Scientific advances and the end of tuberculosis: a report from the *Lancet* Commission on Tuberculosis

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Executive summary

The 2019 Lancet *Commission on Tuberculosis* laid out an optimistic vision for how to build a tuberculosis-free world through smart investments based on sound science and shared responsibility.[1] Since then, several major strides have been made towards ending tuberculosis, including substantive improvements in treatment outcomes for people with drug-resistant disease.[2,3] Although COVID-19 has undermined global progress, many African countries have sustained declines in tuberculosis mortality rates. With excellent short-course preventive regimens and several late-stage vaccine candidates, tuberculosis prevention is also on the cusp of a revolution. Still, much more can be done to fully implement the Commission's recommendations (panel 1) and realise the ambitious targets set out at the UN High-Level Meeting (HLM) on tuberculosis in 2018. In the 5 years since the HLM, more than 7 million people have died of tuberculosis; their deaths are a profound tragedy and a reminder of the urgency of accelerating momentum.

In September, 2023, the UN will convene a follow-up HLM to hold a comprehensive review of global progress towards ending tuberculosis. Before this meeting, we must ask ourselves how we can do better. As background to the HLM and as an update to our initial report, this follow-up report outlines roadblocks that have undermined progress towards ending tuberculosis over the past 5 years; endorses a new set of tools that can catalyse response efforts and should be implemented urgently; provides a revised assessment of the crucial investment priorities; and restates the importance of stronger health systems, emboldened community engagement, action on crucial social determinants of tuberculosis, sustained political will, and increased financial investments as prerequisites to ending tuberculosis.

Although COVID-19 has had a profound negative effect on global tuberculosis efforts, it provides a precedent for what concerted, international collective action can achieve to address a global infectious disease threat. Failings in the global COVID-19 response also underscore the importance of person-centred and equity-oriented tuberculosis programming.[4–6] This updated report will highlight lessons learned from the successes and failures of the COVID-19 response and the intersecting priorities of pandemic preparedness with tuberculosis response efforts and the universal health coverage agenda, including a shared vision to strengthen multilateralism across political, cultural, institutional, and financial dimensions. Can we build a tuberculosis-free world? Yes. Will we? Each country's answer will depend on the decisions made by leaders and institutions at all levels, in all sectors, and across all parts of society. The leadership of national tuberculosis programmes and the adequacy of the resources at their disposal will be of the utmost importance.

Introduction

Countless global reports since the early 2000s have highlighted the feasibility of ending tuberculosis as a global public health concern while also restating indignation that this centuries-old plague continues to be a leading cause of death and—as COVID-deaths subside—will again be the leading infectious cause of death.[7–13] Moreover, the UN High-Level Meeting (HLM) in 2018 offered hope that global momentum was finally building towards investing the resources and political will to catalyse innovation. Shortly after that meeting, the 2019 report of *The Lancet*'s Commission on tuberculosis offered a blueprint for how to deploy those resources, emphasising that with smart investments based on sound science, accelerated research and development, and shared responsibility, a world free of tuberculosis was possible in the near future.[1]

Despite some advances over the past 5 years, the targets outlined in the UN HLM declaration have not yet been achieved. Although there was an increase in tuberculosis detection rates before the COVID-19 pandemic, declines in incidence and mortality rates were too gradual—even before COVID-19 undermined tuberculosis response efforts further.[3] The recent 5-year stagnation of donor and domestic funding in many heavily affected regions has further impeded progress. The world is now not on course towards ending tuberculosis (defined, in part, as a 90% reduction in tuberculosis mortality rates compared with the 2015 global mortality rate).[10] Moreover, none of the ten countries with the highest burden has achieved the targets outlined at the UN HLM in 2018 (appendix p 4) and few of the recommendations made in the initial

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Panel 1: **Commission recommendations**

In a restatement of recommendations made in the original Commission report,[1] we call for all countries to invest in tuberculosis not only as a moral imperative, but as an effective fortification against other pandemics and a central component of universal health coverage.

Optimise access to comprehensive clinical care for all individuals wherever they seek evaluation and care for tuberculosis

- Commit to expanding universal access to molecular assays as the standard of care for diagnosing tuberculosis everywhere
- Commit to ensuring universal access to shorter, less toxic, oral regimens for both drug-sensitive and drug-resistant tuberculosis
- Commit to implementing the social protection strategies necessary to ensure all people seeking or receiving tuberculosis care can access diagnostic and treatment services without risk of catastrophic cost, including in the private health sector

Reach people and populations at higher risk

- Begin outreach with the most easily identified people, such as household members and other close contacts of people with tuberculosis and people with HIV, and support them during care and treatment
- Address stigma and gender and human rights barriers to equitable, quality care, and increase commitment to achieving universal health coverage
- Commit to ensuring every eligible person at risk for tuberculosis, including people living with HIV and all household contacts regardless of their age, is screened and treated if positive for tuberculosis, and offered short, 1-month or once weekly treatment regimens for tuberculosis prevention if negative

Increase development assistance for tuberculosis

- Commit to expanding donor assistance, particularly in low-income countries, including increasing Global Fund allocations for tuberculosis from 18% to 33% of all Global Fund resources
- Donor financing for tuberculosis in middle-income countries should be contingent on countries mobilising additional domestic resources
- Align new pandemic funding priorities with tuberculosis funding priorities; donor assistance for tuberculosis is likely to deliver far-reaching global health benefits and strengthen global pandemic preparedness, especially in low-income and middle-income countries with the highest burdens

Increase investment to accelerate tuberculosis research and development

- Commit to increased, sustained funding for tuberculosis research and development for new and better diagnostics, therapeutics, and vaccines, as these are crucial to ending tuberculosis both among people with low income in middle-income countries and globally
- Prioritise inclusive clinical research as key groups of people affected by tuberculosis, such as children and pregnant people, cannot yet benefit from scientific advances that have enabled treatment to be shortened
- Prioritise research on the implementation of outreach programmes to groups of people at high risk for tuberculosis
- Ensure that new tuberculosis technologies (especially those funded through public investments) are available as public goods; high-burden countries should use legal and other tools to accelerate equitable access to tuberculosis innovation.

Hold countries and key stakeholders accountable

- Empower tuberculosis survivors and other people affected by tuberculosis to serve as leaders in defining and leading the global tuberculosis agenda
- Commit to aligning progress towards tuberculosis targets with strategies for advancing pandemic preparedness and response initiatives at global and national levels, including incorporating tuberculosis within frameworks for pandemic preparedness and response funding and governance
- Continue to hold governments in high-burden countries accountable to ensure they commit financial resources and political action to driving change

Commission have been realised (appendix p 5), perhaps in part because of the COVID-19 pandemic. That said, four of the ten highest burden countries did achieve declines in their tuberculosis mortality rates of 10% per year or more in 2010–17 (table). These important achievements underscore the feasibility of reaching ambitious goals.

This Commission conducted a comprehensive review to better understand why sufficient progress has not been made, what lessons can be learned from the global response to COVID-19, and how a new set of diagnostic, therapeutic, and preventive tools already available or in the pipeline promises the possibility of transformative progress.

Progress since 2018

Progress towards ending tuberculosis has been minimal in some countries and substantial in others. This discrepancy has resulted from a mix of political, societal, scientific, and strategic factors.[1] Health system frailties, little investment in tuberculosis programmes, and over-reliance on one-size-fits-all approaches have all contributed. Especially for the highest burden countries, the biggest challenge to ending tuberculosis has been insufficient case finding and diagnosis. An analysis from 2019 indicates that a country's capacity to screen and diagnose tuberculosis is the most substantial gap in the cascade from incident tuberculosis disease to successful completion of treatment.[14] Although COVID-19 has

	Cumulative % of total tuberculosis deaths in 2021	Number of deaths (1000s) in 2010*	Number of deaths (1000s) in 2017*	Number of deaths (1000s) in 2021*	Death rate (per 100 000 per year) in 2010	Death rate (per 100 000 per year) in 2017	Death rate (per 100 000 per year) in 2021	Rate of decline in death rates from 2010 to 2017†	Rate of decline in death rates from 2017 to 2021†	Improvement in rate of decline in death rates (%)‡
World	100%	1989	1545	1544	28·6	20·4	19·6	8·4%	1·0%	–7·4%
India	33%	552	462	506	44·5	34·1	35·9	6·6%	–1·3%	–7·9%
Indonesia	42%	120	100	150	49·2	37·8	54·8	6·6%	–9·3%	–15·8%
Nigeria	51%	142	157	125	88·2	81·1	58·6	2·1%	8·1%	6·1%
Philippines	55%	28	29	61	29·6	27·2	53·6	2·1%	–17·0%	–19·1%
South Africa	58%	186	60	55	359·2	105·9	92·6	30·5%	3·4%	–27·2%
Pakistan	61%	52	46	50	26·7	21·3	21·6	5·7%	–0·4%	–6·1%
DR Congo	65%	55	59	49	82·8	70·0	51·1	4·2%	7·9%	3·7%
Bangladesh	67%	79	56	43	53·2	34·6	25·4	10·8%	7·7%	–3·0%
Myanmar	70%	54	31	36	109·3	59·3	66·9	15·3%	–3·0%	–18·3%
China	72%	56	39	32	4·2	2·8	2·2	10·2%	5·2%	–4·9%
Kenya	74%	75	43	32	180·6	87·8	60·4	18·0%	9·4%	–8·6%
Tanzania	75%	76	47	26	168·5	83·5	40·9	17·5%	17·9%	0·3%
Angola	77%	25	29	21	107·0	96·0	60·9	2·7%	11·4%	8·7%
Ethiopia	78%	47	31	21	52·7	28·7	17·5	15·2%	12·4%	–2·8%
Nepal	79%	22	18	18	81·0	63·9	59·9	5·9%	1·6%	–4·3%
Ghana	80%	17	16	16	66·5	52·9	48·7	5·7%	2·1%	–3·6%
Mozambique	81%	28	14	14	121·4	49·0	43·6	22·7%	2·9%	–19·8%
Viet Nam	82%	22	14	14	25·2	14·9	14·4	13·1%	0·9%	–12·2%
Madagascar	83%	13	14	13	59·8	53·5	45·0	2·8%	4·3%	1·6%
Afghanistan	84%	12	11	12	42·6	30·9	29·9	8·0%	0·8%	–7·3%
Cameroon	85%	17	13	12	85·5	53·3	44·1	11·8%	4·7%	–7·1%
Uganda	85%	18	22	12	55·7	54·8	26·2	0·4%	18·5%	18·1%
Somalia	86%	11	10	11	91·5	67·3	64·5	7·7%	1·1%	–6·6%
Thailand	87%	16	13	11	23·4	18·3	15·4	6·1%	4·4%	–1·7%
Russia	87%	24	12	8·6	16·8	8·3	5·9	17·7%	8·3%	–9·4%
Brazil	88%	8·2	7·2	8·2	4·2	3·5	3·8	4·8%	–2·6%	–7·3%
Zambia	88%	18	18	7·8	130·5	104·1	40·1	5·7%	23·9%	18·2%
Malawi	89%	21	8·1	7·7	142·7	45·3	38·7	28·7%	3·9%	–24·8%
Côte d'Ivoire	89%	10	8·5	7·6	47·3	34·2	27·7	8·1%	5·3%	–2·8%
Zimbabwe	90%	9·3	5·2	7·3	72·4	35·3	45·6	18·0%	–6·5%	–24·5%

Data are adapted from the *Global Tuberculosis Report 2022*.[3] Countries are ranked from the highest number of deaths in 2021 (India) to the lowest number of deaths (Zimbabwe). Data on China do not include Macau or Hong Kong. All estimates of tuberculosis mortality are based on WHO's model-based projections given that few high burden countries reported vital registry data during the COVID-19 pandemic. *Death numbers include deaths of individuals infected with HIV. †Average annual rate of decline (% per year) between indicated years; a negative rate of decline indicates an increase in death rate. ‡Improvement is defined as the rate of decline from 2017 to 2021 minus the rate of decline from 2010 to 2017.

Table: **Tuberculosis mortality in 2010, 2017, and 2021 in the 30 countries with the highest mortality due to tuberculosis in 2021**

shown the feasibility of massive upscaling in the use of accurate diagnostics (even in lower-middle-income countries [L-MICs]—for example, nearly a billion COVID-19 tests were performed in India in the last 3 years),[15] quality tuberculosis diagnostics remain inaccessible in many countries.[16] Unfortunately, the roll-out of newer tuberculosis diagnostics, such as molecular assays (eg, the Xpert MTB/RIF Ultra),[17] has been too slow, and too many countries still rely on insensitive, inadequate tools such as microscopy. Although WHO recommends molecular diagnostics as the preferred first-line testing option, only 38% of all notified individuals diagnosed with tuberculosis in 2021 were tested with a WHO-recommended rapid molecular diagnostic at initial diagnosis.[3]

In 2020, the COVID-19 pandemic undid years of reductions in tuberculosis mortality rates. For the first time in nearly two decades, global tuberculosis deaths stopped declining (table).[18] In addition, more than a third of people with tuberculosis were undiagnosed and untreated. COVID-19 quickly and substantially disrupted tuberculosis responses as diagnostic infrastructure was diverted away from tuberculosis programmes,[19,20] and shutdowns and lockdowns led to reduced access to tuberculosis treatment services.[21] In almost all high tuberculosis burden countries, COVID-19 resulted in

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See **Online** for appendix

health worker shortages and burn-out,[22] diminishing health systems' capacity to provide essential tuberculosis services.[23,24] Major reductions in notified cases were reported in many countries between 2019 and 2020, including in the Philippines (37%), Indonesia (31%), South Africa (26%), and India (25%),[25] with modelling evidence suggesting concomitant increases in tuberculosis incidence in these countries.[19,20,26] Case notifications recovered during 2021 and 2022, but a gap remains in several countries compared with pre-pandemic numbers.

The COVID-19 pandemic and the associated response also substantially increased projected tuberculosis mortality.[27] WHO and the Stop TB Partnership both forecasted approximately 190 000 additional tuberculosis deaths in 2020 and approximately 1·4 million additional deaths between 2020 and 2025, with the latter projected to worsen for each month taken to restore health services.[28–30] Moreover, among the highest tuberculosis burden countries, there was a deterioration in the rate of decline in tuberculosis mortality, with many high-burden countries seeing an increase in tuberculosis mortality in 2020 and 2021 for the first time in a decade (appendix p 7).[3] Two-thirds of tuberculosis deaths occurred in just eight countries, and over half occurred in India (33%), Indonesia (10%), and Nigeria (8%; appendix p 8).

Nonetheless, not all countries experienced increases in tuberculosis mortality between 2017 and 2021. Several countries, all in sub-Saharan Africa, experienced improvements in the rate of decline in tuberculosis mortality, illustrating that sustained and rapid decreases in tuberculosis mortality are possible even with existing tools and despite pandemic setbacks. Although the achieving the 2030 Sustainable Development Goal (SDG) target for ending tuberculosis is unlikely in many high-burden countries (table), there are still grounds for optimism. Several high-burden countries are on the cusp of achieving substantive gains toward ending tuberculosis, and new tools, programmatic innovation, and cross-sectoral collaborations can help realise those gains in the next decade.

A new set of tools: grounds for optimism?

Making progress despite facing substantial setbacks in the past 5 years provides reasons for being hopeful. Case notification rates in Pakistan, India, and Indonesia in 2022 have rebounded since early in the pandemic,[3,31] suggesting evidence of health system resiliency.[32] Moreover, modest but cumulative investments in better drugs, diagnostics, and vaccines in the last decade are now bearing fruit. As outlined in the Global Plan to End TB,[33] a set of new therapeutic and diagnostic tools collectively offer a range of options that could substantially improve on what was available 10 or even 5 years ago. If adopted wholesale, implemented at a scale that can reach individuals along the care cascade, and accompanied by sustained investment in research and development (R&D) and tuberculosis programmes, the prospect of ending tuberculosis within a generation is still plausible.

Diagnostics

Although existing diagnostic tools have proven effective in reducing the burden of tuberculosis in several countries,[1,34] many high-burden countries still face challenges that cannot be addressed without implementing new diagnostic tools and screening strategies. The COVID-19 pandemic has catalysed unprecedented progress in large-scale molecular testing, point-of-care (POC) diagnostics, sequencing, and digital connectivity of diagnostics, and offers a precedent for what substantive and rapid progress might occur in the next few years.[35] Notably, the pipeline of sputum-based tuberculosis molecular diagnostics has expanded since 2018, with several assays recently endorsed by WHO in 2020.[36] Companies that produced effective and popular POC diagnostics for SARS-CoV-2 are now developing tuberculosis assays.[37] Nonetheless, progress in adopting new technologies has been slow; Cepheid Xpert, for example, has been approved for a decade, but regulatory, pricing, and infrastructure barriers have prevented its widespread use in many L-MICs.[38] Moreover, reliance on sputum-based assays can be problematic in young children and individuals with HIV. Use of less invasive and more convenient samples, such as tongue swabs and urine, shows increasing promise. Other sample types, eg, blood[39] and stool,[40] might offer alternatives to sputum (contingent on improvements in the performance and operating characteristics of such assays).

Several studies have indicated the potential of using tongue swabs for tuberculosis testing, and initiatives are underway to produce the necessary evidence to formulate WHO recommendations.[41–45] Data suggest that these swab-based tests might not show the sensitivity of sputum-based molecular testing.[43] However, similarly to home-based SARS-CoV-2 rapid tests, these tools could substantially increase population coverage of tuberculosis testing and yield, and perhaps diagnose individuals with the most infectious forms of tuberculosis. The COVID-19 pandemic has shown that there is demand for such tools from affected communities,[46,47] leading the way for rapid translation of similar tools for tuberculosis.

In addition to swab-based molecular tests, there is continued interest in urine-based antigen tests, such as lipoarabinomannan (LAM) assays.[48,49] LAM assays offer the promise of affordable, point-of-care testing, especially if more reliable and sensitive assays, currently under development, enter the market in the next 1–2 years.[50] Further innovation is necessary to maximise the diagnostic sensitivity of urine-based assays targeting *Mycobacterium tuberculosis* antigens, particularly in people without HIV.

Besides the need to expand the use of decentralised molecular assays and develop non-sputum-based tests for clinical tuberculosis diagnosis, there is a crucial need for better tuberculosis screening tests, not least because

subclinical tuberculosis might be a key driver of transmission.[51,52] Importantly, screening tools need to be easy and rapid to use, have good specificity for substantial uptake, be cost-effective, and identify people at high risk early. Fortunately, advances in computer-assisted digital reading have enabled more widespread use of chest x-rays for tuberculosis screening. Still, more effort is needed to make x-ray hardware more affordable.[53] Digital health tools (eg, for cough or lung sound detection) that leverage machine learning methods are now being explored to enable more widespread case finding.[54–57]

If countries are to enhance their capacity to diagnose tuberculosis, they will also need to find ways to ensure that diagnostic investments align with care-seeking behaviour, and more effectively integrate new diagnostic tools into existing primary health-care infrastructure, since most people seek initial care from primary care providers, including pharmacies, informal, and private providers. Diagnostic Network Optimisation projects have shown that access to testing can be substantially enhanced by improving integration and aligning access with care-seeking behaviour.[58] In Zambia, for example, better integration of HIV and tuberculosis testing networks increased testing volumes, reduced turnaround times, shortened patient travel times, and are likely to have saved the health-care system money.[59] As outlined in the Lancet *Commission on Diagnostics*,[60] a comprehensive national assessment of diagnostic needs, not just for tuberculosis but also for other illnesses, can help establish frameworks for deploying diagnostic tools that are more accessible to local communities, and are integrated with existing primary health-care services. Such assessments can also ensure that the latest diagnostic technologies are accessible to public health programmes. A recent resolution calling for integrated national diagnostic strategies at the 2023 World Health Assembly highlights how many countries are already looking to pursue strategies to deliver a package of essential diagnostics across health systems.[61] Slow progress in the uptake of WHO-recommended rapid diagnostics prompted WHO to release for the first time the *WHO standard: Universal access to rapid diagnostics* report,[62] setting benchmarks to achieve universal access to WHO-recommended rapid diagnostics that include increasing bacteriologically confirmed tuberculosis and detection of drug-resistant tuberculosis, and reducing the time to diagnosis. This Commission endorses this new WHO standard and recommends universal access to WHO-recommended rapid diagnostics for all people assessed for tuberculosis.

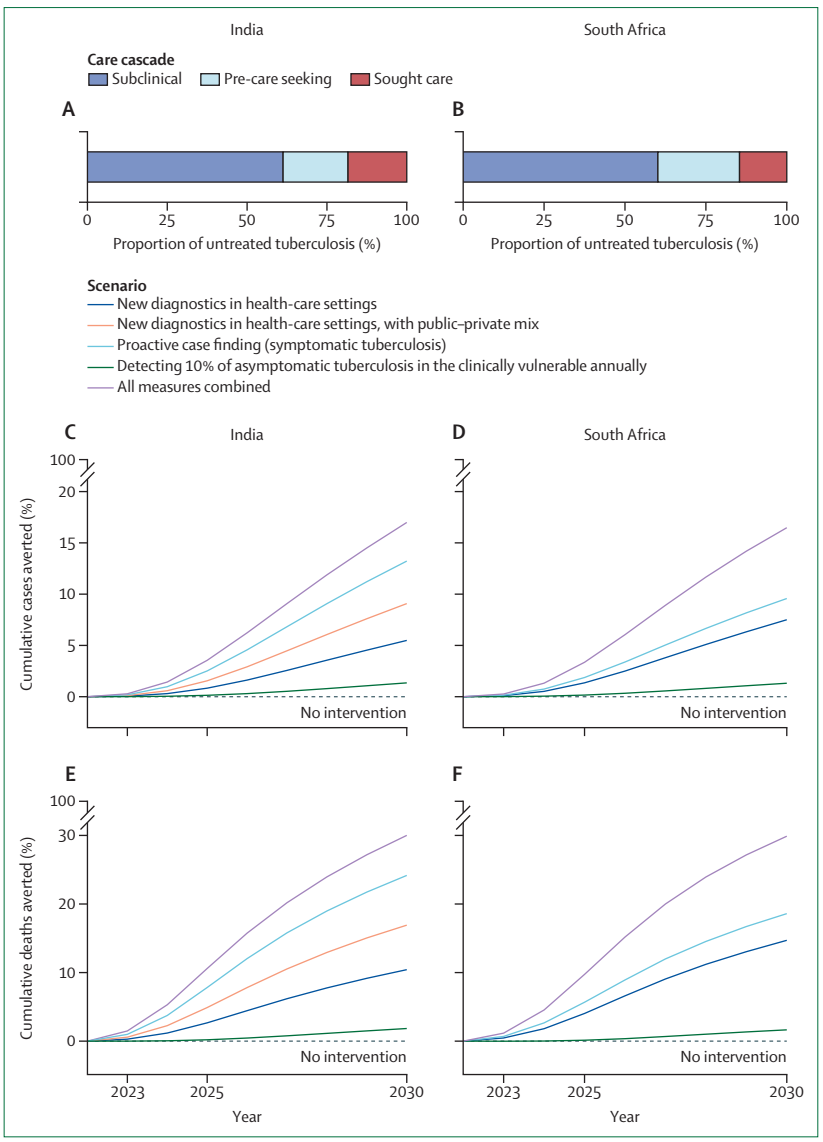

Figure 1: **Modelling the impact of new diagnostic tools for tuberculosis in India and South Africa**
Two examples from high-burden countries are shown. Results from prevalence surveys in India[57] (A) and South Africa[58] (B) are shown, highlighting the proportion of people with prevalent tuberculosis who had sought care yet remained undiagnosed (red); who had symptoms but had not sought care (green); and who did not report symptoms, despite being sputum bacteriologically positive (blue). Depending on the individuals' characteristics, new diagnostic tools could benefit patients at each stage of this sequence. Cumulative cases and deaths averted are shown under different scenarios for the deployment of new diagnostic tools (C–F; see the appendix [pp 14–178] for incidence and mortality curves relating to each of these scenarios). The green curve shows the effect of all interventions implemented in combination, whereas remaining curves show the effects of interventions implemented individually. In India, we assumed the clinically vulnerable population consists of people with undernutrition, whereas in South Africa, we assumed this group consists of people with HIV. See the appendix for the calibration data (p 13) and estimated baseline parameters (p 13), relevant to these interventions, and the overall estimates for cumulative cases and deaths averted by 2030 (p 14).

Assessing the effect of new diagnostic tools

To understand the potential contribution of these new diagnostic tools, we modelled their effect in India[63] and South Africa[64] across different stages of the tuberculosis care cascade. This analysis builds on earlier modelling work on the potential effect of new diagnostic tools.[65] Here, we focused on placing diagnostic tools within the cascade from incident tuberculosis to cure or death. In particular, figure 1A and B show results from national prevalence surveys from the past 5 years, highlighting individuals with tuberculosis who did not report symptoms (subclinical, blue); people suffering symptoms who had not sought care (pre-care-seeking, green); and

those who had sought care, but remained undiagnosed (sought care, red). New diagnostic tools could benefit people with tuberculosis at all stages of this cascade. Oral swabs coupled with molecular diagnostics or urine LAM tests are probably feasible in decentralised settings. Such diagnostic strategies could offer new opportunities to expand timely testing for tuberculosis at the primary care level. Correspondingly, the blue curve in figure 1C–F shows the potential effect arising from a scenario in which the probability of diagnosis and treatment initiation per care-seeking visit is increased to 90%. Such measures would avert around 17% of cumulative tuberculosis deaths in India and 15% of cumulative tuberculosis deaths in South Africa (appendix pp 14–19). In India, expanding public–private mix initiatives would have an important role in amplifying this effect by reaching more providers and thus patients—such measures would augment reductions in incidence and mortality substantially (figure 1C, E).

To reach individuals who have symptoms but are not seeking care, oral swabs or urine samples could be collected at the household level, for example, facilitated by community health-care workers who encourage symptomatic individuals to collect self-samples. The purple curve in figure 1C–F shows the potential effect of twice-yearly screening among all symptomatic people in the community, detecting tuberculosis with an overall sensitivity of 80%. Such measures would avert around 24% and 19% of cumulative tuberculosis deaths in India and South Africa, respectively.

To reach individuals without symptoms, concentrating on clinically vulnerable populations with a high prevalence of tuberculosis will be necessary. Highly portable screening tools will be required (eg, hand-held x-ray combined with artificial intelligence for x-ray interpretation). The pink curves in figure 1C–F suggest that screening individuals with high population-attributable risk factors (for example, undernutrition in India and HIV in South Africa) to identify 10% of subclinical tuberculosis would avert 1·8% and 1·6% of cumulative tuberculosis deaths in India and South Africa, respectively. Notably, combining all these interventions (green curves) would avert around 30% of cumulative tuberculosis deaths in India and South Africa. Importantly, these scenarios involve levels of testing that far exceed what has been reached previously and would involve extending screening beyond specific geographic hotspots (eg, informal urban settlements),[66] but targeting individuals at greatest risk, regardless of where they live. These results highlight the large increase in diagnostic effort needed in the near future to bring about meaningful reductions in global tuberculosis burden.

A paradigm shift in tuberculosis diagnostics

Integrating tuberculosis diagnostics into multidisease testing pathways, and consolidating, integrating, and coordinating laboratory services across disease areas and health system levels, while bringing diagnostic services closer to the individuals being served is likely to expand access to tuberculosis testing and optimise resources.[60,67,68] For example, better integration of tuberculosis and testing for COVID-19 and other respiratory syndromes across all levels of the health system is feasible.[19,69] Donor partners have an important role to play in facilitating the acceleration of regional manufacturing hubs for crucial commodities,[60] such as rapid diagnostics and lab reagents, so that failures in scaling up access to platforms such as Xpert are not repeated. In addition, funders such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and the US Agency for International Development (USAID) can serve a crucial role by creating incentives for countries to scale up rapid molecular diagnostics in underserved communities that need them most.[70] As our modelling illustrates, scaling multiple diagnostic strategies at different points along the case-finding cascade will probably yield substantial dividends in high-burden settings. Nonetheless, these reductions alone are insufficient to meet the tuberculosis SDGs. Previous work has shown that, although diagnostics will be crucial in reducing tuberculosis incidence and mortality, meeting the SDGs requires better treatment tools and more effective prevention interventions.[33,71,72] Reassuringly, the World Health Assembly's 2023 resolution on strengthening diagnostic capacity highlights growing political will to extend the scope of packages of essential diagnostic services and to implement policies that ensure equitable and timely access to diagnostic technologies, including tuberculosis tools, in high-burden countries.[73]

Therapeutics

The 4 years since this Commission's first report have yielded unprecedented advances in the treatment of drug-susceptible tuberculosis and multidrug-resistant and rifampicin-resistant tuberculosis. These include a reduction in treatment duration for drug-susceptible tuberculosis from 6 to 4 months,[74] a reduction in treatment duration for multidrug-resistant and rifampicin-resistant tuberculosis to 6 months,[75,76] and approval of a 6–9 month regimen for highly drug-resistant forms of multidrug-resistant and rifampicin-resistant tuberculosis.[77] All these advances represent improvements in the required duration of tuberculosis treatment, which affects adherence, treatment outcomes, costs, and the demands placed on primary health-care systems and affected communities.[78] This Commission affirms the 1/4/6×24 (one, four, six by 2024) Campaign,[79,80] which urges high-burden countries and their donor partners to invest in these shorter treatment regimens for all eligible people in both public and private sectors (panel 2).

Drug-susceptible tuberculosis

In 2022, WHO and the US Centers for Disease Control

Panel 2: Recommendations for the 1/4/6x24 Campaign to cure tuberculosis quickly

New therapeutic options outlined in this report provide a compelling epidemiological, economic, and moral imperative to accelerate access to shorter, less toxic tuberculosis treatment regimens for both drug-susceptible and drug-resistant tuberculosis. Dr Paul Farmer, whose legacy inspired the 1/4/6x2024 Campaign, insisted that the best available prevention and treatment options be made available to everyone, everywhere.[81] This Commission affirms this strategy, which includes ensuring access to a 1-month or once-weekly regimen for tuberculosis prevention, a 4-month treatment regimen for drug-susceptible tuberculosis, and a 6-month treatment regimen for drug-resistant tuberculosis. Outlined below are the key prerequisites to ensuring access to these shorter, life-saving regimens by the year 2024.

National governments

- Rapidly advance policy changes, including updating national guidelines, strategic plans, essential medicine lists, and conducting health-care worker trainings that include short-course tuberculosis preventive treatment and treatment regimens to expedite the uptake of new regimens
- Leverage legal and other strategies to help improve access to tuberculosis medicines and diagnostic technologies
- Develop patient-centred models of treatment and prevention that deliver care through differentiated, community-based systems

Donors and other funding entities

- Increase investments in tuberculosis programmes to support higher medicine costs and increase health system, human resource, and laboratory infrastructure, and diagnostic technology needs
- Establish new and expand existing sources of funding for civil society and community organisations to work on national 1/4/6x24 campaigns and accountability initiatives
- Expand resources and capacity to accelerate research to fill gaps and shorten treatment regimens even further

Pharmaceutical and diagnostic companies

- Develop fit-for-purpose formulations to support the implementation of short-course prevention and treatment options, including fixed-dose combination regimens and formulations appropriate for children
- Develop fit-for-purpose, affordable diagnostic technologies, including rapid molecular tests that can detect tuberculosis and resistance to key medicines (eg, rifampicin, isoniazid, fluoroquinolones, and bedaquiline) at the point of care
- Commit to rapid registration with stringent regulatory authorities and other national regulatory authorities and early submission to the WHO prequalification programme
- Commit to transparent, evidence-based pricing determined by the cost of goods sold plus a reasonable profit margin or patent non-enforcement

Research networks and academic partners

- Design and implement studies that address the remaining research and data gaps
- Advance fit-for-purpose quantitative and qualitative research to support the introduction and scaling up of shorter regimens and supportive technologies

All health-care providers

- Demand patient-centred care models and links with programmes that deliver care through differentiated, community-based systems (including for post-tuberculosis support)
- Motivate for access to new innovations through rapid updates of national guidelines, strategic plans, and essential medicines lists
- Expedite the uptake of new innovations through health-care worker training on short-course tuberculosis prevention and treatment regimens
- Mobilise through health-care professional associations to network, inform, learn, and build commitment to implementing 1/4/6 campaigns by the end of 2024
- Advocate for legal and policy frameworks that can help improve access to tuberculosis medicines and diagnostic technologies

and Prevention both endorsed the 4-month isoniazid–rifapentine–moxifloxacin–pyrazinamide (4HPMZ) regimen for the treatment of eligible people with drug-susceptible tuberculosis.[75,82] These were the first major changes to drug-susceptible tuberculosis treatment guidelines since the addition of pyrazinamide reduced the duration of therapy to 6 months in 1976.[83] There is a need for more evidence to inform the use of this regimen, and it has not yet been adopted for routine use by most national tuberculosis programmes. Nevertheless, the endorsement of 4HPMZ speaks to the momentum of the development of new treatments for drug-susceptible tuberculosis and the need for urgent translation of research into practice. For example, developing a fixed-dose combination of 4HPMZ and evaluating the regimen in children younger than 12 years, people weighing less than 40 kg, people living with HIV, and pregnant people is important.

In 2023, the TRUNCATE-TB[84] trial highlighted the possibility of even shorter treatment strategies: data now exist to support a 2-month treatment option with bedaquiline–linezolid–isoniazid–pyrazinamide–ethambutol (which might be extended for persistent clinical disease), followed by close monitoring to detect and treat relapse. This strategy was shown to be non-inferior to the standard of care with respect to a composite outcome of death, ongoing treatment, or

active disease at week 96.[84] Although not yet ready for implementation, the TRUNCATE-TB trial shows the promise of differentiated treatment options for patients based on disease severity, comorbidities, and patient and provider preference.

Drug-resistant tuberculosis

Since 2019, treatment options for multidrug-resistant and rifampicin-resistant tuberculosis have expanded considerably. The STREAM Stage 2 trial[85] showed the efficacy of an all-oral treatment regimen,[86] the Nix-TB study[87] and ZeNix trials[88] showed high efficacy of a 6–9-month bedaquiline–pretomanid–linezolid regimen (6–9BPaL), and the TB-PRACTECAL trial[76] provided compelling evidence that a 6-month regimen of BPaL augmented with moxifloxacin (6BPaLM) was non-inferior and superior to the standard-of-care control.[76] These data led to WHO codifying 6BPaLM in their guidelines as the preferred regimen for adults and adolescents aged 14 years and older in 2022.[85] These advances in multidrug-resistant and rifampicin-resistant tuberculosis treatment promise a golden age of innovation that could benefit patients worldwide; addressing cost and access issues will be crucial.

Assessing the cost of new therapeutic tools

In addition to the strong clinical case for adopting newer regimens for multidrug-resistant and rifampicin-resistant tuberculosis that are considerably shorter and less toxic than older regimens, there are also compelling economic arguments to support increased access to these regimens.[89] One study published in 2023 showed that BPaL and BPaLM are expected to yield incremental savings per person in the range of 9–13% in India up to 28–35% in South Africa compared with those countries' current standard-of-care regimen mix.[90] Nonetheless, drug costs remain an important hurdle, even when implementing efficacious treatment regimens, with bedaquiline costs being a crucial driver that might negatively affect uptake of all-oral regimens for multidrug-resistant and rifampicin-resistant tuberculosis in many L-MICs.[91] Thus, donor agencies and global stakeholders must support national tuberculosis programmes to rapidly update their guidelines, protocols, medicine stocks, and drug-susceptibility testing capacity to facilitate the widespread use of these drugs.

In contrast with newer, shorter drug-resistant tuberculosis regimens, data addressing the economic benefits of shorter drug-susceptible tuberculosis regimens are scarce. For this report, we compared the costs and effect on patient outcomes of switching from the 6-month isoniazid–rifampicin–pyrazinamide–ethambutol (6HRZE) regimen to the 4HPMZ regimen, which was shown in 2021 to have similar efficacy to 6HRZE among adults and adolescents with drug-susceptible tuberculosis.[74] As of the writing of this report, 4HPMZ (at US$188 for a full course) is priced substantially higher than 6HRZE ($46),[92] despite recent reductions in the cost of rifapentine in 2022.[93] However, a higher-priced regimen could still yield net savings for tuberculosis programmes and society—for example, if it reduces the need for ancillary services such as clinic visits and laboratory tests. These savings on other components of treatment—including the substantial time and ancillary costs that are borne by patients—should be considered when evaluating the economic value of shorter regimens. We estimated the extent to which the shorter duration of 4HPMZ would result in fewer required clinic visits, fewer monitoring tests, lower costs to patients, fewer cumulative side-effects, less loss to follow-up over the treatment course, and less need for retreatment of recurrent disease compared with 6HRZE—resulting in savings that could compensate for the higher price of 4HPMZ. In the cost effectiveness analysis, we additionally considered the value of health gains, including reduced mortality and disability, resulting from higher rates of completion with the shorter regimen. Comparisons assumed equivalent efficacy and incorporated the costs of moxifloxacin susceptibility testing to minimise effects on drug resistance, which were not explicitly modelled.

We estimated the price thresholds necessary for cost-neutrality (on a 5-year time horizon) and cost-effectiveness of 4HPMZ, relative to 6HRZE, in India, South Africa, and the Philippines (appendix pp 20–30). We used an ingredients-based costing approach with country-specific estimates of unit costs, and we expressed cost-effectiveness thresholds as an incremental cost per disability-adjusted life year (DALY) averted.[94–101] Cost-neutral price thresholds for 4HPMZ ranged from $56 in the Philippines to $74 in India, up to $105 in South Africa (figure 2). The cost-effective price thresholds, which also incorporated willingness to pay for health improvements, were higher than the cost-neutral thresholds, at $108 in India, $126 in the Philippines, and $361 in South Africa. Price thresholds would be substantially lower (ie, harder for HPMZ to reach) if the non-medical out-of-pocket and time costs that patients incur during treatment were not considered (figure 2, red bars *vs* total bar height), but such an analysis ignores the important benefits of a shorter regimen for patients. Conversely, all thresholds could increase by up to $33 if the added costs of confirming moxifloxacin susceptibility before the use of 4HPMZ were reduced (or in settings with rare fluoroquinolone resistance in which testing was deemed non-essential).

This analysis highlights that switching to 4HPMZ could already be cost-effective in some settings (eg, South Africa) with higher incomes, and thus higher unit costs and cost-effectiveness thresholds, but achieving cost-effectiveness in L-MICs such as India and the Philippines is likely to require a reduction in prices for the 4-month regimen. However, economic cost is not the only consideration. The toll that an additional 2 months of treatment—and the associated side-effects—takes on patients and their

caregivers is not to be underestimated. Although outside the scope of this analysis, acceptability and the intrinsic value of meeting patient preferences should be considered as having similar importance to cost-effectiveness estimates. However, in practice, cost considerations might dictate the extent to which a new regimen is taken up in high-burden, low-resource settings.

The future of tuberculosis therapeutics

Substantial research over the last decade has focused on treatment shortening while maintaining non-inferior efficacy of treatment for drug-susceptible and drug-resistant tuberculosis. The next generation of tuberculosis treatment trials will focus on ensuring new regimens are safer and more tolerable than ever before to improve adherence and reduce the risks of treatment interruption, post-treatment relapse, and acquisition of drug resistance. There is also a pipeline of new chemical entities and long-acting injectable agents that might further transform how we treat tuberculosis,[102,103] similarly to how long-acting antiretrovirals promise to disrupt HIV treatment paradigms.[104,105] Making the most of these opportunities will require national tuberculosis programmes to adopt, roll out, and evaluate novel treatment strategies more rapidly, catalysing policy translation to ensure innovations reach the individuals needing them.

Prevention interventions

Preventive treatment

As outlined in our original report,[1] substantive gains in reducing tuberculosis incidence cannot be achieved without substantial investments in scaling up tuberculosis preventive treatment (TPT) for individuals with the highest risk of developing tuberculosis.[1,71] WHO recommends TPT for people living with HIV and household contacts younger than 5 years, with conditional recommendations for older household contacts. Although there have been considerable gains in providing TPT to people with HIV—from 2018 to 2021, 10·3 million people with HIV received TPT, far exceeding the UN HLM global target of 6 million people by 2022—progress towards scaling up access in other high-risk groups has been disappointing. Between 2018 and 2021, only 0·6 million household contacts aged 5 years and older received TPT, far short of the target of 20 million set at the HLM.[3]

With the advent of shorter regimens, such as 12 weeks of once-weekly isoniazid and rifapentine (3HP)[106,107] and 1 month of daily isoniazid and rifapentine (1HP),[108] we contend that global, national, and local stakeholders must all advocate for greater access to short-course TPT, not only for people with HIV and household contacts younger than 5 years but for household contacts of all ages. Prioritising TPT for all household contacts is likely to be very cost-effective. In a 2023 analysis including 29 high-incidence countries, Ryckman and colleagues estimated that performing contact investigation with short-course TPT for all household contacts would, on average, prevent 11·2 tuberculosis cases (95% CI 5·1–20·4) and 6·8 tuberculosis deaths (4·4–9·8) per 1000 contacts.[109] Effect and cost-effectiveness were greatest for contacts younger than 5 years, who particularly benefited from earlier case detection and treatment through contact investigation. Per 1000 contacts in this age group, a programme of contact investigation with TPT was estimated to result in 19·4 cases (95% CI 7·8–35·6) averted through TPT and 33·5 deaths (95% CI 17·3–55·1) averted through contact investigation and TPT, at a cost of $22 per DALY averted (range $14–154; figure 3). However, even among adults older than 15 years, household contact investigation with TPT was cost-effective in many countries ($309 [$155–1637] per DALY averted). Indeed, household contact investigation with TPT was more cost-effective in most countries than TPT for people with HIV, which is widely accepted as providing excellent value for money.[110,111] These data provide evidence for the recommendation that contact investigation be rapidly expanded and TPT offered to the more than 20 million adult household contacts who are at high risk for tuberculosis, and for advocating for global access to shorter TPT regimens.

The commitment from India in March, 2023, to expand 3HP throughout the country[112] illustrates a growing political will to invest in shorter regimens. Nonetheless, two crucial access barriers undermine the likelihood that other countries will follow India's lead: licensing and cost. In many countries, rifapentine is still not registered or licensed, preventing national tuberculosis programmes from considering formal plans to introduce 1HP or 3HP as the primary TPT regimen. Cost is a major impediment in other countries. Market-shaping efforts

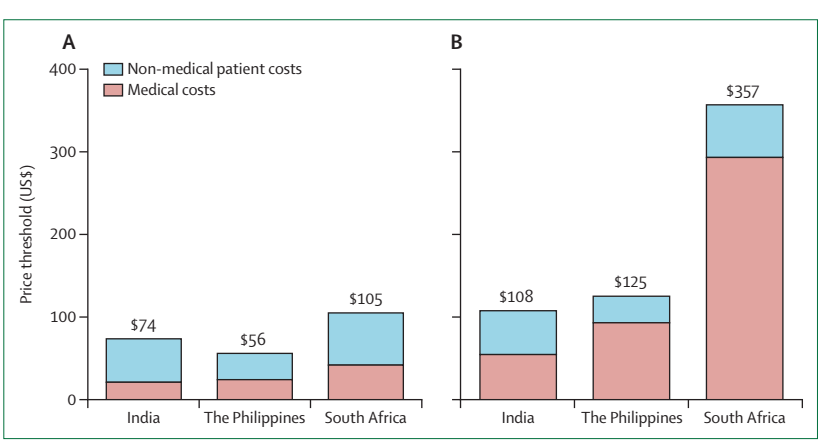

Figure 2: **Price thresholds for 4HPMZ In South Africa, India, and the Philippines**
(A) Cost-neutral (considering the costs of treating a given patient with either regimen and the costs of future retreatments and secondary cases arising from treatment failures within 5 years) and (B) cost-effective (further incorporating willingness to pay for reductions in mortality and other health improvements) price thresholds for the 4HPMZ regimen across three countries, compared with the 6HRZE regimen (current price of US$46). Red bars indicate the thresholds if only medical cost savings are considered, whereas the total bar heights (red plus blue bars) indicate the thresholds when savings on both medical costs and non-medical patient costs (out-of-pocket non-medical costs, such as travel, and indirect time costs from lost wages) are considered. Thresholds are expressed in 2021 US$. 4HPMZ=4-month isoniazid–rifapentine–moxifloxacin–pyrazinamide regimen.

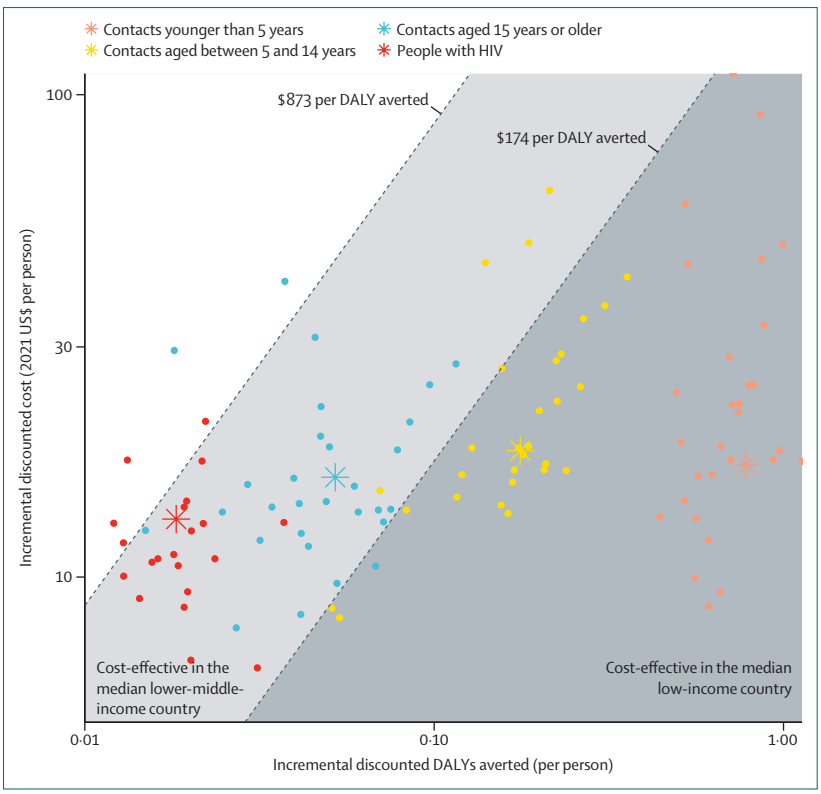

Figure 3: **Cost-effectiveness of tuberculosis preventive treatment (with contact investigation for household contacts) across 29 countries**

Each dot represents a country-specific estimate of discounted incremental DALYs averted per person (household contact or person with HIV) from scaling up short-course TPT (with contact investigation for household contacts) (x-axis) and corresponding discounted incremental costs (y-axis), compared with a scenario of no TPT (and no contact investigation). Population-weighted means across the 29 modelled countries are depicted by larger stars. Shaded areas indicate regions of the graph at which a strategy would be considered cost-effective for the median low-income country (≤$174 per DALY averted; dark grey region) or the median lower-middle-income country (≤$873 per DALY averted; light grey region). These median thresholds ($174 and $873) were estimated from country-specific threshold estimates in Ochalek and colleagues.[94] TPT was estimated to be cost-saving in four countries (not shown). DALY=disability-adjusted life year. TPT=tuberculosis preventive treatment.

to further reduce the price of rifapentine, as part of the 1HP and 3HP formulations, are crucial to making short-course TPT programmes more affordable. As an illustrative example, if the price of a single patient course of 3HP could be reduced by two-thirds, from $15 to $5, the pooled incremental cost-effectiveness ratio of contact investigation and 3HP for household contacts aged 15 years and older could improve from $310 to $250.

In addition to advocating for greater urgency in addressing these barriers to short-course regimens, we assert that the US President's Emergency Plan for AIDS Relief, the largest bilateral funder of HIV programmes globally, should expand its coverage so that short-course TPT is available to all household contacts of people living with HIV diagnosed with tuberculosis in supported countries. Ideally, this coverage should be expanded to household contacts of all people diagnosed with tuberculosis, regardless of their HIV status—as many household contacts could be unaware of their HIV-positive status. Doing so will probably reap substantial economic and epidemiologic dividends.[113]

An essential aspect of increasing the uptake of TPT and other innovations is generating demand from affected communities. As shown by the extraordinary increase in access to antiretroviral therapy for HIV, advocacy for the adoption of new therapeutics by the individuals who would benefit most can influence policy decisions locally, nationally, and globally. Demands from HIV advocacy groups catalysed improvements in the uptake of TPT for people living with HIV. The expanded use of the 3HP regimen has been accelerated by community demand.[114] Galvanising further demand for TPT among the communities most affected by tuberculosis (eg, informal urban settlements in high-burden countries) is essential as these communities are most likely to benefit from TPT, but currently do not have access to this life-saving treatment.

Preventive vaccines

The BCG vaccine, first licensed in 1921, remains the only licensed tuberculosis vaccine. By contrast, in under 3 years, more than a dozen COVID-19 vaccines were approved by WHO for use against SARS-CoV-2 infection.[115] Differences in the global impact, clinical course of infection, and host immune responses partly explain why progress with tuberculosis vaccine research and development has been slower than for SARS-CoV-2. Although developing an effective vaccine for tuberculosis has proven very challenging,[116] a major explanation for poor progress is the severe underinvestment over the last decade.[117] COVID-19 vaccine research received more than $100 billion.[118,119] By contrast, less than $0·1 billion per year has been spent on tuberculosis vaccine research since 2019, constituting only 13% of overall tuberculosis R&D.

As evidence of this chronic underfunding, the most promising candidate tuberculosis vaccine, M72, a fusion protein of two *M tuberculosis* antigens administered with a potent adjuvant, has taken over 19 years to progress from early clinical development studies to a phase 3 trial, which is yet to begin, although the 2023 investment from the Bill & Melinda Gates Foundation and the Wellcome Trust promises to catalyse progress.[120] Nonetheless, this vaccine offers considerable promise given its efficacy in preventing the development of active tuberculosis disease among HIV-negative adults with latent tuberculosis in a phase 2b trial (54·1%, 95% CI 20·3–73·6), not to mention its tolerability and safety profile.[81,121] Previous modelling has highlighted the potential epidemiological dividend of scaling up access to the M72 candidate;[122–125] we modelled the potential economic impact of the vaccine in India. In the best-case scenarios (scenarios 4 and 8), the population between the ages of 5 and 90 years is vaccinated in 2025 and 2030, respectively, with 90% coverage attained over 10 years from initiation. For both scenarios, lifetime protection is

assumed. For other scenarios (scenarios 1–3), the population between the ages of 15 and 49 years is vaccinated in 2025 with 30%, 60%, and 90% coverage attained over 10 years, respectively; for scenarios 5–7, the population between the ages of 15 and 49 years is vaccinated with 30%, 60%, and 90% coverage attained over 10 years. For both cases, the vaccine is assumed to provide a single year of protection. The initial vaccine dose was assumed to be followed up with a second dose after 1 month (although without catch-up vaccination). In scenarios in which the duration of protection is limited to a single year (scenarios 1–3 and 5–7), individuals are assumed to be revaccinated to preserve protection. When vaccination is limited to the 15–49-year-old population, deaths occurring in individuals aged 5–99 years are considered.

Projecting the efficacy shown in the phase 2b trial to the general population with lifetime protection and assuming a vaccination programme that begins in 2025 and attains 90% coverage by 2035, the vaccine could prevent 33·4% of incident cases and 27·2% of deaths (appendix p 45). If vaccination was initiated in 2030 and 90% coverage was attained by 2040, 25% of incident cases and 20% of deaths could be prevented. In addition to the epidemiological dividend, the economic dividend of rolling out this vaccine candidate is very compelling. Figure 4 highlights the vaccine-related costs[126,127,129] of preventing deaths in India; these costs rapidly diminish across a range of different scenarios to levels consistent with other estimates that a vaccine could produce between $283 billion and $474 billion in economic benefits by 2050.[128]

As tuberculosis vaccines are assumed to affect drug-susceptible and drug-resistant tuberculosis equally, introducing a new vaccine is likely to contribute substantially to reducing the programme costs associated with the treatment of drug-resistant tuberculosis.[125] Although the potential impact of the M72 vaccine is promising, a comprehensive vaccine R&D strategy must also invest in the existing pipeline of tuberculosis vaccine candidates, including some candidates showing good promise or evidence of efficacy in animal and human trials.[130] New platforms such as mRNA and viral vectors that were effectively leveraged for COVID-19 vaccines also offer promise.[115]

Key lessons from the success of developing COVID-19 vaccines include mobilisation and effective deployment of large-scale funding, harmonisation of R&D efforts between industry and research institutes, deployment of efficient trial designs, early regulatory input in trial designs, accelerated regulatory review, and mechanisms for scientific exchange.[131,132] The inequities observed with COVID-19 vaccine delivery underscore that diversified vaccine manufacturing capacity (especially in L-MICs) and affordable and equitable vaccine availability are crucial for effective implementation and ensuring the public health impact of mass vaccination programmes.[133] As such, anticipating and preparing for when effective vaccines are available is crucial, including ensuring appropriate community engagement. Such capacity should be developed in tandem with efforts to create a permanent adolescent or adult vaccination programme, analogous to the Essential Programme on Immunization, but capable of delivering tuberculosis vaccine candidates to high-risk adolescent and adult populations.[134]

Taking stock

This new menu of options, including shorter treatment and prevention regimens and more accurate diagnostics that are ready or close to being ready for widespread implementation, offers committed countries drugs and diagnostics that can simplify and accelerate their tuberculosis response. Even with existing tools, a few countries (Cameroon, China, Côte d'Ivoire, Ethiopia, Viet Nam, and Zimbabwe) have managed to reduce tuberculosis mortality rates by 6% or more per year over an extended period.[1] Unfortunately, many countries have been held back by an inability to close the evidence-to-implementation (the know–do) gap. Thus, new implementation frameworks are required to disrupt the status quo of under-diagnosed, inadequately treated, and unevenly prevented tuberculosis.

Reinvigorating national tuberculosis priorities: person-centred, equity-focused approaches

The success of closing the gap between empirical research and policy implementation, including the uptake of a new menu of tools, requires that national tuberculosis programmes rethink the entire cascade of steps involved in implementation planning. Unfortunately, there has been a historical trend of top-down adoption of new biomedical advances. Such approaches eventually reach their impact limit, after which point underlying social and historical factors drive health outcomes. Moving forward, tuberculosis programmes must integrate an equity focus even at the earliest stages of the implementation planning process,[135] ensuring that efforts are responsive to the unique needs of individuals and communities affected by tuberculosis.[1,136] Although these aspirations are not new—WHO has reiterated the need for differentiated approaches to ending various epidemics—a cohesive approach to making and understanding adaptations is needed. Specifically, it is not sufficient that these adaptations are differentiated in so far as they seek to simplify and adapt tuberculosis services across the prevention and treatment cascade in ways that better serve the needs of tuberculosis-affected communities[137]—to succeed, they must explicitly take a person-centred approach (considering the barriers faced by individuals and communities affected by tuberculosis when promoting their health), address the structural causes of health disparities, and evaluate that approach within person-centred conceptual frameworks.[138] Greater

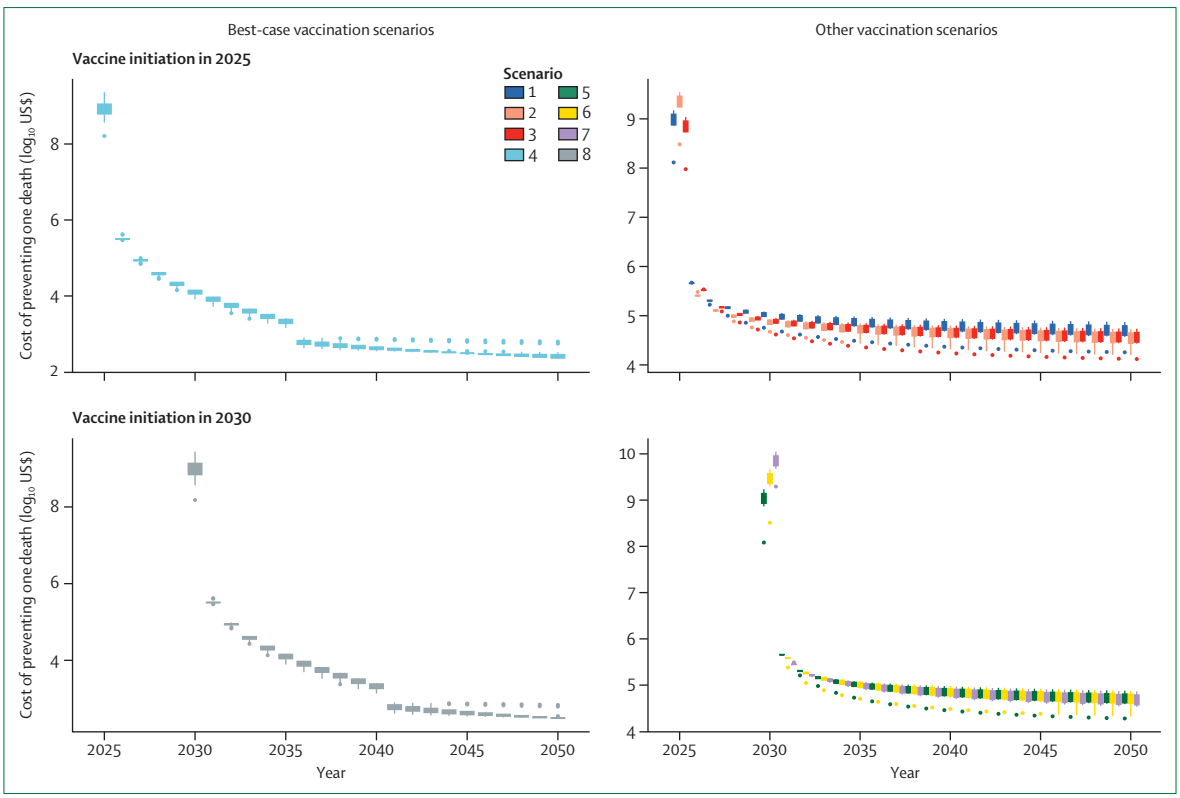

Figure 4: **Assessing the impact of the M72 vaccine with the cost of preventing tuberculosis deaths due to vaccination in India from 2020 to 2050, by vaccination scenario and age group**

Boxplots and outliers represent variation across 5-year age groups from 5–99 years. Vaccine efficacy is assumed to be 54·1% (95% CI 20·3–73·6).[126] Efficacy against infectiousness is assumed to be 50%. The cost of the vaccine was assumed to be $5·30 ($3·34–$5·97) on the basis of pricing for the human papillomavirus vaccine.[108] Vaccine wastage was assumed to be 5%. For vaccine delivery, a routine delivery cost of $2·17 ($1·30–$2·77)[127] and a one-time vaccine introduction cost of $2·77 ($2·49–$3·05) were assumed[128] per regimen. As a fixed cost, a vaccine campaign cost of $29 250 678·71 is also applicable. Vaccine introduction costs were only applied to scenarios 4 and 8 in which the duration of protection was lifelong. All costs are reported in 2022 rates with GDP deflator values from the US Bureau of Economic Analysis. See the appendix (pp 32–45) for a detailed summary of methods and assumptions. GDP=gross domestic product.

understanding and prioritisation of the preferences of people with tuberculosis for diagnosis, treatment, and prevention services will increase the number of people empowered to access and fully benefit from those services.[139] Validated preference elicitation methods,[140] such as discrete choice experiments,[141] might be highly useful in understanding and quantifying these preferences. Additionally, partnering with tuberculosis-affected communities in all steps of the implementation planning process is essential to enhance accessibility and improve clinical outcomes (panel 3). Person-centred care also means respecting the choices people make about where and how they seek care, regardless of whether they seek care in the public or private health sectors.

Civil society engagement in programme design and evaluation through survivor networks and community participation is essential. Reassuringly, national and transnational tuberculosis activism has emerged as a driving force over the last 5 years, facilitating outreach to hard-to-reach populations and supporting community systems. Strengthening community participation to ensure quality tuberculosis services while addressing human rights barriers and gender inequities is vital to ending tuberculosis.[142] The speed and sustainability of the uptake of new tools will be determined by the extent to which these stakeholders are empowered to drive change. Recognising their contribution as a global public good, governments and donor agencies must continue to create opportunities for civil society actors, including community-based tuberculosis organisations, to play an expanded role, not only in programme design but also in strategic planning, evaluation, and accountability.

Addressing the social determinants of tuberculosis

Given the causal role of social determinants in tuberculosis and its outcomes (appendix p 49), it is crucial that tuberculosis is not approached only as a clinical or public health problem.[9] Unfortunately, tackling tuberculosis as part of a broader social problem remains challenging, and progress toward addressing the multisectoral issues undermining the tuberculosis response has been slow. The COVID-19 pandemic exposed profound disparities in socioeconomic opportunities, health-care access, and demographics. It

also increased economic[143] and other social vulnerabilities[144] for individuals at greatest risk for developing tuberculosis disease in high-burden countries.[4] Increased migration, worsening air pollution, and food insecurity resulting from climate change will probably exacerbate tuberculosis risk further in coming years.[66,145,146] Rather than focusing only on a new set of biomedical interventions, urgent interventions to address these determinants are also necessary.

Following the SDG framework to advance a multisectoral agenda for tuberculosis,[147] and as outlined in *The Global Plan to End TB 2023–2030*,[33] it is crucial that high-burden countries and their donor partners track progress with relevant indicators. This includes tracking progress on direct risk factors, such as HIV, diabetes, and smoking (all included in SDG 3), or upstream determinants of poor health and vulnerability, such as poverty and poor social protection (SDG 1), and undernourishment (SDG 2); and mapping indoor air pollution risk (SDG 7) and urban density resulting in poor living conditions (SDG 11). Although assigning targets to track progress across all relevant SDGs is challenging, concerted political advocacy is paramount. Other practical approaches should include addressing tuberculosis in age-specific populations, for example by building links with organisations and facilities devoted to the care of older people, adolescents, or children; addressing tuberculosis screening and TPT among recent migrants, including working closely with specialised governmental and non-governmental agencies, and the International Office of Migration; adopting One Health approaches when zoonotic tuberculosis is an issue; ensuring that people who live in refugee and displacement camps have prompt access to diagnostic and treatment services, requiring collaboration with agencies such as the UN High Commission for Refugees; and adopting comprehensive approaches for tuberculosis, that include both societal and individual interventions, within a person-centred health-care system that ensures high-quality care both for people with tuberculosis and for people at greatest risk for developing tuberculosis.

Undernutrition

Since 2009, undernutrition has been recognised,[10,148] including by WHO, as the leading risk factor contributing to tuberculosis incidence globally, accounting for 2·2 million individuals with tuberculosis (19% of cases) annually (appendix p 50).[149] WHO uses the Food and Agriculture Organization-defined measure of undernourishment (an indirectly modelled estimate based on a country's food balance sheets) to estimate population-attributable fractions related to undernutrition.[150] However, measuring the prevalence of undernutrition (on the basis of height and weight measurements) would enable tuberculosis programmes to leverage already reported surveillance data and target nutritional interventions in geographic regions and among population groups that are most affected.[151]

Recent data have highlighted the importance of addressing undernutrition to avert tuberculosis deaths and reduce tuberculosis incidence. In India, the RATIONS trial[152] showed that supplementary dietary support for people diagnosed with tuberculosis and their household contacts has the potential to reduce the case-fatality rate for people being treated for tuberculosis disease, and reduce tuberculosis incidence among their contacts.[152,153] Providing people with tuberculosis with 1200 kilocalories, 52 g of protein, and micronutrients each day had profound outcomes: a 5% weight gain at month 2 of tuberculosis treatment was associated with a 61% reduction in death (adjusted hazard ratio 0·39, 95% CI 0·18–0·86). Moreover, one tuberculosis death was averted for every 48 people who received this low-cost dietary intervention.[153] The intervention also led to a 39–48% reduction in tuberculosis incidence in household contacts over 2 years of follow-up: an estimated 30 households (111 household contacts) would need to receive nutritional supplementation to prevent one incident tuberculosis case.[154] Addressing undernutrition in patients and clinically vulnerable populations requires action from the agriculture, health, employment, and social protection sectors to address the immediate and basic causes of undernutrition. This collaboration should require the involvement of civil society, non-profit institutions, the private sector, and industry; its benefits are likely to extend far beyond an impact on tuberculosis.

Panel 3: **The perspective of tuberculosis survivors—optimism and impatience**

As tuberculosis survivors and advocates, we are encouraged by new scientific discoveries that have led to shorter tuberculosis treatments and better diagnostics. However, we are also exasperated with the slow pace at which national tuberculosis programmes and donor partners move to increase funding and improve access to these new treatments. We have suffered from the debilitating side-effects of outdated tuberculosis treatment medication and do not want others to go through what we did.

Despite shorter treatments being proven to be safe and effective, they are still not widely available in the countries where we live. We urge the global community to prioritise the roll-out of new treatments—not just for drug-resistant tuberculosis, but also for drug-susceptible disease—and to work with us to ensure these are accessible to all who need them. This includes providing better diagnostics, comprehensive care, and support services, and addressing the social determinants of tuberculosis.

The burden of tuberculosis continues to be borne disproportionately by the poorest and most vulnerable communities; they cannot afford to wait. We call on the global community to fund the initiatives they say they support and redouble efforts to address this urgent public health challenge, keeping tuberculosis patients at the centre of every decision.

New treatments and better diagnostics can revolutionise how we manage tuberculosis. We urge national tuberculosis programmes and donor partners to prioritise roll-outs and to work with us to address the social determinants of tuberculosis, and promote people-centred care. The time for action is now, and we cannot afford to wait any longer.

Tuberculosis programme costs

The cost of ending tuberculosis has risen. In our earlier report,[1] this Commission outlined a plausible cost trajectory for ending tuberculosis within a generation that would require an annual investment of $15 billion for 5–10 years, decreasing to approximately $1–2 billion by the early 2040s.[1] A more recent estimate, commissioned by the STOP TB Partnership in 2023 as part of their Global Plan to End TB,[33] which accounts for the need to make up for losses due to COVID-19 and accelerate the development of new tools, proposes a near-term target of $15 billion a year rising to $20 billion in 2025.[33] Although these estimates represent an increase in current investments, we refer back to the Commission's earlier calculation of a 10 to 1 ratio of benefits to costs from tuberculosis treatment programmes and an indicative cost per death averted through treatment of $7000 for an identified case of drug-susceptible tuberculosis (within a very broad range).[1] 2023 estimates from the Copenhagen Consensus[155] give a much lower estimate of cost per death averted and a correspondingly higher benefit-to-cost ratio; the Copenhagen report estimates that every dollar invested in tuberculosis programmes could generate $46 in societal benefits. The difference results in part from the Copenhagen Consensus assessment making more generous assumptions about transmission reductions from treatments. The STOP TB estimates imply much higher costs per death averted than $7000 and hence far lower benefit-to-cost ratios than the Copenhagen Consensus estimates.

Economic barriers and the burden of debt

Even though tuberculosis programmes offer excellent value for money, the world economy faces a series of severe, mutually reinforcing shocks that threaten to undermine investments in tuberculosis. Although COVID-19 has receded in most regions, the UN estimates that developing economies will have pandemic-related losses in excess of $12 trillion through 2025.[156] Furthermore, the war in Ukraine and related sanctions are disrupting food and energy markets and worsening food insecurity and undernutrition in many L-MICs.[143] In addition to pushing 120 million people into poverty,[157] COVID-19 has triggered an unprecedented increase in debt for the governments of countries with high tuberculosis burdens. Moreover, COVID-19 required that many governments rebalance health spending away from tuberculosis, at least temporarily (figure 5A). In this prevailing economic climate, sustaining or increasing tuberculosis funding has been challenging. 27 of the 30 countries with the highest tuberculosis burden saw a widening gap between the tuberculosis budget required and the amount expended during the period 2017–2021 (figure 5B).

Of the countries with the highest tuberculosis mortality, a substantial number carry a heavy public debt burden that predates the pandemic but has markedly increased over the last 4 years (appendix pp 52–57). On average, public debt levels, as a proportion of gross domestic product (GDP), rose from 46% to 60% between 2017 and 2021 among the 30 highest-burden countries (figure 5C). Many of these countries have such high levels of debt that they are in breach of a debt solvency threshold.[158,159] Higher debt levels typically lead to austerity policies including reductions in spending on public health spending, which is likely to have adverse outcomes for individuals at greatest risk of tuberculosis.[160]

These economic challenges have substantial policy implications for how governments in LICs and L-MICs with high tuberculosis burdens fund their health programmes. First, strengthening the multilateral response to tuberculosis is essential to provide some of these countries with adequate support. It necessitates increased funding from official development assistance (ODA) and non-concessional financing from development banks. Although donor funding can lead to aid substitution (also referred to as fungibility), whereby countries respond to receiving external responses by reducing their domestic contribution to the health sector,[34] the scarce available data suggest that the fungibility of external funds might not necessarily be detrimental to a country's development,[161] and should not preclude sustained global investment in tuberculosis programmes. Concessional financing, such as the $400 million World Bank loan to the Government of India, could be an option for some middle-income, high-burden countries. In this initiative, the Global Fund is providing $40 million to buy down the principal of the loan, and the Gates Foundation is providing independent verification of tuberculosis outcomes as part of a results-based reimbursement mechanism.[162] This mechanism will hopefully allow the Indian government to leverage additional private-sector investment.[162] For India, and for other middle-income countries (MICs) with a high tuberculosis burden, the question that must ultimately be addressed is that of why the government has allowed such a heavy burden of debt to persist. Although external assistance can lessen the need for government commitment, MICs should reasonably expect to mobilise more domestic resources in support of tuberculosis activities.

Second, some high-burden countries require support to address unsustainable debt burdens. Failure to do so will divert resources not only from the tuberculosis response but also from other health programmes. Debt-for-health swaps or outright debt cancellation should be considered to alleviate this burden in low-income countries (LICs). Future multilateral financing should consider health expenditures and financing requirements as a central consideration for ODA. Both concessional financing and debt cancellation could be linked to requirements that countries commit to sustained levels of public spending on health, including strengthening health service delivery and access to essential medicines, in service of tuberculosis programmes.[163]

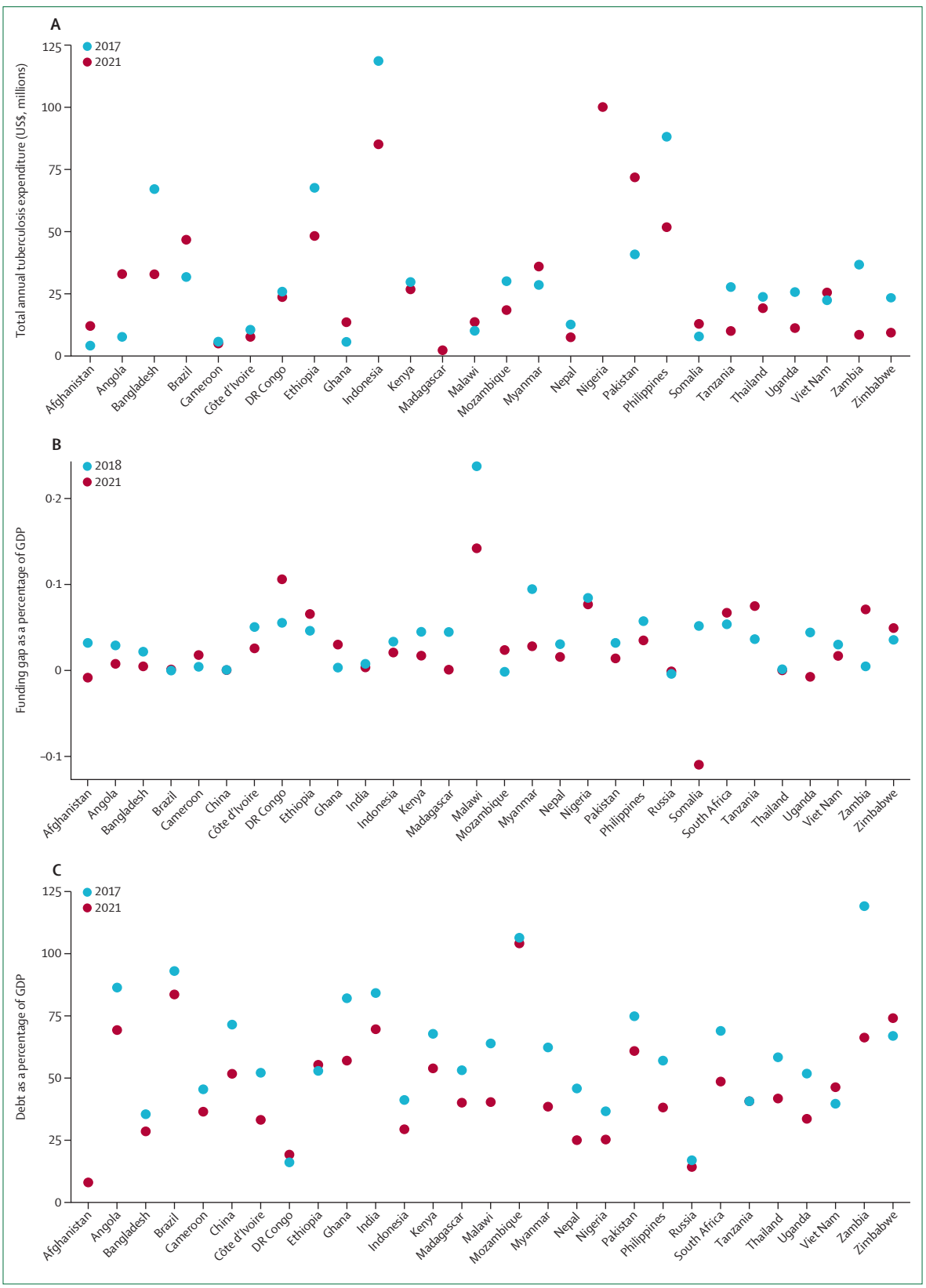

Figure 5: **Annual tuberculosis expenditure, tuberculosis funding gap, and government debt in the 30 countries with the most tuberculosis deaths**
(A) Total annual tuberculosis expenditure. China, India, and Russia are outliers and were excluded. China spent US$419 million in 2017 and $792 million in 2021. India spent $448 million in 2017 and $297 million in 2021. Russia spent $1·43 billion in 2017 and $1·45 billion in 2021. South Africa is not shown due to the unavailability of data. 2021 data are not available for Nigeria and Madagascar. (B) Tuberculosis funding gap (required budget minus actual expenditure) as a percentage of GDP. National tuberculosis budget data are unavailable before and including 2017, so 2018 was used. (C) General government gross debt as a percent of GDP. Somalia is not shown due to the unavailability of data. 2021 data are unavailable for Afghanistan. All tuberculosis expenditure and budget data come from the WHO Global Tuberculosis Programme. All GDP and debt data comes from the IMF World Economic Outlook database, 2023. GDP=gross domestic product.

Tuberculosis donor financing and COVID-19

Even though tuberculosis is primarily funded by domestic resources (79% in 2021),[3] ODA is essential to tuberculosis efforts in many L-MICs and LICs, with the Global Fund providing almost two-thirds (64·4%) of all tuberculosis ODA in 2021.[3] Our analysis for this report shows a clear association between tuberculosis ODA relative to a measure of need and the percentage decline in tuberculosis death rate: for every $10 000 increase in aid per tuberculosis death in 2010, there was a 6% decline in the tuberculosis death rate between 2010 and 2021 (appendix p 52). However, there are outliers: Tanzania, South Africa, Malawi, Ethiopia, and Kenya performed exceptionally well in absolute terms and relative to aid received, whereas India and Pakistan fared poorly. Many factors are at play, but there is a strong suggestion in these data that the payoff from external aid to tuberculosis response is real and substantial (appendix p 58). For almost all these countries, the Global Fund has been the single largest source of tuberculosis ODA. However, of the three diseases supported by the Global Fund, tuberculosis has consistently been allocated less funding (18% of total allocations) than HIV (50%) or malaria (32%). This allocation results, in part, from patterns of country demand. Greater allocation of funds for tuberculosis is essential.[3] Furthermore, we argue that greater representation from communities affected by tuberculosis in how Global Fund resources are disbursed is crucial. We also highlight the intersecting priorities between donor financing for tuberculosis and the new Financial Intermediary Fund for Pandemic Prevention.[164]

Rethinking the Global Fund's tuberculosis allocation

In 2022, the Global Fund board approved an increase in funding for tuberculosis for the 2023–25 allocation (18% of country allocations up to $12 billion and then 25% on all funds above that figure);[165] this was the first increase in the Global Fund's allocation for tuberculosis in 20 years. Unfortunately, since the Global Fund's 2022 replenishment conference was less successful than hoped,[165] the dividend of this new allocation strategy is likely to be modest. For the 2023–25 period, the total allocation for tuberculosis amounts to $2·442 billion. This is a $156 million increase compared with the previous 3-year period, a small amount once inflation is considered. The Global Fund's allocation model will be evaluated in 2024, providing a window of opportunity to make more substantial adjustments and increase future funding for tuberculosis. Accordingly, this Commission strongly recommends that the Global Fund revise the model on the basis of disease burden and cost-effectiveness; it is neither economically, epidemiologically, nor morally justifiable that tuberculosis receives so much less Global Fund funding than the two other diseases (figure 6). We argue that an increase in tuberculosis funding up to 33% of the total allocation is appropriate. However, rather than disbursing an increase in tuberculosis support to all currently eligible countries, we argue that the increase should be prioritised for LICs with higher tuberculosis mortality.

New Global Fund ambitions

To fully realise the potential of increased Global Fund support for tuberculosis, recipient countries must also set ambitious targets in their national strategic plans (NSPs) and develop Global Fund application proposals that disrupt the status quo of underdiagnosed, inadequately treated, and unevenly prevented tuberculosis. Unfortunately, many national tuberculosis programmes in high-burden countries have been hampered by low levels of government ambition, reflected in the contents of NSPs that set modest and inadequate targets. These NSPs in turn translate into proposals to the Global Fund that, with limited budgets and finite scopes, are unable to implement new diagnostic platforms, methods, and tools; shorter and less toxic effective regimens for both drug-susceptible and drug-resistant tuberculosis; and shorter, well-tolerated preventive regimens, all of which are essential to eliminating tuberculosis. The Global Fund Country Coordinating Mechanisms (CCMs) develop and submit proposals on the basis of the NSPs that frequently do not include informed, engaged input from people affected by tuberculosis and their allies. In one study, only 14% of CCMs had tuberculosis-specific expertise, and even this expertise was concentrated in a small number of CCMs.[166] This Commission argues that more effective representation from tuberculosis community-based civil society groups in CCMs is vital. These stakeholders can play a crucial role in marshalling the available evidence, formulating precise demands, and engaging national stakeholders to ensure each country's Global Fund application is sufficiently ambitious.

Intersecting donor financing priorities

In September, 2022, the World Bank launched its Pandemic Fund, a new financing mechanism to strengthen pandemic prevention, preparedness, and response capacities in LICs and L-MICs.[164] This fund is promising for global tuberculosis efforts if it can incentivise countries to increase pandemic preparedness and response financing, including allocating resources to strengthen country's abilities to respond to long-standing infectious disease threats, such as tuberculosis. Nonetheless, the Pandemic Fund must not repeat the mistakes of the past, when health security focused on short-term surveillance and outbreak containment funding was siloed and kept separate from other investments. Instead, we suggest co-investing some of the funds in the building blocks necessary to create robust, resilient health systems able to prevent and respond to future pandemic threats, which—given that the next pandemic or epidemic is highly likely to be airborne—will also strengthen responses to ongoing infectious epidemics such as tuberculosis.[167] Unfortunately, investments in tuberculosis ODA between 2020 and 2021

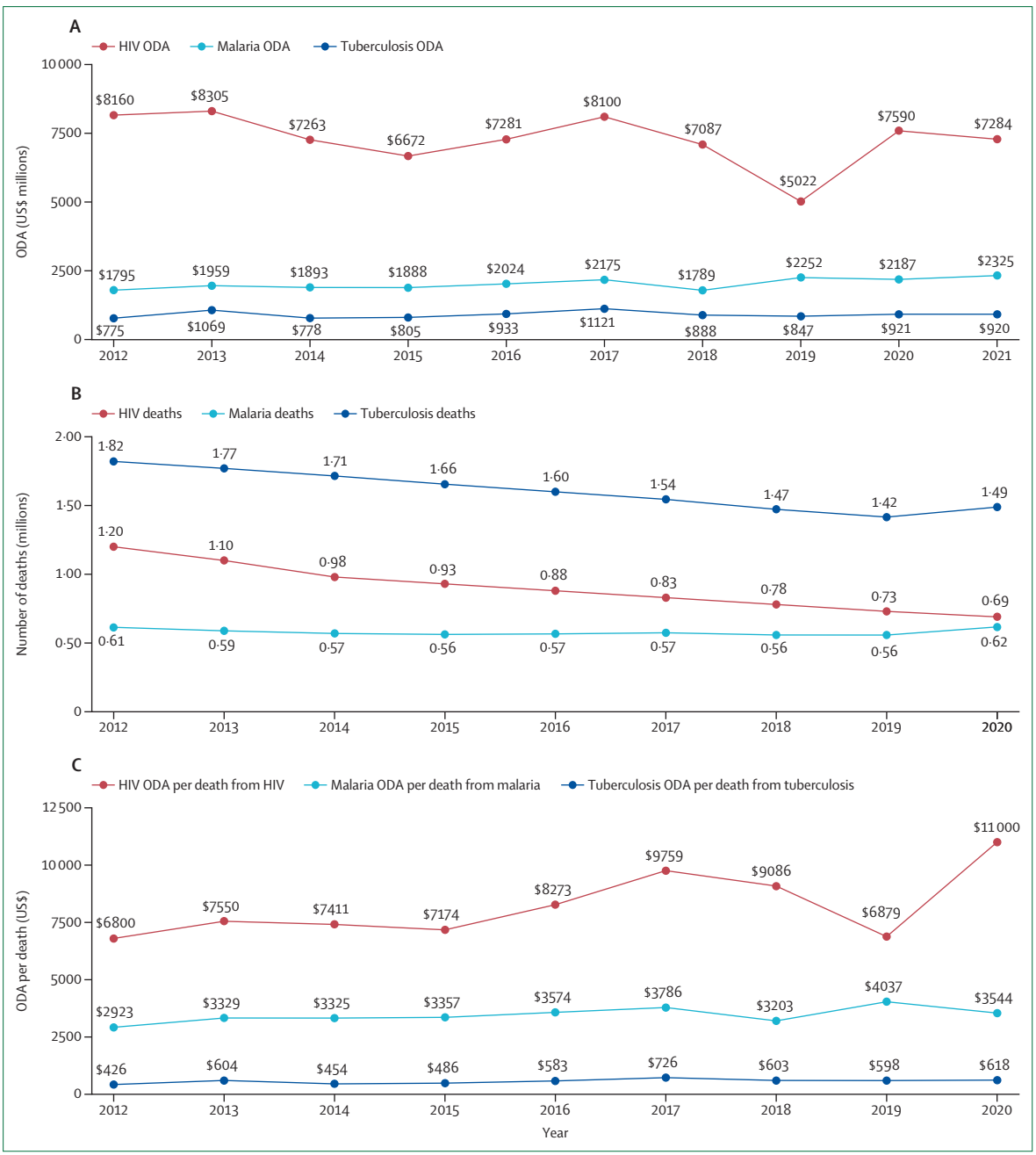

Figure 6: **Trends In ODA, deaths, and ODA per death for HIV, malaria, and tuberculosis**
(A) Trends in total ODA for HIV, malaria, and tuberculosis. (B) Deaths from HIV, malaria, and tuberculosis. (C) HIV, malaria, and tuberculosis ODA per HIV, malaria, and tuberculosis death. Values reflect ODA from all sources. All ODA data are from the OECD Creditor Reporting System. All mortality data are from the WHO Global Tuberculosis Programme, WHO Global Malaria Programme, and UNAIDS Epidemic and Response database. ODA=official development assistance.

For more on the **UNAIDS Epidemic and Response database** see https://aidsinfo.unaids.org/

were adversely affected by the COVID-related ODA: among the countries with the highest burdens from tuberculosis, each 1% increase in annual COVID-19 donor assistance was associated with a 2% decrease in annual ODA for tuberculosis (appendix p 52).

Neglecting to leverage pandemic preparedness and response assets to support tuberculosis will probably result in unnecessary duplication and siloing of expertise and undermine effective pandemic prevention and response agendas. Conversely, investing in tuberculosis will probably lead to public health benefits between pandemics while preventing the cycles of panic and neglect that have historically undermined pandemic funding initiatives.[168,169] In line with other stakeholders,[170] this Commission recommends that the Global Fund occupy a central position in implementing the Pandemic

Fund; investing in preparedness through the Global Fund's existing programmes will reduce siloing of funding, better integrate with preparedness with health systems, and offer the best chance of ensuring that pandemic investments align with tuberculosis-specific investments.

Seizing the moment

Driving progress towards ending tuberculosis after the setbacks of the COVID-19 pandemic will demand a substantial increase in financial resources; it will also require substantial political capital and a coordinated global agenda. In September, 2023, the UN will hold three HLMs on pandemic preparedness and response, universal health coverage, and tuberculosis. These events (and their aftermath) constitute a crucial moment for the global health community to align on intersecting priorities and leverage the synergistic impact of a coordinated strategy toward meeting the aims of all three agendas. In this section, we summarise several areas in which coordinating global tuberculosis efforts with both the pandemic preparedness and response and universal health coverage agendas can serve mutually beneficial aims. We also highlight the importance of global coordination to ensure increased investment in tuberculosis R&D and affordable and equitable access to the resulting technologies in the countries with the highest tuberculosis burden.

Aligning with the pandemic preparedness and response agenda

The COVID-19 pandemic has illustrated that pandemic preparedness and response systems are crucially important and chronically weak. The capacity of some high-burden countries to quickly leverage tuberculosis infrastructure to respond to SARS-CoV-2[19,156] underscores the importance of tuberculosis programming as part of a rapid and robust pandemic preparedness and response. Although investing in pandemic detection and responsibility capability is important, these investments should be synergistic with efforts to end tuberculosis. Countries battling multiple parallel health challenges cannot afford to invest in siloed pandemic preparedness and response programmes. Coordinating any investments focused on pandemic preparedness and response with efforts to tackle existing diseases, including tuberculosis—itself an airborne pandemic—would ensure immediate benefit for citizens while simultaneously enhancing readiness for future pandemics.[171]

Panel 4 highlights potential alignment opportunities between pandemic preparedness and response and tuberculosis policies. Four key opportunities include aligning incentives and metrics, expanding multidisease diagnostic capacity, enhancing adult vaccine delivery capacity, and investing in resilient response systems. First, as global stakeholders develop pandemic preparedness and response results frameworks to measure impact and hold nations accountable for pandemic preparedness funding,[172] tuberculosis should be included within a package of tracer indicators that can give a better, real-time understanding of a country's capacity to detect, diagnose, and respond to emerging airborne infectious disease threats. Because of the parallels in clinical presentation, diagnostic infrastructure, and public health response (eg, contact tracing), and the need for equity-informed programming, an assessment of any country's tuberculosis response programme could be a reliable proxy for its capacity to address the pathogenic potential of other respiratory pathogens. Aligning monitoring, accountability, and incentive metrics for pandemic preparedness and response and tuberculosis funding would enable concrete measures of pandemic preparedness while expanding accountability for current tuberculosis efforts.

Second, increasing decentralised access to molecular tuberculosis diagnosis will also increase the chances of detecting a novel airborne outbreak early. Unfortunately, the COVID-19 pandemic diverted substantial tuberculosis detection capacity and showed the fragility of existing infrastructure under the threat of a novel pandemic.[23,173] Tuberculosis case detection decreased by 18% globally from 2019 to 2020.[19] An ideal detection system should rapidly diagnose patients with respiratory symptoms and respond to newly detected pathogen threats without jeopardising existing tuberculosis diagnostic capacity. Investing in high-functioning laboratory systems with interoperable, multidisease diagnostic platforms, as outlined above, and investing in community health and respiratory workforce development could enhance tuberculosis efforts while creating a system capable of detecting emerging pandemics.[174]

Third, as the COVID-19 pandemic showed, we must drastically enhance country capacity to efficiently deliver adult vaccines, especially given the promising tuberculosis vaccine candidates in the pipeline. Although we have seen great strides in the Expanded Programme on Immunization for children, a similar capacity for adult vaccines lags.[175] Establishing vaccine delivery capacity, including localised vaccine manufacturing, primary care and community-based vaccine delivery, reliable cold chains, and digital health tools to identify, prioritise, recruit, and track adults for vaccination[134] is a crucial component of the global pandemic preparedness and response agenda, and a prerequisite to successful tuberculosis vaccine roll-out. By building this capacity now for tuberculosis, we will be better prepared for the next pandemic.

Finally, to sustain tuberculosis efforts while responding to future pandemics, we must develop resilient and affordable medical procurement systems and supply chains, strengthen infection prevention and control capacities, expand contact tracing capabilities, and improve surge planning policies. Moreover, engaging and mobilising community and private sector partners in dual-purpose pandemic preparedness and response and

Panel 4: **Strategic alignment between global tuberculosis efforts and the pandemic preparedness and response agenda**

Governance and accountability
- Inclusion of tuberculosis within pandemic accountability and results frameworks, tracking tuberculosis as a tracer indicator for pandemic preparedness
- National biosafety legislation and regulation to coordinate tuberculosis-specific efforts with broader pandemic preparedness and response efforts
- Harmonisation of standards between regulatory agencies at national and regional levels
- Coordination of in-country spending on pandemic preparedness and response and tuberculosis at the level of ministries of health or public health institutes to avoid duplication of efforts

Prevention
- Expansion of drug susceptibility testing
- Case-based surveillance, including antimicrobial resistance
- Building One Health capacity to detect and prevent both zoonotic tuberculosis and new zoonotic pandemic threats
- Utilisation of the reserve or watch categories of WHO's Access, Watch, Reserve (known as AWaRE) system to monitor antibiotic consumption and stewardship while balancing access to essential antimicrobials

Detection
- High-functioning laboratory systems with interoperable, multidisease diagnostic platforms (eg, GeneXpert, NAAT, microbial culturing, investment in drug-susceptibility testing)
- Modernisation of epidemiological surveillance and data systems capable of continuous surveillance and real-time notifications, and regular compilation of national and global data
- Expansion of the community health workforce
- Upgrading infection control and prevention systems for infectious respiratory pathogens including both tuberculosis and novel threats (eg, ventilation systems and particulate respirators)

Response
- Strengthening multisectoral coordination, investing in community-led systems, and engaging with private sector partners
- Creating and investing in social protection programmes
- Development of digital, resilient, and affordable medical procurement systems and supply chains
- Establishment of robust national drug stockpiles for essential medicines
- Publication of national strategic plans for health-care-associated infections to protect the health-care workforce

Innovation
- Dual-use research and development for point-of-care diagnostics, drug-susceptibility tests, child-friendly diagnostics, and effective information technology and communication systems
- Bolstering research capacity

tuberculosis efforts can support a more resilient, robust, and comprehensive response. Coordinated investments will deliver dividends for tuberculosis programmes in the near term while also enhancing pandemic preparedness in the long term. Pandemic preparedness and response should not be a stand-alone, hypothetical investment in potential threats. Instead, we can coordinate and build our pandemic preparedness and response on the foundation laid by the response to pathogens such as tuberculosis.

Aligning with the universal health coverage agenda

This Commission previously argued that progress towards ending tuberculosis should occur in tandem with expanding universal health coverage through the expansion of primary care services to communities with the highest risk of acquiring tuberculosis.[1] Strengthening population health systems, improving primary health systems, and improving performance from private providers is crucial to ending tuberculosis.[176] Additionally, countries committed to universal health coverage will need to invest in a package of essential services (including tools for tuberculosis diagnosis, treatment, and prevention) that is publicly financed and available at no or minimal cost. However, more than simply providing populations with a package of services is required. As highlighted in our previous report and by other *Lancet* Commissions,[177] an important gap in the effective implementation of tuberculosis services is low-quality care (especially in the private and informal health sectors) and scarce human resources. Although a new menu of tuberculosis tools offers promise, their incorporation into tuberculosis programmes will depend on addressing human resource constraints.[34,178] In many countries, incentives must be realigned to ensure an adequate supply of health-care workers in the regions of greatest need. Additionally, the uptake of new tools in many L-MICs is undermined by a low regulatory capacity to approve new drugs and diagnostics.[179] Donor support to strengthen regulatory capacity at national and regional levels is crucial to advancing new tuberculosis tools and improving health security through the expansion of local manufacturing of quality, safe, effective, and affordable medicines, vaccines, and other health interventions.

Optimising private sector engagement

We endorse a progressive pathway to universal health coverage that involves zero user fees for interventions in the universal health coverage benefits package.[180] We recognise that the private sector is dominant in many

countries with high tuberculosis burdens and can complement and extend services offered in the public sector.[181] In 2021, the national tuberculosis programmes of the seven highest-burden countries with substantial private health-care sectors (India, Indonesia, the Philippines, Pakistan, Bangladesh, Myanmar, and Nigeria) reported to WHO that private health-care providers diagnosed a total of 1·2 million tuberculosis patients, or 32% of the total notified patients that year (appendix p 59). However, private-sector care, with no intervention, can be suboptimal in many settings.[177,182]

In 2021, the private sector contributions to the total number of individuals diagnosed with tuberculosis ranged from 22% in the Philippines to 41% in Pakistan. These numbers reflect a steady increase in private provider engagement in most of the highest burden countries in recent years as part of the global drive to find the missing tuberculosis patients—ie, the difference between the estimated number of individuals who developed tuberculosis and the number who were diagnosed and reported in a given year. Data suggest that tuberculosis-related care and treatment in the private health sector in several countries bounced back quickly after successive COVID-19 outbreaks and made a positive contribution to overall recovery (appendix p 60).[31]

Apart from in India, public–private mix engagement at scale is mainly funded by international donors, particularly the Global Fund and USAID. In some countries (notably India, the Philippines, and Indonesia), notification of diagnosed tuberculosis patients to the national tuberculosis programme is not always accompanied by the same standard of diagnostic and treatment services available to patients notified by public sector providers or by verifiable use of similar drugs and diagnostics purchased from private suppliers. As such, Global Fund investments to ensure private sector quality and mitigate the negative externalities of the cross-border spread of acquired drug resistance represents an important, albeit unappreciated, global public good.[183]

Tuberculosis programmes and their partners in countries with substantial private health-care sectors face several challenges in delivering quality tuberculosis services, including the high cost of WHO-recommended rapid diagnostics in the private sector and scarcity of sample transportation and other systems to deliver publicly funded WHO-recommended rapid diagnostics; logistics and support systems to deliver programme drugs and support privately managed patients through the complete course of treatment; delivery of contact investigation and other public health functions; development of unified, user-friendly digital tuberculosis case notification data systems that include private providers; and a progressive transition from international funding to domestically financed strategic purchasing schemes, including the adjustment of payment systems in social health insurance programmes.

A priority for all countries with a large private sector is to strengthen the capacity of ministries of health to move beyond case notifications as the key indicator and improve the reach and quality of tuberculosis services, whether provided by public or private providers.[184] Although much has been learnt since the early 2000s about how to do this, a large gap remains between patients' early care-seeking preferences and the availability of publicly funded tuberculosis services. Future research priorities should include improving understanding of patient and provider behaviours and their determinants, as outlined earlier, and increasing the efficiency and equity of efforts to deploy affordable tuberculosis services wherever patients first seek care.

Preventing catastrophic costs

Although the provision of tuberculosis services is the purview of the health sector, other sectors (eg, those responsible for urban planning, labour, and welfare) also have vital roles in preventing or mitigating other causes of economic and financial hardship for people with tuberculosis. Unfortunately, in WHO's 2022 report on national survey of costs faced by tuberculosis patients and their households,[185] only four of the 19 countries surveyed had any form of non-contributory social protections. Although many countries have contributory social protection schemes, these tend to be tied to employment and are unlikely to cover individuals at greatest risk of tuberculosis. Moreover, many packages to mitigate catastrophic costs are only available to patients with drug-resistant tuberculosis.[98] As such, it is crucial that the national authorities responsible for health (including tuberculosis) and social affairs are held jointly accountable for designing policies that ensure individuals who are the most clinically vulnerable to tuberculosis can access affordable or free health-care services and are protected from the indirect costs resulting from tuberculosis. The epidemiological dividend of extending social protection coverage is likely to be substantial. Modelling analysis from 2018 has shown that expanding social protection to 50% global coverage could lead to a reduction in tuberculosis incidence of 42% by 2035.[186]

The COVID-19 pandemic has taught the world that multiple mutually reinforcing interventions best control epidemics; biomedical tools (eg, diagnostics and vaccinations) must be used with other societal interventions (eg, social protection). The tuberculosis pandemic demands an approach that combines both societal-level and individual-level interventions within a person-centred health-care system.[19] Cross-sectoral approaches that promote poverty reduction and social protection expansion will be crucial complements to health interventions, accelerating progress towards the End TB Strategy targets.[186] At the same time, focused tuberculosis programmes can themselves provide important pathways out of poverty.

Ensuring equitable access to tuberculosis innovations: overcoming financing and pricing challenges

As outlined earlier in this report, the R&D pipelines for tuberculosis diagnostics, therapeutics, and vaccines offer substantial promise. The uptake of existing, proven tuberculosis technologies has been slow in many high-burden countries. Failure to fully scale access to Cepheid's Xpert MTB/RIF assay, for example, offers a cautionary tale.[187] In 2012, WHO (in collaboration with UNITAID, the Gates Foundation, and the US Government) entered into an agreement with Cepheid to buy down the cost of its test for use in 145 L-MICs.[188] By agreeing to buy down the cost of the test, WHO hoped to catalyse rapid uptake in countries that would not otherwise have been able to afford to use it. Unfortunately, although country procurement of Xpert tuberculosis tests initially increased[187] and manufacturing costs decreased,[189] the agreement did not require Cepheid to further reduce the price of their test with rising sales volumes, nor obligate them to ensure platform calibration and maintenance was affordable. This failure of volume-based adjustments in price explains in part why many countries have not been able to maximise Xpert's impact in line with WHO recommendations[3,188] or modelling projections.[190–192] Moreover, the failure highlights the importance of ensuring transparent, equitable, and affordable access to the new array of tools for tuberculosis, especially for those technologies developed with public investments.[193,194]

Grants, loans, licensing agreements, advanced market commitments, buy-downs, and other market interventions are all important tools for catalysing the development of new and vitally needed diagnostics and therapeutics for tuberculosis.[187,195,196] For new and emerging tuberculosis therapeutics, voluntary licensing, in which the patent holder voluntarily authorises a generic manufacturer to make generic versions might also be of importance. The Medicines Patent Pool is a major global mechanism for issuing voluntary licenses. It has signed agreements with 18 patent holders for 35 medical products, including the tuberculosis drug, sutelozid. Although there is evidence that voluntary licensing drives down prices and expands access,[165,197] such licensing can have limitations. Medicines Patent Pool licenses often exclude key MICs that have a high tuberculosis burden. Additionally, voluntary licenses might include secretive and restrictive conditions and limits on where and to whom the generic version can be sold, and the patent holder might maintain control over the supply of active pharmaceutical ingredients.[197,198] For example, Otsuka granted a voluntary license to Mylan on delamanid, but Mylan "can only produce and supply delamanid tablets using active pharmaceutical ingredients from Otsuka at prices set by Otsuka".[198]

To ensure that public investments in tuberculosis R&D result in equitable access to new tuberculosis diagnostics, therapeutics, and vaccines, this Commission endorses licensing principles such as those outlined by the Drugs for Neglected Diseases initiative: voluntary licensing agreements should be non-exclusive, perpetual, irrevocable, royalty-free, fully paid up, sublicensable, and require that distribution be contingent on pricing of the final product at the lowest sustainable level covering manufacturing and distribution costs and including a reasonable margin (appendix p 61).[199] However, the utmost priority lies in ensuring that tuberculosis programmes continue to invest in existing tools that are already affordable and accessible.

Conclusion

Since this Commission's last report in 2019, global progress towards ending tuberculosis has slowed because of the COVID-19 pandemic, but a newly expanded set of tools and strategies offers hope for a brighter future. The UN HLM on tuberculosis in September, 2023, provides a unique opportunity to galvanise global efforts and draw attention to new approaches that make ending tuberculosis more achievable than ever before. However, we must act quickly, as further delays will only result in more needless suffering and loss of life. An equity-focused human rights agenda, coupled with efforts to secure universal health coverage, is essential to end tuberculosis. The COVID-19 pandemic has also underscored the importance of optimising coordination between pandemic preparedness and tuberculosis elimination efforts.

To end tuberculosis, governments, especially in MICs, must prioritise funding for tuberculosis prevention, diagnosis, and treatment, and donors must increase their contributions to support national tuberculosis programmes in LICs. Increased funding for tuberculosis R&D is crucial to expedite access to new technologies that are in the pipeline. Ensuring that tuberculosis programmes are not overpaying for new tuberculosis technologies (especially those that have benefited from public funding) is essential to ensure that investments in tuberculosis programmes can do more. We must recognise that the fight against tuberculosis is not just a public health or scientific endeavour, but also a moral one. We must acknowledge the tremendous human toll of tuberculosis and work to eliminate it with urgency and compassion. We must redouble our efforts, engage diverse stakeholders, including the individuals most affected by tuberculosis, and hold ourselves accountable. This *Lancet* Commission urges governments, donors, civil society, and other partners to prioritise this urgent task and invest in the necessary resources to end the tuberculosis epidemic once and for all.

For more on the **Medicines Patent Pool** see https://medicinespatentpool.org/

Contributors

The first draft of this report was written by a core writing team led by MRe, with input from DJ, NA, and EG. Extensive consultation with commissioners from the original report and additional authors listed below was crucial to the development of the report structure and concepts, writing and editing of subsequent drafts, and conclusions. The report was prepared under the general direction of EG, and co-chair DJ,

with inputs from SSw. The Introduction and section on progress since 2018 were drafted by MRe with inputs from DJ, EG, HC, LD, and AKi. The section on diagnostics was drafted with input from CMD, AC, NA, MRe, and MP, with concomitant modelling analysis from NA and C-CK. The section on therapeutics was drafted with input from GEV, PN, MRe, HC, DD, EK, and TR, with complimentary modelling analysis from TR, DD, and EK. The section on prevention was drafted with input from MRe, TR, DD, RC, GC, and SSw, with modelling analyses from TR, EK, DD (tuberculosis preventive therapy analysis), and SSw (vaccine analysis). The first draft of the section on social determinants was written by MRe and MRa; the section on undernutrition was written by ABh, MB, and MRe. The section on tuberculosis financing was drafted by MRe with inputs from DJ, GY, MS, EG, MG, and MD. Donor financing analysis and assessment of economic headwinds were performed by MS and AZ. The section on seizing the moment was drafted by MRe and AKi with inputs from DJ, EG, MO, JH, MS, DD, GY, and AZ. Perspectives of tuberculosis survivors were provided by EF and NV. The perspectives of the tuberculosis community throughout the document were provided by EF, NV, AHS, YJPA, SK, and EVM. Data gathering was done by MRe, AKi, and ABe, with additional inputs from a supporting research team listed in the Acknowledgments. In addition to the participation and inputs of Commission members, several contributory authors prepared and shared background papers and analyses to support the report, as outlined above.

Declaration of interests

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