

## Accelerate investment and action to find the missing patients with tuberculosis



Globally, there were about 10 million new cases of active tuberculosis in 2020 and an estimated 1.5 million deaths.<sup>1</sup> In the same year, in many African countries, there were more deaths from tuberculosis than from COVID-19.<sup>1-3</sup> Early detection and effective treatment is the key strategy to combat tuberculosis. Unfortunately, even before 2020, about a third of people newly ill with tuberculosis remained undetected—the missing tuberculosis diagnoses.<sup>4,5</sup> Detecting these individuals with active tuberculosis is important not only to prevent morbidity and mortality but also to subvert amplification of this airborne epidemic, since almost a third of these people are likely to be highly infectious with smear-positive or cavitary disease.<sup>6</sup> Indeed, for example, a 2018 South African national door-to-door survey showed that 58% of people with culture-positive tuberculosis did not report any symptoms.<sup>7</sup> Currently deployed global and national health strategies are not fundamentally configured to detect this missing burden of disease, because they rely on patients self-reporting to clinics or health-care facilities (passive case finding). All these considerations also apply to the multidrug-resistant tuberculosis epidemic response.<sup>8</sup>

COVID-19 was associated with an estimated increase in the number of missing new tuberculosis diagnoses to about 4 million worldwide in 2020.<sup>1</sup> The COVID-19 pandemic has disrupted access to tuberculosis services, resulting in multidimensional effects, including increased tuberculosis morbidity and mortality.<sup>9</sup> However, the scientific and public health response to COVID-19 has also brought many lessons. Within months of the advent of COVID-19, in tandem with massive investments in research and development and ratification of global treaties, new diagnostics, drugs, and vaccines were developed and rolled out on an unprecedented scale.

Why has this response not occurred for tuberculosis? Tuberculosis typically kills over months to years with individuals from marginalised communities dying at home or in outlying hospitals. More than 98% of people who die from tuberculosis live in countries where the majority are people of colour. The disease is also associated with resource limited or historically neglected populations—euphemisms for medical racism—fuelled

by structural violence and entrenched systems of socioeconomic exploitation.<sup>10,11</sup> Investment in the global public sector research and development funding for tuberculosis grew from a pitiful US\$389 million in 2010 to a shameful \$642 million in 2020.<sup>12</sup> In stark comparison, about \$104 billion was spent by governments on research and development in the first 11 months of the COVID-19 pandemic.<sup>12,13</sup> Although newer tuberculosis diagnostics, such as GeneXpert Ultra,<sup>14</sup> and newer drugs, such as bedaquiline and pretomanid, have been rolled out slowly,<sup>8</sup> a tuberculosis vaccine with about 50% efficacy has not yet started enrolling patients for phase 3 evaluation 8 years after the phase 2b trial began.<sup>15</sup> This pace, compared with COVID-19 vaccine trials, can only be described as glacial.

The 2018 UN General Assembly High-Level Meeting on Tuberculosis and the WHO End TB Strategy set and endorsed ambitious targets, but more solid and tangible commitments are needed.<sup>16,17</sup> Steps to improve visibility and accountability would include global and regional treaties to facilitate the targets, public facing global and national dashboards for tuberculosis, as done for COVID-19,<sup>18</sup> and greater direct investment specifically by all affected countries in research and development and roll-out of interventions, in proportion to the tuberculosis-associated reduction in gross domestic product (GDP) in

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Active case finding model in peri-urban tuberculosis hotspots in Harare, Zimbabwe, and Cape Town, South Africa, using a mini-mobile clinic

Photo taken by staff at the Centre for Lung Infection and Immunity and provided courtesy of Keeran Dheda

these countries. In many African countries, tuberculosis results in an estimated 2–4% reduction in GDP, making investments in tuberculosis highly cost-effective and financially cogent.<sup>19</sup>

An expansion of measures that can be implemented at the community level is also needed to find people with tuberculosis sooner. Multinational agencies need to prioritise research and development funding to develop a high-sensitivity, low-cost, sputum-independent screening test for symptomatic and subclinical tuberculosis. More incentives need to be provided for companies to develop screening tests, and regulatory harmonisation and an accelerated global approval process is required to minimise delays. Test approval processes (including by WHO) rely on availability of a substantial evidence base that takes years, if not decades, to accumulate. Emergency use authorisation, on the basis of a moderate amount of clinical data but with checks and balances, is more appropriate for a devastating pandemic like tuberculosis. Although computer assisted x-ray diagnosis (CAD) might be a promising screening tool, data suggest that the target product profiles for a tuberculosis screening test<sup>20</sup> will not be met in several major subgroups of individuals, including those with smear-negative disease, children, and people living with HIV.<sup>21,22</sup> Research into developing new screening tests using bioaerosols, tongue swabs, exhaled breath, sweat, saliva, or urine, including with alternative molecular platforms,<sup>23</sup> requires a major injection of funding. Investment by organisations should have subprogrammes focusing on tuberculosis that are linked to regional and international treaties. Designated regional centres of excellence in Africa, Asia, and South America should be established, in tandem, to facilitate testing and evaluation of new tuberculosis screening tests, including access to high quality biobanks.

Concerted efforts by all stakeholders are needed to move more aggressively towards an active case finding strategy. Even in the absence of a low-cost and highly sensitive screening test, active tuberculosis case finding should be prioritised in high prevalence populations, including household contacts, people with HIV, prisoners, individuals who visit health-care facilities for non-tuberculosis related symptoms, and those living in peri-urban informal housing in high burden countries. Such efforts are likely to vary according to the population being targeted (hot spots and high prevalence groups), the approach that is used (door-to-door vs mobile clinic), and

the specific tuberculosis tools used (portable molecular testing or transporting samples to the laboratory). An example of one approach, but by no means a magic bullet, is the use of Xpert Edge for scalable active case finding within mini-mobile clinics. Two multicountry randomised controlled trials (RIA2018D-2505 and RIA2020S-3295) are evaluating such an approach with and without CAD. Further investment in conceptually similar trials are urgently needed.

Lives threatened by tuberculosis matter just as much as those threatened by COVID-19. Investments must be increased and action accelerated to find the missing people with tuberculosis, together with increased economic development in low-income and middle-income countries and global poverty alleviation strategies, without which tuberculosis will never be eliminated.<sup>10</sup>

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Dedicated in loving memory to Paul Farmer (1959–2022), “a man who would cure the world”. Thank you from the bottom of our hearts for not only shining the light on the devastating ongoing impact of structural violence, but also for tirelessly leading the way towards dismantling it. You lived for true justice, a shared aspiration which we must continue to grow from strength to strength, through the countless lives you have changed.

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