. These functions are person-  
1744 centered, rights-based, and data-informed. The priority is ensuring high quality care for persons with TB  
1745 who present followed closely by a focus on active case-finding strategies and TB prevention  
1746 interventions targeted at high-risk groups. A strong TB response needs to be guided by country-owned,  
1747 multisector and multi-stakeholder coordination, accountability and good governance at all levels to  
1748 achieve sustained long-term efforts. Civil society is a vital constituency to ensure that TB programs and  
1749 stakeholders are held accountable at global, national and subnational levels. In addition, the  
1750 framework underscores the importance of addressing TB as a core component in achieving UHC. While  
1751 countries are in varying stages of progress towards UHC, for high TB burden countries, prioritizing  
1752 investments in TB to realize UHC will be critical. UHC, backed by donor assistance when needed, also  
1753 offers an opportunity to tackle TB with multisectoral initiatives that are consistent with the principles of  
1754 the Sustainable Development Goals.

1755

#### 1756 **4.1 Ending TB is important on the pathway to achieving UHC**

1757 As this report highlights, progress towards ending TB ideally will occur together with achieving UHC.  
1758 UHC means all people have access to high-quality health services—at a minimum, health promotion and  
1759 primary care—at no or little cost at the point of service. This Commission asserts that ending the TB  
1760 epidemic must involve strong national TB programs that can prioritize specific TB care and prevention  
1761 functions within a progressive universalist pathway to UHC. This pathway is a publicly financed  
1762 approach covering those core health-care services that directly benefit the poor, who are  
1763 disproportionately affected by TB.<sup>360</sup> To this end, TB care and prevention functions should be addressed  
1764 specifically and included within essential service packages.<sup>361,362</sup> Social insurance models that prioritize  
1765 diseases that disproportionately affect low-income and other vulnerable populations will automatically  
1766 incorporate TB. To realize the End TB targets, this Commission proposes to reach populations at highest  
1767 risk for TB early in the roll-out of such schemes. In countries with high TB burdens, maintaining a  
1768 separate TB budget and program within a broader UHC framework typically will prove efficient. Even as

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1769 the TB burden declines, ensuring that TB programs maintain a very visible position within primary care  
1770 budgets and Ministry of Health activities is advocated

1771  
1772 Several other system-wide frameworks are integral to a TB-inclusive UHC agenda. These include  
1773 ensuring the uninterrupted availability of and access to appropriately regulated TB medications and  
1774 diagnostic tests, strong information and performance systems and new or merged risk financing  
1775 pools.<sup>363</sup> Regulation should address how medical products are subsidized as well as the types of medical  
1776 professionals authorized to prescribe or dispense TB medicines. High-burden countries will also need to  
1777 establish an optimal mix of skilled health workers to deliver services, and to design appropriate pay  
1778 incentives for health professionals to support scaling up the TB response as well as a broader UHC  
1779 agenda.<sup>364</sup> Robust information systems that are sensitive to TB indicators<sup>365</sup> and infection control  
1780 measures in health facilities are important.<sup>154</sup> In addition, technical solutions applied to TB programs,  
1781 such as network optimization and quality management, as highlighted in Section 1, are necessary to that  
1782 UHC agenda, and underscore how success in ending TB is tied to each country's success in ensuring high  
1783 quality health for all.<sup>366</sup>

### 1784 1785 **4.2 Social protection**

1786 The adverse financial consequences of TB on households resulting from lost income during long periods  
1787 of illness can be profound and long-lasting, as illustrated in Panel 3 To reduce the risk of  
1788 impoverishment from TB requires policies that protect patients and their households against ruinous  
1789 financial costs associated with TB.<sup>34</sup> Especially in those settings where private sector care predominates,  
1790 strategies must be adopted that ensure financial protection and adequate quality of care, in both public  
1791 and private sectors. This Commission argues that, as part of the UHC agenda, public finance should be  
1792 extended to private providers for TB care, and that private finance in public facilities (user fees) should  
1793 be minimized. Beyond public financing of treatment and case-finding, many TB patients also may need  
1794 economic and social support. These measures, particularly, social support, can enhance treatment  
1795 adherence and positively affect clinical outcomes.<sup>142</sup>

1796  
1797 Social protection interventions—policies and programs designed to protect individuals from social and  
1798 economic risk<sup>367</sup>—are a promising approach to improving TB outcomes<sup>368,369</sup> and achieving these larger  
1799 policy goals. Examples include cash transfers and nutrition programs offered as part of national policies.  
1800 Such interventions can contribute to successful TB outcomes indirectly by addressing social, biological,

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1801 and structural determinants or directly by enabling access to care.<sup>66,370,371</sup> Such interventions can  
1802 significantly affect tuberculosis trends by enhancing access to TB care and by mitigating the effect of TB-  
1803 related catastrophic costs.<sup>372</sup>

1804

### 1805 **4.3 Sustaining top-level political support and leadership**

1806 Strong national and local political leadership creates an environment conducive to sustained attention  
1807 and funding. To end TB, governments of high-burden countries will need to propose bold plans to end  
1808 TB rather than be content with modest incremental gains. Encouragingly, there is growing political  
1809 recognition that countries need to act now to address the TB epidemic. Since its establishment in 2014,  
1810 the Global TB Caucus,<sup>373</sup> which supports 2,300 parliamentarians in 130 countries, has become a driving  
1811 force to mobilize political capital to address TB. TB legislation in the Philippines<sup>374</sup> and Peru<sup>375</sup> that  
1812 mobilized national finances to drive improvements in TB care and prevention, highlights successes that  
1813 can be achieved because political leaders in these countries championed the cause. In South Africa, key  
1814 political leaders from Ministries of Health and Finance have been instrumental in formulating a TB  
1815 investment case, to marshal additional resources to find new cases and treat more drug-resistant TB  
1816 (Figure 5). Progress as dramatic as that envisioned in the End TB strategy can be achieved only when  
1817 each country's leadership outlines a long-term strategy to combat TB within its borders, similar to  
1818 longstanding strategies established to fight HIV/AIDS.

1819

1820 Effective leadership at the National Tuberculosis Programme (NTP) level is also a critical element of a  
1821 successful TB response and evidence of high-level commitment to addressing TB. The size and capacity  
1822 of the NTP's central coordination team and the level of decentralization and integration of specific  
1823 services depend on many factors, including the country's size, governance, administrative structure, and  
1824 TB epidemiology. However, chronic underinvestment in TB control efforts can undermine all aspects of  
1825 TB programming, including the caliber of NTP key personnel, human resource planning, capacity  
1826 strengthening, and supervision and monitoring of service quality. Empowering NTP managers to take the  
1827 necessary steps to institute effective strategies will require increased financing and recognition that NTP  
1828 leaders must play an inter-sectoral, convening role with stakeholders of other government ministries,  
1829 including finance, justice, labor, social welfare, housing, mining, and agriculture. Furthermore, a high  
1830 priority must be placed on ensuring that these leaders have access to senior government leadership  
1831 (Heads of Government and Ministers of Finance) who can authorize mobilization of funds to realize the  
1832 goals identified. To ensure the high-caliber NTP leadership needed to fulfill these expanded roles



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1833 demands that these managers receive adequate pay, reasonable autonomy, and opportunities to  
1834 maintain up-to-date technical knowledge.

1835

### 1836 **4.4 Maintaining multisectoral engagement**

1837 In the SDG era, addressing TB must occur as part of a broader multisectoral framework that addresses  
1838 key social determinants— especially poverty and overcrowding,<sup>376</sup> malnutrition<sup>8</sup>, smoking,<sup>377</sup> and air  
1839 pollution<sup>378</sup>—clearly linked with TB and TB mortality. Success will require collaboration among multiple  
1840 ministries, agencies, and civil society. The health sector, particularly the NTP, can play a key role in  
1841 identifying and communicating the potential health impact of policies on food security, improved  
1842 housing, poverty reduction, employment safeguards, and human rights protections for migrant,  
1843 prisoners, and other marginalized groups.<sup>364</sup> Numerous policy tools, including taxes and subsidies, laws  
1844 and regulations, information and communication and improvements in urban planning, should be  
1845 employed to address these issues. As highlighted below, accountability to address these determinants,  
1846 at both a national and subnational level may be valuable, especially in addressing issues such as tobacco  
1847 control and under-nutrition.

1848

1849 While not disavowing the critical importance of a multisectoral agenda to address determinants of TB  
1850 disease, this Commission recommends that improving access to diagnostic, treatment, and preventive  
1851 services, especially for high-risk populations, should be the primary means of ending TB as a disease of  
1852 global public health significance, in most high burden countries. Over the next generation, substantial  
1853 progress can be made by ensuring that individuals with TB can access curative treatment, and those at  
1854 highest risk for TB disease can access preventive therapy, especially since so many currently lack that  
1855 access. Continued improvements in TB control tools and the systems for delivering TB programs  
1856 coupled with greater financial resource mobilization for health offer the most concrete likelihood of  
1857 ending the epidemic.<sup>94</sup>

1858

### 1859 **4.5 Strengthen civil society involvement in all aspects of the TB response**

1860 A critical lesson learned from HIV/AIDS response is that engaging stakeholders from the civil, public, and  
1861 private sectors requires national leadership to bring disparate actors together, overcome  
1862 communication barriers, enable policies, and scale up access to effective medical tools. Civil society  
1863 dramatically changed the global response to HIV/AIDS, making it a top priority at all levels and driving  
1864 unprecedented growth of donor support for lifesaving interventions.<sup>379 339</sup>

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1865

1866 Until recently, few TB survivors or other people affected by the disease have served as public advocates,  
1867 in part because of TB's curable nature, the top-down orientation of TB control efforts, and the  
1868 persistent stigma of TB worldwide, the lack of funding to support community involvement in TB  
1869 programming.<sup>380,381</sup> Fortunately, this is changing. A growing cadre of healthcare workers and students  
1870 who are TB survivors are using their dual perspectives and professional networks as platforms to call for  
1871 rights-based services and accelerated access to diagnostics, new treatment regimens, and vaccines.<sup>380</sup>  
1872 National and transnational TB activism is emerging as a vital force advocating for services in hard-to-  
1873 reach populations, mobilizing communities and strengthening community systems. TB survivors can play  
1874 an essential role in creating incentives for political leaders to make difficult and risky decisions, by  
1875 generating public support for those decisions, and in holding leaders and service providers accountable  
1876 for how resources, commitments, and services are delivered.

1877

1878 In the post UNHLM-era, the continued input of TB-affected civil actors is essential to ensure the  
1879 accountability of politicians and program planners. Recognizing their contribution as a global public  
1880 good, governments and international organizations must create conditions for civil society actors to play  
1881 an expanded role in the fight against TB, supporting their contribution through direct investments and  
1882 assembly to raise inconvenient truths. This should include involving such advocates in national TB  
1883 strategic planning processes, national TB research-agenda setting activities, and national and regional  
1884 accountability mechanisms.

1885

### 1886 **4.6 Strategies to reduce TB-stigma and ensure a human rights-based approach to TB**

1887 An important lesson from the HIV epidemic (and for global health generally) is that only by committing  
1888 to universal human rights for everyone can the highest available standard of physical and mental health  
1889 care be fulfilled.<sup>339</sup> To uphold and defend the human rights of people with TB or those at most risk of TB  
1890 can bring down rates of infection and death. Practical solutions are needed to expedite changes in the  
1891 laws, policies and public attitudes that violate human rights of vulnerable populations who might be at  
1892 particular risk of developing TB disease, including people living with HIV, prisoners, refugees and  
1893 migrants, miners, and health care workers. Furthermore, human rights must be an integral part of the  
1894 design, implementation and evaluation of an integrated and multisectoral response to TB.<sup>138</sup> A human  
1895 rights approach to TB research is required to ensure that legislative and policy frameworks exist to  
1896 enable the widespread application of encouraging new scientific discoveries, provide accountability for

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1897 R&D investments<sup>382</sup> and remove barriers that preclude new TB research technologies being broadly  
1898 available for public benefit.<sup>383</sup>

1899

1900 In addition to addressing legal frameworks that undermine TB control efforts, action must be taken to  
1901 address TB stigma, which is pervasive throughout health care systems. Burdensome legal and  
1902 social practices that systematically infantilize, impoverish, and expose people with or at risk for TB must  
1903 be removed to end TB stigma.<sup>384,385</sup> Public awareness campaigns that dispel fears and promote positive  
1904 messages about TB, drawing on patient testimonials, can also help reduce stigmatizing attitudes.<sup>386-388</sup>  
1905 <sup>388,389</sup> Furthermore, campaigns that highlight the unfairness of obstacles faced by people who are sick  
1906 can evoke public support for greater investment in the welfare of stigmatized groups.<sup>390</sup> Social  
1907 protection interventions, such as conditional cash transfer programs also can build resiliency to  
1908 stigma,<sup>76,391-393</sup> especially among patients whose self-identity and social capital are linked to their ability  
1909 to sustain their families and themselves.<sup>394</sup> It may also be useful to learn from and model successful  
1910 campaigns from HIV/AIDS, where community engagement, advocacy, and political buy-in have aligned  
1911 to ensure that policymaking and program planning mitigate stigma.

1912

### 1913 **4.7 WHO – a new role for a new era**

1914 With greater emphasis on sustainable domestic resources and the centrality of national health systems,  
1915 the SDG era also offers an opportunity to better define the role of WHO in ending the TB epidemic. This  
1916 Commission has identified several priorities for which WHO can be a leading catalyst for change. First,  
1917 technical assistance to countries and strategic leadership may not be unique to WHO, it must ensure  
1918 that critical technical assistance is available to member states.<sup>329</sup> Second, the WHO global TB program  
1919 must catalyze a rethinking of TB surveillance systems and the use of data platforms. In particular, WHO  
1920 has a crucial role to play in modernizing and expanding health information systems relevant to TB.  
1921 Incorporating routine reporting of social protection indices and non-health SDGs into global TB reports is  
1922 one key responsibility WHO has already embraced.<sup>365</sup> However, by advocating for the better use of,  
1923 subnational, real-time data and dashboard technologies, including performance data, the WHO can  
1924 encourage countries to use these systems to improve the quality and efficiency of their TB programs,  
1925 enable greater accountability, and facilitate more responsive and targeted technical assistance.

1926

1927 WHO's Director-General has repeatedly asserted the importance of UHC to his tenure,<sup>395</sup> committing to  
1928 'making universal health coverage happen in our lifetime.'<sup>396</sup> Accordingly, WHO must continue to

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1929 support robust TB programs as a central component of UHC. To end TB, both a focused commitment to  
1930 TB activities and a progressive, inclusive vision of health care are essential. WHO must work to support  
1931 countries to hold these two complementary priorities in tension is critical.

1932

### 1933 **4.8 Establishing local, national, and global accountability**

1934 Turning written commitments into substantive actions requires an accountability framework that tracks  
1935 all elements of the TB response occurring at local, national and global levels. This framework must  
1936 measure progress towards ending TB worldwide and include timely reviews of results through  
1937 government and civil society accountability mechanisms, both national and global. It also must  
1938 incorporate a means for taking appropriate corrective actions.<sup>86</sup>

1939

1940 At a national level, this Commission proposes a framework to ensure that accountability extends beyond  
1941 national TB programs and reports directly to Heads of State. TB accountability should, as an exception,  
1942 be reported to Heads of State because of the health security risk that TB poses, and its adverse impact  
1943 on national economies and health systems. Consistent with national strategic plans, such a framework  
1944 should include specific targets for reducing mortality and detecting more cases, screening populations at  
1945 high risk and scaling up access to preventive therapy, and addressing inequities in TB risk across  
1946 populations. As highlighted earlier in this report, country-specific targets deriving from the global  
1947 targets agreed upon at the UNHLM have been developed and provide benchmarks that all countries  
1948 should achieve between 2018 and 2022.<sup>397</sup> In addition the framework also needs to ensure that  
1949 financial resources are matched to achieving these targets. Furthermore, it should engage ministers  
1950 across government to ensure multisectoral accountability on issues such as tobacco taxation and the  
1951 regulation of air pollution, as well as progress towards addressing relevant SDGs. National TB  
1952 Commissions or cabinets that can monitor progress across sectors and/or ensure implementation of TB  
1953 specific national strategic plans may be appropriate in high-burden countries. Enabling subnational  
1954 accountability, using regional data to highlight gaps in services and opportunities for allocative  
1955 efficiency, is also likely to be effective. Linking accountability mechanisms to financial resources that are  
1956 allocated separately from health budgets can enable responsive, targeted responses. Such approaches  
1957 have proven effective in addressing the HIV/AIDS epidemic in several countries;<sup>339</sup> given the health  
1958 security risks and adverse economic impact of TB, similar approaches are justified to address the TB  
1959 epidemic in many high-burden countries.

1960

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1961 Separate mechanisms must also include accountability for nation states at a global level. We propose  
1962 that Heads of State should be accountable for their countries progress at the United Nations General  
1963 Assembly on a biannual basis. Unfortunately, the political declaration arising from the UNHLM did not  
1964 include any specific accountability framework, but rather a commitment to support WHO to develop  
1965 such a framework at the level of the World Health Assembly. As such, it is unclear that Heads of State  
1966 would be held to account for inaction to end this disease. This Commission asserts that accountability at  
1967 the level of the UN, and independent of the WHO, offers the the best chance of driving global political  
1968 action and recommends that a report card be established to hold nations accountable for their  
1969 commitments and determine where additional assistance is needed. This approach has been an  
1970 important political component of the global fight to end HIV/AIDS, as it has maintained global  
1971 recognition and financial investment to address this disease. While the details of any national report  
1972 card would need to be drafted and approved to ensure stakeholder consensus, commitments on  
1973 accountability should include progress towards key End TB milestones and other relevant SDGs;  
1974 adoption and implementation of WHO recommended policies; registration of and access to the newest  
1975 and best medical tools; and TB financing. <sup>86</sup> Table 7, gives an example of a report card, highlighting the  
1976 current performance of ten high TB burden countries on several epidemiologic, programmatic, financial  
1977 and multisectoral indicators.

1978

1979 Finally, OECD donor countries; international multilateral funding agencies such as the Global Fund and  
1980 UNITAID; non-governmental funders, like the Bill and Melinda Gates Foundation; and the agencies of  
1981 the United Nations, including WHO, UNICEF and UNAIDS all play vital roles in global efforts to end TB,  
1982 for which they also must be held to account. Leveraging the Quality of ODA metrics already published  
1983 by the Center for Global Development Appendix Table xx provides a report card that highlights strengths  
1984 and weaknesses of major bilateral TB donors. Its purpose is to illustrate metrics on which these donors  
1985 can be evaluated. Donor accountability to address DR-TB and TB R&D must be a focus in these report  
1986 cards, including the allocation of funds to address DR-TB related activities and/or the investment in TB  
1987 R&D. Similar report cards for multilateral funders and major non-state actors are also necessary to  
1988 ensure that these institutions also are held accountable for their efforts towards ending the epidemic,  
1989 and to ensure that investments are synergistic with domestic investments. Enhanced accountability  
1990 of these institutions, not just to their board members or citizenry, but to TB survivors and their  
1991 advocates in recipient countries, represents a global public good. While the indicators and governance  
1992 for these proposed report cards will need to be drafted and agreed to by consensus, dimensions should

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1993 include performance monitoring and assessment, efficiency and effectiveness, sustainability,  
1994 transparency and responsiveness to corrective feedback.

1995

### 1996 **4.9 The Lancet TB Observatory**

1997 To spur political action and monitor progress towards ending TB after the United Nations High-Level

1998 Meeting) on Tuberculosis, *The Lancet* Commission and experts participating in this Commission will

1999 launch *The Lancet TB Observatory*. The idea for this *Observatory* was first proposed in 2010<sup>16</sup> to

2000 promote urgent global action to control the TB epidemic. It is needed now more than ever. *The*

2001 *Observatory* will be composed of global experts and stakeholders from high-burden countries and will

2002 meet annually between now and 2022, to critically evaluate progress towards targets made at the UN

2003 High-Level Meeting. Leveraging the TB report card, it also will monitor domestic and global financing for

2004 efforts to End TB and identify corrective actions and investments necessary to achieve targets. By

2005 providing an independent perspective on the the activities of key global stakeholders, including WHO,

2006 the Stop TB Partnership and the Global Fund, *The Lancet TB Observatory* can also help optimize

2007 alignment of these different bodies towards ending the epidemic.

2008

2009

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### 2010 **Section 5: Conclusions**

2011 We can build a TB-free world. Many countries – even many low- and middle-income countries – have  
2012 demonstrated that that it is achievable, despite the limitations of existing tools. The prospect of a TB-  
2013 free world is not a distant aspiration. It is a realistic objective that can be achieved with the right  
2014 commitment of leadership and resources. It will be a difficult task, with potential setbacks including the  
2015 challenge of drug-resistance, funding obstacles and uncertainties about the correct prioritization of tools  
2016 and implementation approaches. However, the Commission hopes that the recommendations and  
2017 supporting evidence provided in this Report gives countries a roadmap to end their TB epidemics. With  
2018 targeted, proven strategies, smart investments based on sound science, accelerated research and  
2019 development, and a shared responsibility, we can defeat TB within a generation.

2020

2021

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2022

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