

# Getting TB eradication back on track

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## Executive Summary

### Why Prioritise Tuberculosis (TB)

According to the WHO, “Tuberculosis is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide”. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. TB is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are sick with TB expel bacteria into the air (e.g., by coughing). The disease typically affects the lungs (pulmonary TB) but can affect other sites. Most people (about 90 %) who develop the disease are adults, with more cases among men than women.

TB is a treatable disease. However, in order to treat it in a timely manner, one must be able to diagnose it. Screening for active TB disease alone is not enough as the reservoir of latent TB cases will continue to reseed the active TB case population. A suspected active TB patient undergoes a chest X-ray and culturing of a sputum sample which takes many days. CT and MRI scans as well as invasive biopsies may also be performed. Screening for latent TB falls into two categories: Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs). Both detect host memory T cell responses to mycobacterial antigens but IGRAs are the new wave of blood-based tests that employ technologies based around detecting interferon-gamma (a cellular communication molecule, or cytokine) released into the blood (ELISAs) or more sensitive techniques which detect interferon-gamma-secreting cells (ELISpot).

Not all interferon-gamma release assays (IGRAs) are equal, and specificity and accuracy can be improved through ensuring that the same number of cells is placed into such tests (a process called normalisation) so that standardisation can be achieved. This ensures that more challenging samples such as paediatric and immune-compromised patient-derived samples that typically have low numbers of these responsive interferon-gamma secreting cells, give valid results. The need for the urgent deployment of strategies for the systematic screening for TB is a central component of the first pillar of the End TB initiative to ensure diagnosis of TB. Focusing on looking for active TB misses the large reservoir of latent TB cases. The adoption of an IGRA-based screening tool offers specificity, body-location-independent detection of latent *and* active versions of TB and is therefore a ‘catch-all’ approach to help curb the spread of TB. This whitepaper also highlights a series of case studies which demonstrate how local geographic infrastructures, ease of sample collection as well as performance metrics in certain population demographics have a major impact on the choice of IGRA adopted for latent screening strategies.

### The Economic case for TB prioritisation

Treatment of the active disease is a much more costly and time-consuming regime than treating latent TB. Ethambutol, rifampicin as well as isoniazid and pyrazinamide are amongst the group of drug agents commonly used in combination therapy to treat active TB. However, some forms of TB are developing resistance to these drugs too. Multi-drug resistant TB has come about due to several factors such as inappropriate use, incorrect prescribing, poor quality drugs and patients stopping treatment prematurely. The cost of treating active drug-susceptible TB (estimated at \$ 20,211 in 2020), versus multi-drug resistant TB results in a cost increase by a factor of nine. Treatment of extensively drug resistant TB patients increases this by a further factor of three. Therefore, it is essential that a coordinated strategy is utilised to identify latent TB infected patients, who are more likely to reactivate, allowing early intervention and treatment to effectively tackle the reservoir of latent infection and stop the spread of further cases of multi-drug resistant TB strains.

## Key Global Targets

The Political Declaration signed by all Heads of State adopted by the United Nations General Assembly in September 2018 committed to diagnosing and treating 40 million people with TB by 2022.

The UN Sustainable Development Goals targeted a 90 % reduction in tuberculosis deaths from 2015 figures by 2030, however meeting this goal now seems unachievable given the impact of the COVID-19 pandemic on resources for combating TB. If this target is revised to 2050, research estimates that 31.8 million tuberculosis deaths will occur, corresponding to an economic loss of US\$ 17.5 trillion, with effects of this time delay having the greatest impact in Sub-Saharan Africa. Affected countries, donor nations, and the private sector should redouble efforts to finance tuberculosis screening programmes and research because the economic dividend of such strategies is likely to be substantial.

Efforts to end TB and achieving universal health coverage (UHC) are co-dependent. TB targets the most vulnerable people in our societies, those marginalised socially and economically are often “left behind” by healthcare services. Indeed 98 % of TB cases come from low- and middle-income countries (LMICs) where funding for TB prevention, diagnosis, and treatment services continues to fall far short of estimated global needs, and the United Nations global target. Building health infrastructure, with quality and accessible services aimed at reaching *all* people with TB, provides an important pathway towards achieving true UHC globally. Effective and accessible testing, robust treatment programs, and TB disease surveillance systems form the core of effective TB eradication programs.

## Key Recommendations

The key recommendations for combating the TB epidemic must include the **early detection of latently infected individuals**, who are most at risk of moving to active disease states, **with prompt testing of contacts of those with active TB disease**. This should be accompanied **by follow-up treatment upon latent infection identification** using Directly Observed Treatment (DOTs) Therapy in community settings.

## Conclusion

TB is an epidemic and should be prioritised as such – it occurs in every part of the world and is the leading cause of death from infectious disease after COVID-19. Strategies to end TB must be based around reducing transmission in the population using effective, accessible detection and treatment policies. No one is immune from TB and among the most vulnerable are children, the immunosuppressed and those with HIV/AIDS.

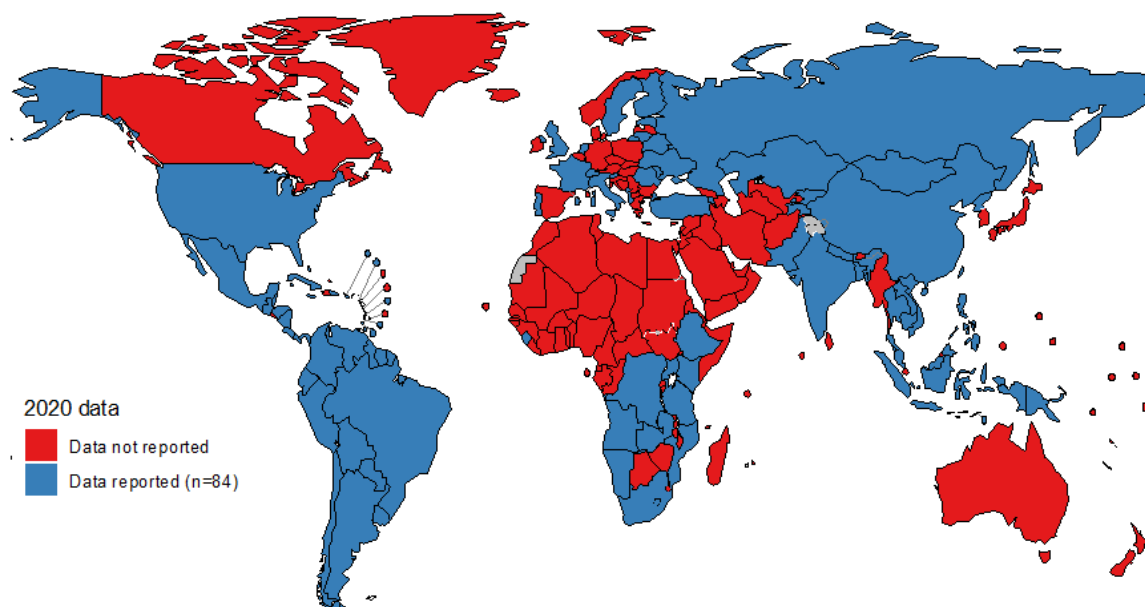
Together, in collaboration we can beat TB.

## 1.0 Introduction

According to the World Health Organization (WHO) global disruption to the provision of, and access to tuberculosis (TB) diagnostics and treatment services due to the COVID-19 pandemic are estimated to have caused an additional 100,000 TB deaths between 2019 and 2020 (an increase from 1.2 million to 1.3 million in HIV-negative people, with about 5,000 additional TB deaths among HIV-positive people).<sup>1</sup> Furthermore, the United Nations (UN) high-level meeting target of treating 40 million people diagnosed with TB in the 5-year period 2018–2022 is off-track.

The COVID-19 pandemic has shown us what we can do when countries come together with strong leadership, and evidence-based responses are married with rapid development, approval and administration of vaccines around the world and companion diagnostics. The lessons learnt in this pandemic can be put to good use in the next one and could help to solve the issue of the age-old scourge that has plagued humans since ancient times, TB<sup>2</sup>. However, the COVID-19 pandemic has created a massive global setback towards achieving the goals outlined in the End TB Strategy as TB services were disrupted at every level of the healthcare system. It is estimated that 1.4 million fewer people received care for TB in 2020 than in 2019 - a reduction of 21 % from 2019<sup>3</sup>. This has reversed recent progress towards global TB eradication targets.

Figure 1: Countries reporting monthly or quarterly TB case notification data for 2020 (as of 17 March 2021)<sup>4</sup>



<sup>1</sup> Global Tuberculosis Report, 2021, WHO

<sup>2</sup> <https://blogs.bmj.com/bmj/2021/03/24/covid-19-has-shown-we-can-end-the-worlds-biggest-infectious-disease-killer-tb-once-and-for-all/>

<sup>3</sup> Impact of the COVID-19 Pandemic on TB Detection and Mortality in 2020, WHO

<sup>4</sup> <https://www.who.int/publications/m/item/impact-of-the-covid-19-pandemic-on-tb-detection-and-mortality-in-2020>

March 2022 marked 140 years since Dr Robert Koch announced before the Physiological Society of Berlin that he had isolated and grown the tubercle bacillus, *Mycobacterium tuberculosis*, which he believed to be the cause of all forms of tuberculosis.<sup>5</sup> This is a timely reminder of how important it is to get global eradication programs back on track.

In the UN General Assembly High Level Meeting on ending TB held in New York on September 26<sup>th</sup>, 2018, the main theme was “United to end tuberculosis: an urgent global response to a global epidemic”. **The political declarations agreed by the Heads of States included:** -

- **Treat 40 million affected people 2018-2022**
- **Provide 30 million people with preventive treatment**
- **Reach vulnerable and marginalised populations, including children, and protection and promotion of human rights, including community engagement**
- **Overcome the global public health crisis of multi-drug resistant-TB, in line with anti-microbial resistance efforts**
- **Develop an integrated response to address TB/HIV, health systems, global public health collaboration, surveillance, and implementation of WHO guidance**
- **Mobilise financing: \$ 13 billion annually by 2022 for implementation; \$ 2 billion annually for research**
- **Develop accountability mechanisms at country level**
- **Present comprehensive review by Heads of State at the next meeting in 2023<sup>6</sup>**

## 2.0 Why focus on tuberculosis – an infectious disease

According to the WHO, “Tuberculosis is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide”. Until the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS. TB is caused by the bacillus *Mycobacterium tuberculosis*, which is spread when people who are sick with TB expel bacteria into the air (e.g., by coughing). The disease typically affects the lungs (pulmonary TB) but can affect other sites. Most people (about 90 %) who develop the disease are adults, with more cases among men than women.

The Bacilli Calmette-Guérin (BCG) vaccine was named after Dr Albert Calmette and Dr Camille Guérin, who developed the vaccine from a related strain called *Mycobacterium bovis* around 100 years ago. The vaccine does not prevent infection from *M. tuberculosis* but it does have a documented protective effect against meningitis and disseminated TB in children. It does not prevent primary infection or reactivation of latent pulmonary infection, which is the principal source of bacillary spread in the community.<sup>7</sup> The impact of BCG vaccination on transmission of TB is therefore limited and in fact about a quarter of the world’s population is infected with *M. tuberculosis*. But despite these alarming facts, TB infection is curable and preventable. About 85 % of people who develop active TB disease can be successfully treated with a six month drug regimen, and regimens of 1–6 months can be used to treat latent TB infections. Universal health coverage (UHC) is necessary to ensure that all those with TB disease or infection can access these treatments.<sup>8</sup>

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<sup>5</sup> <https://www.britannica.com/biography/Robert-Koch/Studies-of-tuberculosis-and-cholera>

<sup>6</sup> [UN high-level meeting visual highlights, WHO 2018](#)

<sup>7</sup> <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccines-quality/bcg>

<sup>8</sup> [Global Tuberculosis Report 2021, WHO](#)



The WHO collated some staggering statistics that make for difficult reading.

**5.6 million men, 3.3 million women and 1.1 million children newly infected with TB in 2020 and a further 10 million people fell ill with TB worldwide.<sup>9</sup>**

**TB is present in all countries, in all age groups, all genders, all races, all incomes and can affect any organ of the body**

### 2.1 Three stages of disease – exposure, latent and active TB: diagnosis and treatment

With so many of the world's population harbouring a latent tuberculosis infection, an asymptomatic immunological state that gives a heightened risk of subsequently developing active TB disease, it is crucial to accurately detect and treat latent TB cases to realise the End TB Strategy<sup>10</sup>. Early identification of clinical, sub-clinical, latent and resistant cases will be key.

Studies have shown that TB screening is most likely to be cost-effective in high TB prevalence populations and whilst this tends to align challenging, low resource settings due to socio-economic conditions, it is imperative to have a global perspective.

The WHO recommends treating latent TB in populations at high risk of progressing from latent TB to active TB disease<sup>11</sup>. Included in this are patients with immunosuppressive conditions, such as people living with HIV, children, and those who have come into contact with cases of active TB<sup>12</sup>.

### 2.2 At risk groups and why it is important to diagnose and treat latent TB?

Historically the risk of TB infection has been associated with poor living conditions, overcrowding and lack of ventilation in environments with a TB infected person. However, this is a very simplistic viewpoint and in fact there are many at-risk groups and vulnerable populations that have increased chances of developing the disease. Risk factors include: -

- Smoking and living in air polluted environments
- HIV infection
- Malnutrition
- Alcoholism
- Diabetes
- Silicosis
- Immune-depressive treatments e.g., chemotherapy and TNF- $\alpha$
- Immune-compromised
- Prisoners, migrants and socially marginalised people
- Children<sup>13</sup>

With many risk factors associated with increased susceptibility to TB, this increases the likelihood of TB infection and the incidence of latent TB converting to active disease. Active

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<sup>9</sup> WHO, 2021

<sup>10</sup> <https://www.sciencedirect.com/science/article/pii/S1201971216312231>

<sup>11</sup> <https://erj.ersjournals.com/content/erj/46/6/1563.full.pdf>

<sup>12</sup> <https://www.sciencedirect.com/science/article/pii/S1201971216312000#bib0160>

<sup>13</sup> [Vulnerable populations: risk factors and social determinants](#)

TB, if uncontrolled, will become an even more difficult to treat disease with the rising wave of multi-drug resistant strains.

Treating latent TB infection helps eradicate TB – 10-15 % of latent TB cases will progress to active TB<sup>14</sup> and treating latent TB infections is less costly than treating active TB<sup>15</sup> and the treatment regime is considerably shorter<sup>16</sup>.

### 3.0 Methods of diagnosing latent TB infection

Current available tests to detect *Mycobacterium tuberculosis* infection in both active and latent TB fall into two categories:

- Tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)

The TST and IGRA both detect host memory T cell responses to mycobacterial antigens. The TST was the only diagnostic test for TB infection for nearly 100 years. It is comprised of a mixture of over 200 proteins derived from *Mycobacterium tuberculosis*, which is injected under the skin. A delayed-type hypersensitivity reaction develops 48–72 hours after the TST is administered in people who have been infected with *Mycobacterium tuberculosis*. This manifests as an induration at the injection site. A trained individual then measures the diameter of the induration and interprets the result.

The second category of TB tests are blood-based tests known as IGRAs. Commercially available IGRAs can be performed using three different technologies:

- Multi-tube ELISA
- Multi-tube CLIA
- ELISPOT

Multi-tube ELISA or CLIA assays (such as the FDA approved QuantiFERON-TB Gold Plus – QIAGEN, Hilden, Germany) are based on detecting interferon-gamma release in whole blood; a sample of a patient's whole blood is stimulated with synthetic antigens specific to *M. tuberculosis*. The amount of interferon-gamma released by cells in the blood is then measured by ELISA and optical density, or CLIA and luminescence, and compared with negative and positive controls.

To perform the ELISPOT technology (such as the FDA approved T-SPOT.TB test - Oxford Immunotec, Abingdon, UK), a blood sample is obtained using routine phlebotomy and a standard blood collection tube. Peripheral blood mononuclear cells (PBMCs), including the T cells, are isolated from the whole blood. The cells are washed, counted, and normalised to create a standard cell suspension and deliver reliable results.

Normalising the number of T cells in the reaction reduces the impact of variability in patient T cell numbers on the ELISPOT test. This means that the test is able to maintain clinical performance even in more challenging to diagnose populations, like the immunosuppressed<sup>17</sup>

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<sup>14</sup> [TB Elimination The Difference Between Latent TB Infection and TB Disease, CDC Nov 2011](#)

<sup>15</sup> <https://www.cdc.gov/nchstp/newsroom/2018/treatment-of-latent-TB-infection.html>

<sup>16</sup> <https://apps.who.int/iris/bitstream/handle/10665/331525/9789240002906-eng.pdf?sequence=1&isAllowed=y>

<sup>17</sup> Sunny H Wong, Qinyan Gao et al; Effect of immunosuppressive therapy on interferon- $\gamma$  release assay for latent tuberculosis screening in patients with autoimmune diseases: a systematic review and meta-analysis *Thorax* 2016;71:64–72



and paediatric patients<sup>18</sup>. The selection of the right test is fundamental to correctly identify latent TB infection patients.

### 3.1 Accuracy of detecting TB

The Political Declaration adopted by the United Nations General Assembly in September 2018 committed to diagnosing and treating 40 million people with TB by 2022. Due to the COVID-19 pandemic this target was not achieved and therefore there is an urgent need to deploy strategies to improve diagnosis and initiation of care for people with TB. One of them is systematic screening for TB disease, which is included in the End TB Strategy as a central component of its first pillar to ensure early diagnosis for all with TB. The *WHO operational handbook on tuberculosis. Module 2: Screening - Systematic screening for tuberculosis disease* is the companion, implementation guide to the 2021 WHO guidelines on TB screening.<sup>19</sup> This handbook is part of a modular series of practical guides meant for the implementers of various aspects of the programmatic management of TB.

There are a number of screening tools for TB such as chest radiography with computer-aided detection, however such techniques lack specificity and the diagnostic accuracy required<sup>17</sup>. The use of a four-symptom screen (current cough, fever, weight loss or night sweats), C-reactive protein level from fingerprick blood (> 5mg/l), and molecular WHO-recommended rapid diagnostic tests for TB are all looking for active TB disease. These tools are not effective in screening for latent TB.

However as previously stated, there is a large reservoir of latent TB infected persons globally and detection and treatment of latent TB infection is fundamental in preventing TB disease and overall TB elimination efforts. Interferon-Gamma Release Assays (IGRAs) are whole-blood tests that can aid in diagnosing *Mycobacterium tuberculosis* infection irrespective of the location of the TB infection in the body. IGRAs measure a person's immune reactivity to *M. tuberculosis*. White blood cells from most persons that have been infected with *M. tuberculosis* will release interferon-gamma (IFN- $\gamma$ ) when mixed with antigens (substances that can produce an immune response) derived from *M. tuberculosis*. IGRAs do not help differentiate latent tuberculosis infection from tuberculosis disease, however prior BCG (Bacille Calmette-Guérin) vaccination or exposure to non-tuberculosis mycobacterial (NTM) species does not cause a false-positive IGRA test<sup>20</sup> result which can be seen with other tests such as the tuberculin skin test (TST), or Mantoux test<sup>21</sup>. Therefore, there needs to be careful consideration over the choice of assay used for TB screening and diagnosis.

With a skin test, all of the patients have to be seen twice, (one to administer the injection, and one to read the induration on the skin) whereas with an IGRA, just one visit is required for all patients, and positive cases are then triaged further.

The adoption of an IGRA-based screening tool offers specificity, body-location-independent detection of both active and latent versions of TB and is therefore a 'catch-all' approach to help curb the spread of TB.

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<sup>18</sup> Mandalakas AM, et al. T-SPOT®.TB Performance in Routine Pediatric Practice in a Low TB Burden Setting *Pediatr Infect Dis J.* 2017 Nov 14

<sup>19</sup> <https://www.who.int/publications/i/item/9789240022614>

<sup>20</sup> <https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm>

<sup>21</sup> [https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s\\_cid=rr5905a1\\_e](https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_e)

## 4.0 COVID and increased susceptibility to TB

As COVID-19 and TB both affect the respiratory system, co-infection can make both diseases considerably worse. Patients with a COVID-19 and TB co-infection suffer more severe disease than COVID-19 only patients<sup>22</sup> and COVID-19 infection in those people harbouring latent TB could accelerate the activation of a dormant TB infection. According to the World Health Organization, latent TB already affects a quarter of the world's population. If the novel coronavirus activates a sizable proportion of these dormant infections, it could severely upset the global health and economic situation.<sup>23</sup>

TB is an opportunistic pathogen and can remain latent, waiting for people's immune system to be compromised due to, for example, HIV or COVID infection, before activating. Synergy between TB and AIDS (HIV) has already been seen and so there is a distinct possibility that COVID-19 could also contribute to the reactivation and transmission of TB<sup>24</sup>

The COVID-19 pandemic has in fact reversed years of global progress in tackling TB, with TB deaths increasing for the first time in over a decade, as services and other resources were diverted and reallocated from TB to the COVID-19 response.<sup>25</sup>

However, the WHO recommends the use of accurate diagnostic tests for both TB and COVID-19 and the provision of TB preventative treatment should be maintained as much as possible as well as the use of TB laboratory networks for joint COVID-19 diagnosis and surveillance.<sup>26</sup>

## 5.0 Making the economic case for investment in TB

Within the UN Sustainable Development Goals, a 90 % reduction in tuberculosis deaths from 2015 figures was targeted by 2030, however meeting this goal seems highly unlikely given the impact of the COVID-19 pandemic on resources for combating TB. If the revised target of meeting this reduction is not until 2050, research suggests that 31.8 million tuberculosis deaths are estimated to occur, corresponding to an economic loss of US\$ 17.5 trillion, with effects of delay greatest in Sub-Saharan Africa. Affected countries, donor nations, and the private sector should redouble efforts to finance tuberculosis programmes and research because the economic dividend of such strategies is likely to be substantial.<sup>27</sup>

Co-infection of TB with HIV has been found to result in a dangerous interaction in the body, with HIV being linked to the progression of a TB infection and TB being reported to worsen HIV infection.<sup>28</sup> The creation of the USA's President's Emergency Plan for AIDS Relief (PEPFAR) in 2003 marked a significant increase in funding and attention to the HIV/AIDS epidemic.<sup>29</sup> The PEPFAR strategy is now entering its next phase, Vision 2025, which aims to support the international community's efforts to put countries on track to reach the Sustainable

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<sup>22</sup> [COVID-19 and Tuberculosis Co-Infection. Front. Med., 24 August 2021](#)

<sup>23</sup> [COVID-19 could accelerate activation of dormant tuberculosis \(TB\), May 2020](#)

<sup>24</sup> <https://redetb.org.br/covid-19-could-activate-latent-tuberculosis/>

<sup>25</sup> <https://www.who.int/news/item/14-10-2021-tuberculosis-deaths-rise-for-the-first-time-in-more-than-a-decade-due-to-the-covid-19-pandemic>

<sup>26</sup> <https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tb-covid-19.pdf>

<sup>27</sup> [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(21\)00299-0/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00299-0/fulltext)

<sup>28</sup> <https://www.nap.edu/read/24737/chapter/1>

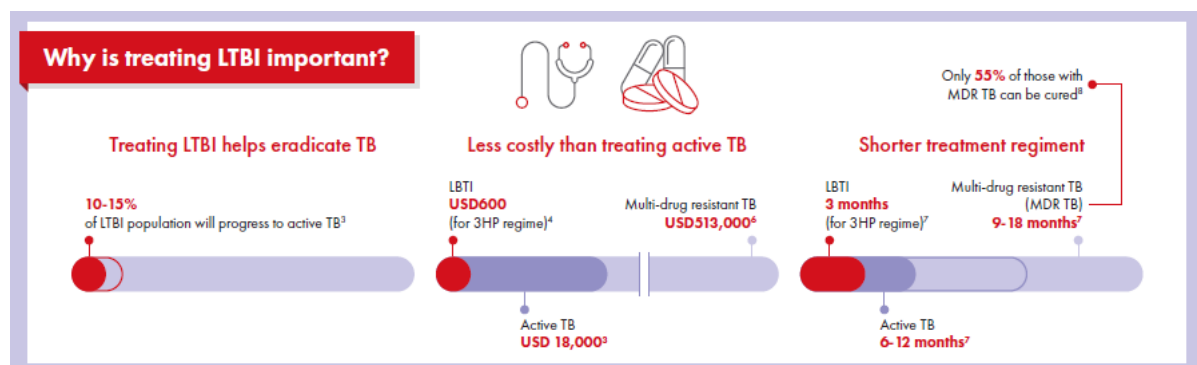
<sup>29</sup> <https://www.kff.org/global-health-policy/fact-sheet/the-u-s-presidents-emergency-plan-for-aids-relief-pepfar/#:~:text=Of%20the%20approximately%20%2410.8%20billion,is%20for%20the%20Global%20Fund.>

Development Goal 3 target of ending the global AIDS epidemic as a public health threat by 2030, through the attainment of key milestones by 2025.<sup>30</sup> Addressing HIV/TB coinfection continues to be an essential aspect of effective control of the HIV epidemic.<sup>31</sup> In the WHO African Region, where the burden of HIV-associated TB is highest, 85 % of TB patients had a documented HIV test result. Overall, in 2020, 88 % of TB patients known to be living with HIV were on anti-retroviral therapy.<sup>32</sup>

An added worrisome public health crisis and security threat is the increased rise of multi-drug resistant tuberculosis. This has come about due to a number of factors such as inappropriate use, incorrect prescribing, poor quality drugs and patients stopping treatment prematurely. Isoniazid and rifampicin are two of the most common first line drugs to be used, however if the TB is drug-resistant then a more complex, expensive and toxic set of chemotherapy needs to be embarked upon, and this can take up to two years to be completed.<sup>33</sup>

The cost of treating active drug-susceptible TB, versus multi-drug resistant TB versus extensively drug resistant TB patients is estimated to be \$ 20,211, versus \$182,186 versus \$ 567,708 respectively (2020 figures).<sup>34</sup> Therefore it is essential that a coordinated strategy is utilised to identify latent TB infected patients who most likely will reactivate allowing intervention and early treatment to effectively tackle the reservoir of latent infection and eliminate TB by 2050<sup>35</sup>. People with active TB can infect 5–15 other people through close contact over the course of a year. Without proper treatment, 45 % of HIV-negative people with TB on average and nearly all HIV-positive people with TB will die.<sup>36</sup>

**Waiting for TB to become active is not only an irresponsible approach but a costly one**



In the past diagnostics have not received the attention they deserve in the fight to achieve equitable global health in comparison to drugs and vaccines. However, the onset of COVID-19 has shown how important early and rapid diagnosis is in controlling outbreaks in a pandemic situation.<sup>37</sup> There is soon to be another update to the WHO Model List of Essential In-Vitro Diagnostics<sup>38</sup> and the T-SPOT®.TB test from Oxford Immunotec is one of the three

<sup>30</sup> <https://www.state.gov/development-of-the-next-pepfar-strategy-vision-2025/>

<sup>31</sup> <https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-3.0-%E2%80%93Controlling-the-Epidemic-Delivering-on-the-Promise-of-an-AIDS-free-Generation.pdf>

<sup>32</sup> <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>

<sup>33</sup> <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>

<sup>34</sup> <https://www.cdc.gov/tb/publications/infographic/appendix.htm>

<sup>35</sup> <https://royalsocietypublishing.org/doi/10.1098/rstb.2013.0437>

<sup>36</sup> <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>

<sup>37</sup> <https://www.forbes.com/sites/madhukarpai/2021/02/01/who-essential-diagnostics-list-expands-to-include-covid-19-and-much-more/?sh=973af193323e>

<sup>38</sup> <https://edl.who.healthtechnologies.org/>

commercially available IGRAs recommended as a quality product for diagnosing latent TB along with QuantiFERON®-TB Gold In-Tube from QIAGEN and WANTAI's TB-IGRA.

Further details on the T-SPOT®.TB IGRA test and others can be found in the Global Fund Facility Stop TB partnership catalogue<sup>39</sup>

## 6.0 Case study examples

### 6.1 Maldives

The Maldives has long been at the forefront of TB control in South Asia. With a small population of around 400,000 spread across 26 atolls, outbreaks of TB are more effectively controlled than in many other countries in the region. Since the 1970s, the country has also run a successful programme for TB control, which includes BCG vaccination, screening, diagnosis, and treatment. As a result, the incidence of TB in the late 1990s was reduced to only a handful of cases.

Since then, increased tourism in the Maldives and immigration from countries with a high burden of TB have led to an increase in the number of cases and has made TB a renewed public health concern. Dr Mohamed Ismail, respiratory physician at the Indira Gandhi Memorial Hospital in Malé and the chair of the Maldives' technical advisory group on TB says: "In recent years, we are doing more work in diagnosing, especially sputum negative tuberculosis. We have been using the GeneXpert® molecular test for the last three years and we will start doing TB culture later this year. However, the national strategic plan is to eliminate TB completely, so we are now aiming to become a TB-free country by 2025. This is the main target of the national TB programme".

The Maldives has set itself the ambitious goal of gaining TB-free status by 2025. To achieve this, detecting and treating cases of latent TB infection is crucial. Over the next five years, doctors will carry out an estimated 100,000 tests per year, both on migrant workers from high-TB countries and the local population, screening for latent TB. Currently the Mantoux test is used as and when needed, but this test requires two visits and suffers from low reliability. Moving forward, Dr Ismail wants to follow WHO guidelines for tackling latent TB, which recommend the use of interferon-gamma release assays (IGRAs) for screening.

When choosing an IGRA to be used as part of the nationwide TB programme, it was essential to take local infrastructure characteristics into account. Although every atoll in the Maldives has a hospital, the resources that are available in each hospital vary. For this reason, it was important that sample collection was as simple as possible so that each hospital could carry out collection and send the samples elsewhere for analysis. Commenting on choosing the T-SPOT®.TB test, Dr Ismail says: "It has excellent sensitivity, and its easy sample collection makes it well suited for a country like the Maldives. In some of the peripheral islands we do not always have well-trained laboratory staff, so we have to transport the samples to larger centres. With the T-SPOT®.TB test, sample collection is easier and more convenient, leading to fewer errors due to sample handling."

"The other important aspect," Dr Ismail continues, "is the performance of the T-SPOT®.TB test in the immunosuppressed population and in children, where it is better and more sensitive than other IGRAs. Latent TB is more common in these groups, and it is also more likely to develop into active TB compared to the general population, so reliable detection in these groups is vital".

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<sup>39</sup> <https://www.stoptb.org/sites/default/files/gfdiagnosticsmedicaldevootherhealthproductscatalog.pdf>

For the T-SPOT<sup>®</sup>. *TB* test, a single blood sample is collected into a single standard tube. From this sample, peripheral blood mononuclear cells (PBMCs) are isolated. A specific number of PBMCs is then used for detecting the interferon-gamma released in response to TB-specific antigen stimulation. This ensures reliability regardless of a person's immune status. A substrate is then added that visualises a spot at every location where an interferon-gamma-releasing T cell was positioned, providing easy, visual assessment of the result. This method creates a normalised IGRA, which is key to reducing the variability often seen in other test methods. This approach to latent TB screening avoids treatment delays, is suitable for use in vulnerable patients and reduces unnecessary treatments, which can cause side effects such as hepatotoxicity.

From March 2020, doctors at the Indira Gandhi Memorial Hospital are planning to screen an estimated 100,000 people per year. Over the coming years, the entire local population will be offered screening and there will be annual testing for migrant workers from high-risk countries. As part of this process, more hospitals in other atolls will be equipped with test analysis capabilities to reduce transport time and therefore overall time-to-result. Using the T-SPOT<sup>®</sup>. *TB* test will ensure reliable detection of latent TB, even in groups that are hard to screen, which means the Maldives are on track to achieve TB-free status in 2025.<sup>40</sup>

## 6.2 UK

Adopting latent TB infection screening has resulted in significant reductions in active TB cases in several parts of the UK. The Royal Borough of Greenwich had the seventh highest incidence of TB of any local authority in England. A successful collaboration between Public Health Greenwich, Greenwich CCG, the Oxleas TB team and Lewisham and Greenwich NHS Trust contributed to a 35–40% reduction of the incidence of TB in the borough. The decline was predominantly due to pre-entry screening, changes in migration pattern and TB services, as well as efforts to encourage eligible patients to undergo screening for latent tuberculosis infection.<sup>41</sup> Similarly, back in 2015, NHS England set up the Collaborative Tuberculosis Strategy for England to control the spread of tuberculosis (TB). Through this programme, Bradford District Care Foundation Trust received funding to screen patients for latent tuberculosis since 2015. The Bradford TB team are optimistic about bringing down the incidence of TB in the city even further.<sup>42</sup>

## 6.3 China

Fevers of unknown origin was defined by Petersdorf and Beeson as an illness of more than three weeks' duration, fever greater than 38.3°C (101°F) on several occasions, and diagnosis uncertain after one week of observation in hospital.<sup>43</sup> The common causes of classic fevers are infections, connective tissue diseases, neoplasms, and miscellaneous diseases. Unfortunately, some cases end without a diagnosis despite exhaustive workup. TB, especially extrapulmonary TB is still the leading cause of fevers in China. As a result of this, a clinical study was conducted in Peking Union Medical College Hospital in China from September 2010 to August 2013 to evaluate the diagnostic value of T-SPOT<sup>®</sup>. *TB* for etiological diagnosis of fevers in adult patients in a high TB endemic area. 387 hospitalised patients (male n = 194, female n = 193; median age 46 (range 29–59) years) with fevers were prospectively enrolled into this study. 68 cases were diagnosed as active TB eventually. For patients presenting with fevers in this TB endemic setting, T-SPOT<sup>®</sup>. *TB* appears valuable for excluding active TB, with a high negative predictive value.<sup>44</sup>

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<sup>40</sup> Case study – Maldives: Ending TB in five years

<sup>41</sup> Case study – Royal Borough of Greenwich and Greenwich CCG

<sup>42</sup> Case study – Bradford District Care Foundation Trust – Oxford Immunotech

<sup>43</sup> Petersdorf RG, Beeson PB (1961) Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 40: 1–30.

<sup>44</sup> <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0146879>



Tuberculosis is a major health problem among refugees and asylum seekers from high TB burden areas and should be given special attention in any host continent. To protect this vulnerable population, ensuring access to healthcare for early detection for prevention and treatment of the disease is essential.<sup>45</sup> Sadly the war in Ukraine is threatening the continuity of care for patients with tuberculosis in the country. Ukraine has the fourth-highest TB incidence in the WHO European Region and the fifth-highest number of confirmed cases of extensively drug-resistant TB in the world. Medical organisations, such as the Red Cross, already working in the country to deliver TB care before the war have said that they are continuing to provide services, including medicine deliveries, but are finding it increasingly difficult due to security worries and transportation issues, with roads clogged with refugees or Russian troops.

Alliance for Public Health, one of the biggest non-state organisations involved in Ukraine's TB response, has stated that: "Before, we and our partners provided a wide spectrum of services, but now in some places it's just checking that TB patients are sticking to their regimen, and in some places finding active TB cases has stopped". More than three million people have fled the country since the start of the invasion, and the risk of TB among refugees has also come into focus. The European Centre for Disease Prevention and Control (ECDC) urged Ukraine's neighbouring states to ensure refugees had access to health-care services to help in the early detection of infectious diseases.<sup>46</sup>

## 7.0 Achieving Universal Health Coverage and Integrated Healthcare

Efforts to end TB and achieving universal health coverage (UHC) are co-dependent. The WHO laid this out clearly in the 2019 Global TB Report: "The End TB Strategy milestones for 2020 and 2025 can only be achieved if TB diagnosis, treatment and prevention services are provided within the context of progress towards UHC."<sup>47</sup>

All UN member states committed at the UN High Level Meeting on UHC<sup>48</sup> to "strengthen efforts to address communicable diseases including HIV/AIDS, tuberculosis, malaria, and hepatitis as part of UHC and to ensure that the fragile gains are sustained and expanded by advancing comprehensive approaches and integrated service delivery and ensuring that no one is left behind".<sup>49</sup>

Given that the people most vulnerable to TB are often those "left behind" by healthcare services more generally, for example, due to social marginalisation or economic status, building health infrastructure aimed at reaching all people with TB provides an important pathway towards achieving universal health coverage. Making quality and accessible services affordable for everyone, is an important step to reach all people with TB globally.<sup>50</sup> UHC means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation, and palliative care across the life course.

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<sup>45</sup> <https://bmcpublihealth.biomedcentral.com/articles/10.1186/s12889-020-08907-y>

<sup>46</sup> [https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(22\)00214-6/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00214-6/fulltext)

<sup>47</sup> WHO, Global TB Report 2019, available at <https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1>

<sup>48</sup> UN High Level Meeting on UHC, 23 September 2019

<sup>49</sup> Political Declaration of the UN High-Level Meeting on UHC, September 2019, paragraph 32, available at <https://www.un.org/pga>

<sup>50</sup> <https://www.results.org.uk/blog/tuberculosis-and-universal-health-coverage-terms-and-conditions-apply>



Achieving UHC requires multiple approaches. The WHO together with the World Bank has developed a framework to track the progress of UHC using 16 essential health services in four categories as indicators of the level and equity of coverage in countries:

Reproductive, maternal, new-born and child health:

- family planning
- antenatal and delivery care
- full child immunisation
- health-seeking behaviour for pneumonia.

Infectious diseases:

- tuberculosis treatment
- HIV antiretroviral treatment
- use of insecticide-treated bed nets for malaria prevention
- adequate sanitation.

Noncommunicable diseases:

- prevention and treatment of raised blood pressure
- prevention and treatment of raised blood glucose
- cervical cancer screening
- tobacco (non-)smoking.

Service capacity and access:

- basic hospital access
- health worker density
- access to essential medicines
- health security: compliance with the International Health Regulations.

## 8.0 Building resilience and surveillance to prevent the spread of TB

The key targets of the post-2015 global TB strategy is presented below<sup>51</sup>: -

<b>VISION</b>	A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis
<b>GOAL</b>	End the global tuberculosis epidemic
<b>MILESTONES FOR 2025</b>	75% reduction in tuberculosis deaths (compared with 2015) 50% reduction in tuberculosis incidence rate (less than 55 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
<b>TARGETS FOR 2035</b>	95% reduction in tuberculosis deaths (compared with 2015) 90% reduction in tuberculosis incidence rate (less than 10 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
<b>PRINCIPLES</b>	
<ol style="list-style-type: none"> <li>1. Government stewardship and accountability, with monitoring and evaluation</li> <li>2. Strong coalition with civil society organizations and communities</li> <li>3. Protection and promotion of human rights, ethics and equity</li> <li>4. Adaptation of the strategy and targets at country level, with global collaboration</li> </ol>	
<b>PILLARS AND COMPONENTS</b>	
<b>1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION</b>	
<ol style="list-style-type: none"> <li>A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups</li> <li>B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support</li> <li>C. Collaborative tuberculosis/HIV activities, and management of comorbidities</li> <li>D. Preventive treatment of persons at high risk, and vaccination against tuberculosis</li> </ol>	
<b>2. BOLD POLICIES AND SUPPORTIVE SYSTEMS</b>	
<ol style="list-style-type: none"> <li>A. Political commitment with adequate resources for tuberculosis care and prevention</li> <li>B. Engagement of communities, civil society organizations, and public and private care providers</li> <li>C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control</li> <li>D. Social protection, poverty alleviation and actions on other determinants of tuberculosis</li> </ol>	
<b>3. INTENSIFIED RESEARCH AND INNOVATION</b>	
<ol style="list-style-type: none"> <li>A. Discovery, development and rapid uptake of new tools, interventions and strategies</li> <li>B. Research to optimize implementation and impact, and promote innovations</li> </ol>	

At the UN High-Level Meeting on TB in 2018, world leaders agreed to mobilise US\$ 13 billion per year to finance TB prevention and treatment by 2022 and promised another US\$ 2 billion per year for TB research in the face of growing concerns around drug-resistant TB. However, funding for TB prevention, diagnosis, and treatment services in low and middle-income countries (LMICs) that account for 98 % of reported TB cases continues to fall far short of estimated global needs, and the United Nations global target. In 2020, global spending on TB services fell to US\$ 5.3 billion (less than half, (41 %) of the global target), and funding for research was US\$ 901 million. This is an 8.7% decline in spending between 2019 and 2020 with TB funding in 2020 back to the level of 2016. While national strategic plans and accompanying budgets for tuberculosis have grown in ambition, mobilisation of funding has not kept pace.<sup>52</sup>

The End TB Strategy outlined interventions aimed at decreasing TB-related morbidity, death and transmission which included the following:

- early diagnosis of TB via sputum-smear microscopy,
- treatment (usually a six-month course of antibiotics for drug-sensitive TB) and patient support for all people with TB,
- scaled-up diagnosis and management of MDR- and XDR-TB,

<sup>51</sup> <https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy#:~:text=The%20End%20TB%20Strategy%20builds,Strategy%20at%20the%20country%20level>

<sup>52</sup> <https://www.afro.who.int/regional-director/speeches-messages/world-tb-day-2022>

- systematic screening for and management of TB among people living with HIV and others in high-risk groups,
- preventive treatment and vaccination for high-risk groups
- research and development (R&D) of new tools (e.g., new TB diagnostics, drugs, and vaccines) and improved approaches.<sup>53</sup>

One could argue that the emphasis here is on the detection of active TB cases rather than latent TB. Because “reactivated” TB is contagious, eradicating latent infection is a cornerstone of global TB control<sup>54</sup> and achieving a better understanding of latent infection is deemed a research priority.<sup>55</sup> The World Bank Group is taking broad, fast action to help developing countries strengthen their pandemic response to COVID-19, increase disease surveillance, improve public health interventions, and help the private sector continue to operate and sustain jobs.<sup>56</sup> The same preparedness, resilience and surveillance needs to apply to the eradication of TB.

FIND, the global alliance for diagnostics, and the Global Fund to Fight AIDS, Tuberculosis and Malaria announced that it has been awarded over US\$ 37 million to ensure the inception and continuation of three projects dedicated to advancing tuberculosis prevention and control in India: project SHAQTI (Strengthening Health systems for sustainable Access to Quality diagnosis towards TB elimination in India); project JEET (the Joint Effort for Elimination of TB); and Unite to ACT (Amplifying Community action for TB elimination). India accounts for more than one-quarter (26 %) of the global TB burden and has the largest share of the global burden of drug-resistant TB. The investment by the Global Fund will optimise TB diagnostic capacity, improve laboratory quality and data management across India’s public sector laboratory network thereby renewing focus on early diagnosis to guide appropriate TB treatment. The grant will strengthen capacity for genome sequencing for TB surveillance and will expand laboratory capacity for drug-resistant TB treatment monitoring at district level. Further, the funding will catalyse addressing the latent tuberculosis infection burden in India; sustain the gains under JEET; and build capacity of TB-affected communities by engaging TB survivors as champions and enable meaningful contribution to the design and implementation of the program by promoting rights-based, gender responsive and equitable services to all.<sup>57</sup>

## 9.0 Recommendations – prevention is better than cure

The global epidemic of TB is driven by three major factors:

- Reactivation of latent TB in immunosuppressed populations
- Delayed TB diagnosis and misdiagnosis
- Migration from high TB burden countries

As such, strategies to end TB must be based around reducing transmission in the population using effective, accessible detection and treatment policies. Currently, close contacts of active TB cases receive a chest X-ray and tuberculin skin test (TST), or the TB blood test to test for an *M. tuberculosis* infection. However, the approach of testing suspected active cases is not going to stop the transmission of TB.

<sup>53</sup> <https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-tuberculosis-efforts/>

<sup>54</sup> Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health* 2013; 34:271-86. doi:10.1146/annurev-publhealth-031912-114431 pmid:23244049

<sup>55</sup> <https://www.bmj.com/content/362/bmj.k2738>

<sup>56</sup> <https://www.worldbank.org/en/about/what-we-do/brief/world-bank-group-operational-response-covid-19-coronavirus-projects-list>

<sup>57</sup> <https://www.theglobalfund.org/en/news/2021-08-13-global-fund-grants-usd37-million-to-find-to-advance-tuberculosis-prevention-and-control-in-india/>

**Early detection of latent TB infection through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as prophylactic treatment to prevent the development of active TB. These measures will play a critical role in reducing the burden of TB and will move us closer to eliminating TB permanently.**

Therefore, the T-SPOT®.TB test is a useful diagnostic tool to enable earlier detection and management of latent TB.

Those patients at increased risk of TB include:

- People living with HIV (PLHIV are 18 times more likely to develop active TB)
- People who are immunocompromised - this also includes PLHIV, and conditions such as diabetes, substance abuse, silicosis, severe kidney disease, low body weight, organ transplants, head and neck cancer, medical treatments such as corticosteroids, specialised treatment for rheumatoid arthritis and Crohn's disease
- People who are undernourished are three times more at risk
- People with alcohol use disorder are 3.3 times more at risk
- People who tobacco smoke are 1.6 times more at risk
- Children less than five years of age who have a positive TB test
- Close contacts of a person with infectious active TB disease
- Groups with high rates of TB transmission, such as homeless persons, injection drug users, and persons with HIV infection
- Persons who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, prisons, nursing homes, and residential homes for those with HIV<sup>58</sup>

## 10.0 Conclusion – TB is a pandemic

TB occurs in every part of the world and is the leading cause of death from a single infectious agent aside from COVID-19.

No one is immune from TB and among the most vulnerable are children, the immunosuppressed and those with HIV/AIDS. Effective and accessible testing, robust treatment programs, and TB disease surveillance systems form the core of effective TB eradication programs.<sup>59</sup>

However, the COVID-19 pandemic has proved that health systems can make drastic changes when the need arises. It is time to apply the same determination to fighting TB.<sup>60</sup> In fact, COVID-19 and TB together pose a syndemic, which has the potential to wreak havoc with social inequalities and poverty. Given the massive setback to progress in reaching tuberculosis targets, it is crucial to leverage COVID-19 innovations and systems to improve tuberculosis care and control.<sup>61</sup>

The Bacillus Calmette-Guerin (BCG) vaccine is the only licensed vaccine for prevention of TB infection and was developed over 100 years ago. This has been used widely and is effective in preventing severe forms of TB in children. However, there is no vaccine that prevents TB infection in adults, either before or after exposure to active TB and yet this group makes up to

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<sup>58</sup> <https://www.cdc.gov/tb/topic/basics/risk.htm>

<sup>59</sup> <https://www.cdc.gov/globalhivtb/who-we-are/resources/keyareafactsheets/disease-surveillance-for-targeting-efforts-to-end-tb.pdf>

<sup>60</sup> <https://www.ucl.ac.uk/news/2021/oct/opinion-how-covid-19-threatens-undo-years-progress-tb-control>

<sup>61</sup> [https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(21\)00057-4/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00057-4/fulltext)

90% of TB cases.<sup>62</sup> Contrast this with the creation of the COVID-19 vaccine in less than one year and the Pfizer vaccine becoming the first to receive emergency use authorisation from the Food and Drug Administration (FDA).<sup>63</sup>

The COVID-19 response has shown what can be achieved when there is investment and collaboration on a global scale.

**Key recommendations** for combating the TB pandemic highlighted below form part of the 18 recommendations in the *WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* which cover a cascade of critical steps in the programmatic management of TB preventive treatment.<sup>64</sup>

- **Early detection of latently infected individuals who are most at risk of moving to active disease states**
- **Follow-up treatment upon latent infection identification**
- **Prompt testing of contacts of those with active disease**
- **Directly Observed Treatment (DOTs) Therapy in community settings**

Has COVID taught us anything about pandemic preparedness?

It is hoped that the above efforts will be made to utilise existing technologies and implement solutions to deploy early screening strategies to detect and treat to eradicate TB, an ancient disease that has caused millions of deaths. COVID-19 is the blueprint to dealing with a pandemic on such a global scale and urgent action is needed to reimagine tuberculosis care.<sup>65</sup> Together, in collaboration we can beat TB.



<sup>62</sup> [Tuberculosis vaccines in the spotlight following WHO report \(biopharma-reporter.com\)](https://www.biopharma-reporter.com)

<sup>63</sup> <https://www.medicalnewstoday.com/articles/how-did-we-develop-a-covid-19-vaccine-so-quickly>

<sup>64</sup> <https://www.who.int/publications/i/item/9789240001503>

<sup>65</sup> [https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(21\)00057-4/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00057-4/fulltext)