Reference material excerpted from Area for Intervention:

Accelerating tools to drive tuberculosis detection

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For details of work that Unitaid is soliciting related to this area,
please refer to the scope of any relevant call for proposals.

Contents

Executive Summary

The updated Disease Narrative for Tuberculosis (TB), published in December 2019, recognized tools for diagnosis for TB as a potential high-impact area for intervention that could advance both the WHO End TB strategy targets and the Sustainable Development Goals (SDGs) for TB. In October 2020, the Secretariat provided an update to the Policy and Strategy Committee (PSC), who expressed support for further work on diagnostics for TB and noted the need to consider integrated tools that could be applied to TB and other pathogens including COVID-19 to be able to reach the estimated 3 million missing TB cases per year.[1]

Without substantial intervention in this area, TB transmission will remain out of control, perpetuating the epidemic and leading to continued morbidity and mortality. TB continues to be the deadliest infectious disease with many synergies with other major epidemics, the threat of drug resistance, and a burden disproportionately borne by the world's most vulnerable. Even with recent advances in treatment and diagnosis, existing tools are not enough to close the gap in missing cases.

WHO and partners clearly identified TB detection as the key priority to achieving targets

Both the End TB Strategy and the SDGs aim to eliminate TB as a public health problem in the near future. The End TB Strategy has targets to reduce the incidence rate of TB by 90% and TB deaths by 95% by 2035, while the SDGs target to reduce TB incidence rate by 80% and TB deaths by 90% by 2030. Complementing these strategies, the "top TB Partnership's Global Plan to End TB 2018-2022 recommends additional targets, which include finding at least 90% of all people with TB who require treatment and ensuring they receive an appropriate therapy.

The success of all these strategies hinges on increased and timely detection of TB, and the global response is falling short on this objective. Some progress has been achieved in improving TB detection, especially with the advent and adoption of molecular testing for TB, endorsed by WHO in early 2011. This has helped improve case finding, especially in key populations such as people affected by HIV and multidrug-resistant tuberculosis (MDR-TB); however, testing has been limited to mid-sized, district-level health services.[2] For reference, there was a 45% increase in TB case detection among people living with HIV in South Africa.[3] Yet, there still remains no real diagnostic solution that reaches people in the communities where disease transmission occurs and in the peripheral health centres where people with TB often first present with symptoms.

Effective TB detection tools are more critical than ever given disruptions in TB care due to COVID-19

Although TB has seen significant reductions in mortality and morbidity over the last decades, the COVID-19 pandemic has threatened to undo this progress. There are major disruptions to TB programs and supply chains and substantial reductions in numbers of individuals seeking care.[4,5] COVID-19-related lockdowns have limited the mobility of people and access to healthcare, highlighting the need to bring care closer to those in need. In this context, there is a need for rapid

[1] Global TB Report 2019
[2] Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children - Policy update
[3] Xpert MTB/RIF increases timely TB detection among people living with HIV and saves lives: Information note
[4] http://www.stoptb.org/news/stories/2020/ns20_014.html
[5] https://www.theglobalfight.org/covid-aids-tb-malaria/

diagnostic tools that can be implemented in facilities such as local health clinics, medical offices, health posts, or even by health workers during home visits, and used to test for many pathogens.

Unitaid has identified opportunities to enable availability and access to tools for TB detection

Recent research and evidence on the patient pathway for TB highlights gaps where affected individuals are lost to follow-up or not served, leading to delays, misdiagnoses, and/or drug resistance.[6,7] Often those affected by TB must interact with the health system many times before receiving accurate diagnosis and appropriate care. This leads to wasted resources, high costs for both the individual and the system, and poorer health outcomes. One of the key gaps identified was at the first point of contact with the health system.

For the first time in many years, tests emerging from the pipeline or recently on the market could be adapted through interventions in the short and long term to overcome challenges of making a test available at the primary level or community level.

The most promising short-term opportunities address these challenges with the diagnosis of TB at the primary and community healthcare level and focus on integration in two categories:

1. **Enabling non-sputum-based and integrated TB diagnostic solutions**: Molecular testing allows for molecular detection of TB and drug-resistant cases, faster and more cost-effectively than culture-based testing. Many of these platforms can sequentially or simultaneously test for multiple infectious agents, pathogen variation and antimicrobial resistance (AMR). To enable these tests to be used at the point of care, there needs to be a greater expansion of these machines to process other samples (i.e., urine, stool, blood), more affordable pricing to accommodate higher testing volumes, and technical improvements adapted for rural and low-resource settings. In addition, the rapid evolution of TB lipoarabinomannan (LAM) tests, antigen (Ag) detection tests which detect the LAM antigen in urine (and potentially blood), offer another alternative to sputum sampling for TB diagnosis. Currently, TB LAM is used only in people with advanced HIV disease. These tests could be used as point-of-care tests for TB more broadly if there are improvements in concentration of the sample, amplification of the signal in the assay, and/or detection sensitivity for TB. Also, the deployment of chest x-ray with computer-aided design and further advancements in its portability could offer an additional diagnostic solution that could further improve TB detection with added benefit to COVID-19 policies and other respiratory infections.

[6] Conducting Patient - Pathway Analysis to Inform Programming of Tuberculosis Services, JID 2017:216 (Suppl 7). http://stoptb-strategicinitiative.org/wp-content/uploads/2018/07/Conducting-PPA-to-inform-TB-Services.pdf

[7] TB patients endure tortuous pathways and broken care cascades by Madhukar Pai. https://naturemicrobiologycommunity.nature.com/posts/22350-tb-patients-endure-tortuous-pathways-broken-care-cascades

2. **Adapting and leveraging COVID-19 diagnostic and case detection solutions for TB detection:** Innovation for the detection of COVID-19 has occurred at a rapid pace and given its synergies with TB, many of the tools that have been developed could be adapted for use in TB or integrated to allow for bidirectional case detection. For example, new efficient contact tracing approaches and applications could help improve the historically low implementation of one of the most effective means of detecting a person at risk for TB.

Tools for TB detection fit strategically with Unitaid's portfolio

The current Unitaid TB portfolio addresses important equity gaps in the TB response, but clear opportunities exist to help detect the 3 million missing cases of TB each year. Overall, Unitaid has championed the efforts of a global diagnostic network in optimizing and integrating of testing for various diseases including HIV, TB, malaria, hepatitis C, HPV, and more. Unitaid is well placed to respond to TB in the new context of COVID-19, continuing to address the HIV and TB co-pandemics, and implementing solutions that can be leveraged for potential future pandemics. For TB LAM tests and for some newer molecular tests, specific interventions could build on Unitaid's existing work to enable innovative diagnostic tools and access to tools for care of advanced HIV disease. These interventions could pave the way for the introduction and adoption of even better innovative solutions that emerge from the pipeline. In addition, demonstration studies and operational research could help drive adoption of newer tools that better meet target product profiles and leverage the innovation in COVID-19.

There are new opportunities to accelerate the availability, adoption and uptake of new or emerging diagnostic solutions for TB detection. The TB community is at a critical juncture with a major threat of COVID-19 undoing years of progress. Given Unitaid's investments and contribution to the global TB response to date, enabling tools for TB detection can maximize impact of the current portfolio and help finally defeat this deadly yet curable disease.

1. Introduction and Background

The updated Disease Narrative for Tuberculosis, published in December 2019, recognized tools for diagnosis for TB as the key potential AfI that could have the greatest impact on advancing both the WHO End TB Strategy targets and the SDGs for TB. This document contains some of the material that served as a basis for a new area for intervention (AfI) on *Accelerating tools to drive TB detection.*

Without substantial intervention to reach the estimated 3 million missing TB cases per year, TB transmission will remain out of control, perpetuating the epidemic leading to continued morbidity and mortality.[8] Some progress has been achieved in improving TB detection, especially with the advent and adoption of large-scale molecular testing for TB, endorsed by WHO in early 2011[9]. Even so, there is still a huge gap between the estimated 10 million people who get sick with TB each year and the current 7 million TB cases that are reported to national programmes and WHO.

TB remains, after more than a century relying on smear microscopy, without a simple, easy to use, affordable, and effective test. This led the global response to highlight a need to pursue a simple, friendly, affordable, preferably not sputum-based test. This would ideally be a point-of-care test usable at the lowest health care level and even at the community level as a triage test. The Unitaid Secretariat explored the TB diagnostic landscape through key stakeholder consultation, identifying major barriers to availability and access and opportunities where Unitaid could have significant impact.

2. Why now and what are the key issues?

2.1. Tuberculosis targets will not be achieved on the current trajectory

Both the WHO End TB Strategy and the SDGs aim to eliminate TB as a public health problem in the near future. The End TB Strategy has targets to reduce the incidence rate of TB by 90% and TB deaths by 95% by 2035, while the SDGs target to reduce TB incidence rate by 80% and TB deaths by 90% by 2030. Complementing these strategies, the “top TB Partnership’s Global Plan to End TB 2018-2022 recommends additional targets for 2025, which includes to find at least 90% of all people with TB who require treatment and place them on appropriate therapy. The UN Political Declaration on TB also sets out specific targets for the Members States to achieve by 2022, and among these targets the first one is "successfully treat 40 million people with TB, including 3.5 million children".[10]

Progress toward these global targets are falling short (see Figure 1). For example, while the target for preventive therapy is 30 million by 2022, only 6.3 million people have been treated during 2018 and 2019. While the target for funding TB care and prevention is US$13 billion annually, only US$6.5 billion were raised during 2020.[11]

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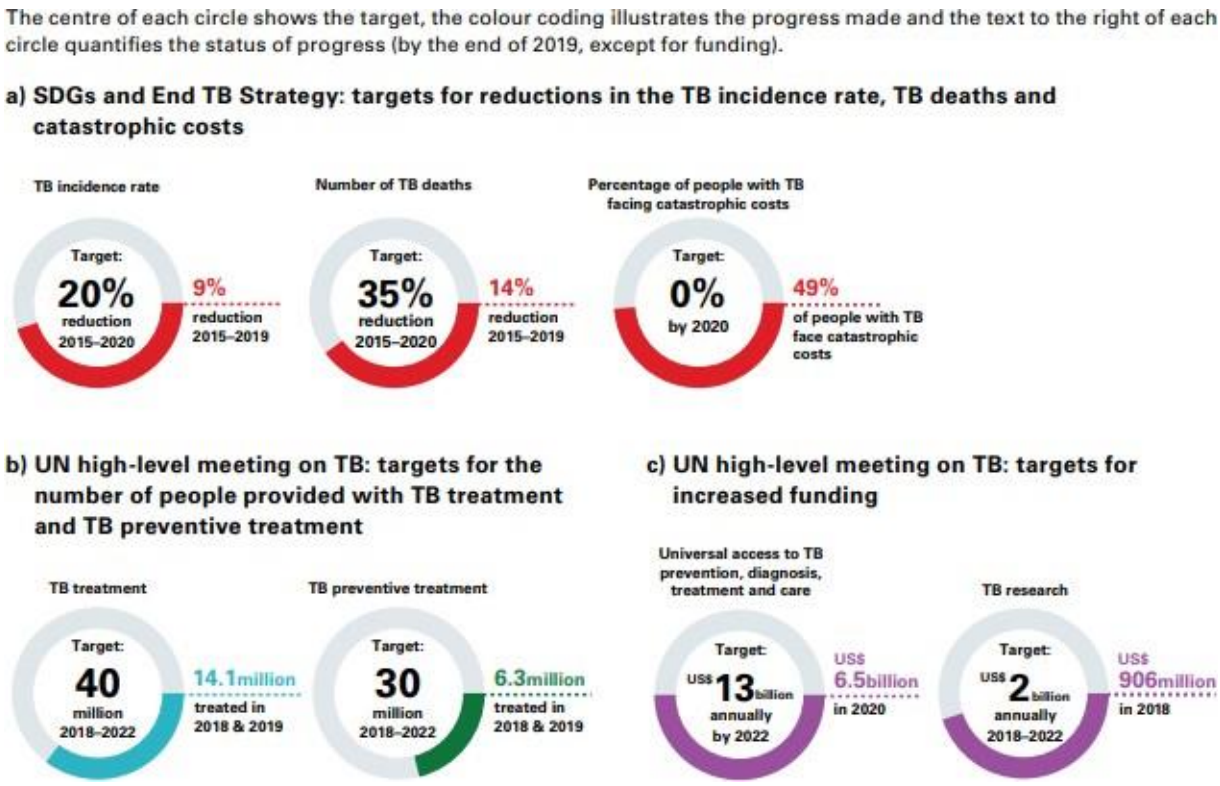
[8] Global TB Report 2019

[9] Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children - Policy update

[10] UN General Assembly adopts Declaration of the first-ever United Nations High Level Meeting on TB. World Health Organization, 11 OCTOBER 2018, GENEVA. https://www.who.int/tb/features_archive/UNGA-adopts-TB-declaration/en/

[11] Global TB Report 2020

Figure 1. Overview of progress towards global TB targets



Source: WHO Global TB Report 2020

The success of all these strategies hinges on increased detection of TB, and the global response is falling short on this objective. Each year, 10 million people continue to fall ill with TB, and TB remains the world's top infectious disease killer with an estimated 1.4 million deaths a year.[12] Some progress has been achieved in improving TB detection, especially with the advent and adoption of large-scale molecular testing for TB, endorsed by WHO in early 2011.[13] But there still remains no real tool for TB detection that reaches people in the communities where disease transmission occurs and in the peripheral health centres where people with TB often first present with symptoms.

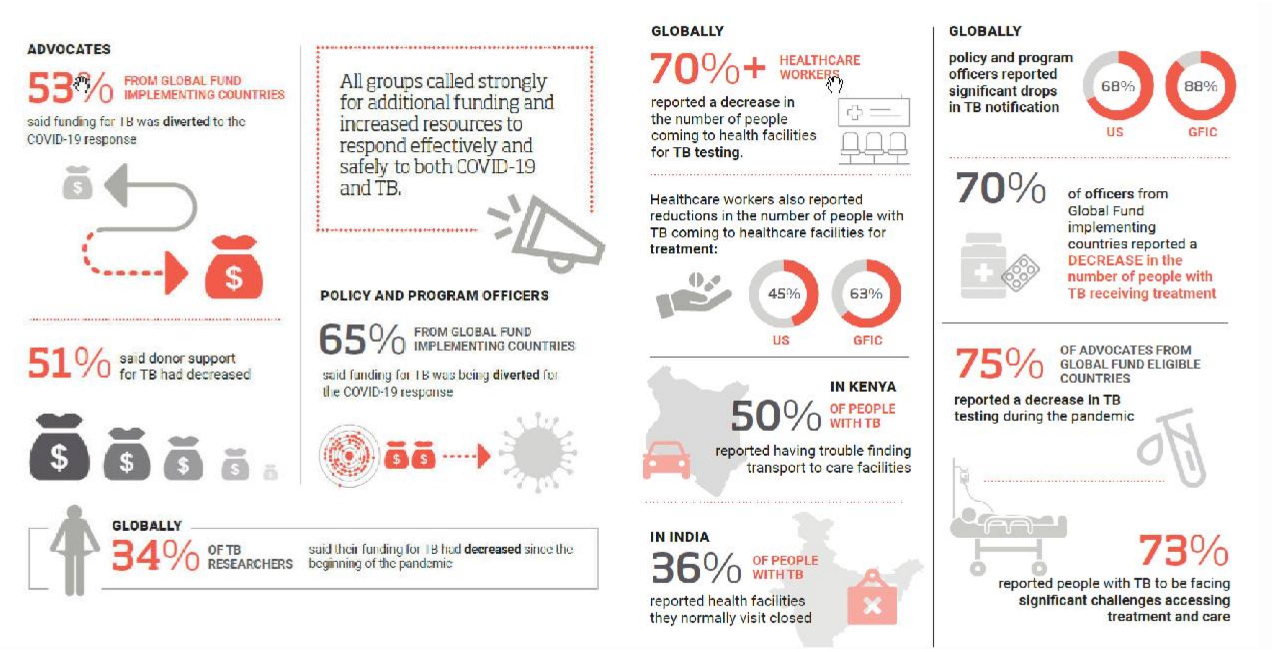
2.2. Effective TB detection tools in the near-term is even more critical given disruptions in TB care due to COVID-19

Although TB has seen significant reductions in mortality and morbidity over the last decades, the COVID-19 pandemic has threatened to undo this progress. There are major disruptions to TB programs and supply chains and substantial reductions in individuals seeking care.[14,15] Due to these disruptions, the Stop TB Partnership estimates that there will be 6.9 million additional people developing TB and an additional 1.4 million TB deaths by 2025.

[12] WHO Global TB Report 2020
[13] Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children - Policy update
[14] http://www.stoptb.org/news/stories/2020/ns20_014.html
[15] https://www.theglobalfight.org/covid-aids-tb-malaria/

As predicted, the COVID-19 pandemic is making things worse. In September 2020, civil society organizations working on TB released the results of a large survey on the impact of the pandemic on TB care, research and funding (Figure 2). Around the world, policy and program officers reported significant drops in TB notification (88% in Global Fund implementing countries and 68% in the USA). Over 70% of healthcare workers and advocates reported a decrease in the number of people coming to health facilities for TB testing. In Kenya, 50% of people with TB reported having trouble finding transport to care and in India, 36% of people with TB reported health facilities they normally visit closed.[16]

Figure 2. Results of a civil society-led survey on impact of COVID-19 on TB services

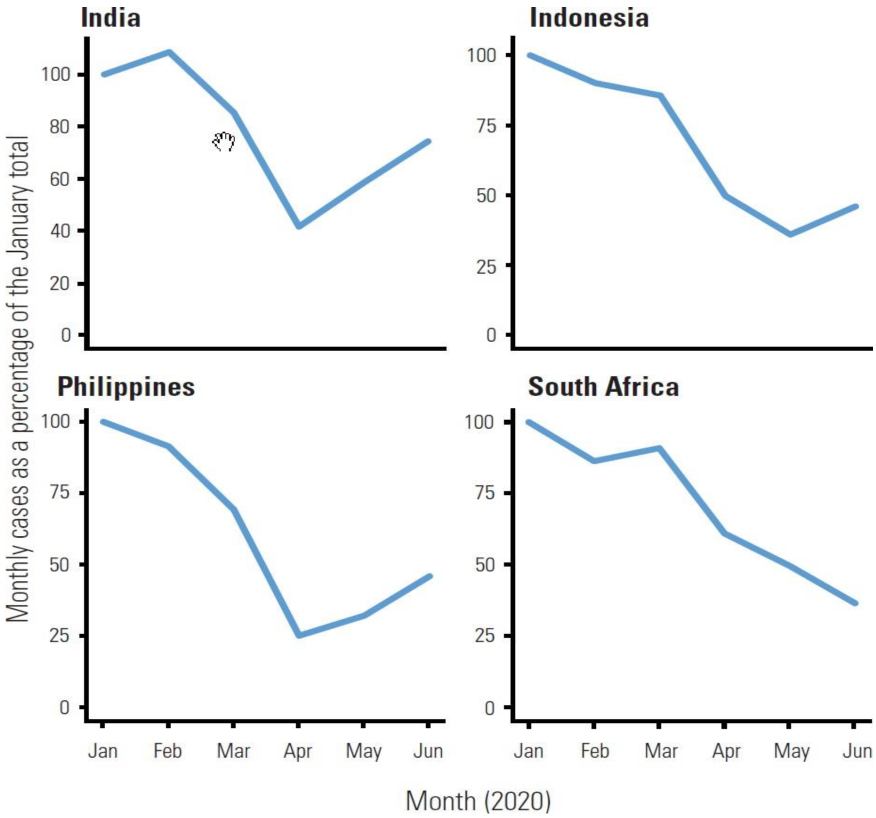


Source: The Impact of COVID-19 on the TB Epidemic: A Community Perspective 2020

The WHO Global TB Report 2020 includes data on drops in TB notifications. The data show 25-30% drops in TB notifications reported in 3 high burden countries – India, Indonesia, the Philippines – between January and June 2020 compared to the same 6-month period in 2019 (Figure 3). According to WHO, negative impacts on essential TB services include the reallocation of human, financial and other resources from TB to the COVID-19 response. Many countries have reported the use of GeneXpert machines for COVID-19 testing instead of diagnostic testing for TB, reassignment of staff in national TB programmes to COVID-19 related duties, and reallocation of budgets.[17]

[16] The Impact of COVID-19 on the TB Epidemic: A Community Perspective. Stop TB Partnership 2020.

Figure 3. Data on TB notifications during COVID-19



Source: WHO Global TB Report 2020

Another model by Imperial College and the Stop TB Partnership estimated that a 3-month suspension of TB services, followed by 10 months to restore them to normal, would cause, over the next 5 years, an additional 1.19 million TB cases and 361,000 TB deaths in India, 24,700 TB cases and 12,500 deaths in Kenya, and 4,350 cases and 1,340 deaths in Ukraine. The principal driver of these adverse impacts is the accumulation of undetected TB during a lockdown. The modeling analysis demonstrates how long-term increases in TB burden could be averted in the short term through supplementary "catch-up" TB case detection and treatment, once restrictions are eased.[18] In this context, there is a need for rapid diagnostic solutions that can be implemented in facilities such as local health clinics, medical offices, health posts, or even by health workers during home visits, and used to test for many pathogens.

Despite the negative impact of the COVID-19 pandemic, there are also lessons and potential synergies in the response given the relationship of the two diseases and the advances made to combat this new infectious disease threat.

[18] Cilloni L, Fu H, Vesga JF, et al. The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis. EClinicalMedicine November 2020 28(100603):1-9.

2.3. Effective tools for TB detection could be highly cost-effective and high impact

An additional contributing factor for the large gap in TB detection is the complexity and cost of available tests which are centralized at secondary and tertiary levels of the health system. The technical challenges relate to the lack of the ability to process samples without a specialized lab, lack of durable and consistent power sources, and high-maintenance costs for rural and tropical settings. At present, the price per test also has precluded the use of current diagnostics for triage at the lower health care levels. Cartridges cost approximately US$ 10, excluding capital costs, maintenance, and warranty of the machines.

2.4. TB detection strategies are key for the most vulnerable groups

A TB test on the first visit to a health unit is rare. Often, a test requires a scheduled appointment, with results obtained at a second appointment. This is a major barrier for people affected by TB, usually the poorest and most vulnerable, including people who are unemployed or with informal jobs without any labour rights, and those who have difficulties in reaching health services, such as those living in rural areas, refugee camps, shelters, prisons or who are homeless. For all these hard-to-reach populations, among whom TB is highly prevalent, it is essential to have a diagnostic tool to detect TB at the first contact.

Triage tests that could differentiate between TB infection and TB disease at first contact at the lowest level of the health system or even at the community level would allow detection strategies to identify people infected by *M. tuberculosis* and already with TB disease.

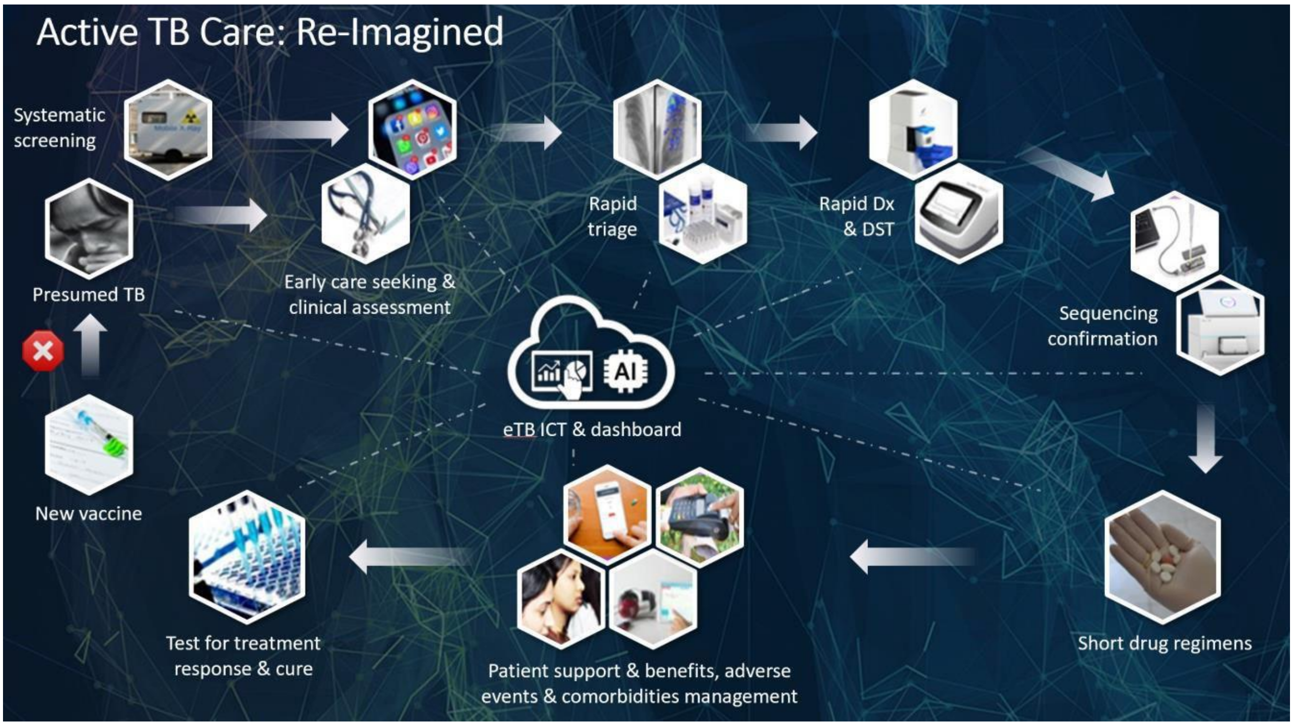
3. Why are there insufficient tools for TB detection?

The lack of tools for TB detection that fully meet the needs for those at risk are in part because of inadequate scale-up of available TB diagnostic tools according to WHO recommendations. Secondly, many of the diagnostic tools currently available and recommended by the WHO do not sufficiently meet the needs of people at risk of TB or of health systems in terms of accuracy, time to results, affordability, and appropriateness for use at lower health care levels.[19,20]

There are efforts underway to reimagine TB care including using different technology and tools in more efficient and cost-effective ways (Figure 4). Country programs and providers (both public and private) are increasingly fatigued with introduction of individual tools. They are struggling with challenges due to fragmentation of vendors and services, complex procurement and supply chains, and inability to deal with the entire cascade of care. High TB burden countries need a packaged set of solutions across the care model in order to make solutions more convenient to procure and purchase; provide an end-to-end solution; and improve the quality of care.

[19] Treatment Action Group TB Diagnostic Pipeline Report 2020
[20] TAG's an Activist's Guide to Tuberculosis Diagnostic Tools

Figure 4. Coordinated and comprehensive integrated TB care model



Source: The Reimagined TB Care Project

4. Unitaid is well-positioned to address TB diagnostics for more decentralized use

Unitaid's TB portfolio is helping to address everything from preventive therapies to latent TB, detection of resistant TB, digital technologies to improve treatment adherence, improving coordination between different clinics and TB clinics to improve detection and treatment for childhood TB, exploring better and shorter MDR-TB treatments for adults and children, and supporting innovative technologies of long-acting drugs for TB prevention and treatment. Notably in diagnostics, Unitaid is investing in enabling next-generation sequencing (NGS) platforms for drug-resistance testing and optimizing MDR-TB treatment for use in lower- and middle-income countries (LMICs). This technology will be important in efforts to provide integrated diagnostic solutions for countries and provide a key solution at the centralized and tertiary levels of care. Unitaid is addressing important equity gaps in the TB response, yet none of these projects target sufficiently the key factor needed to find the 3 million missing cases of TB each year.

Having identified this key remaining challenge and considering the existing Unitaid portfolio, there is a clear need for new investments and interventions to address the diagnostic gap. Thereafter, the Secretariat has debated what could be addressed by ongoing projects through expanding or appending specific activities or targets, or what needs additional work through new projects.

Overall, Unitaid has championed the efforts of a global diagnostic network in optimizing and integrating of testing for various diseases including HIV, TB, malaria, hepatitis C, HPV, and more. Unitaid’s involvement in the Access to COVID-19 Tools (ACT) Accelerator to advance innovations for both therapeutics and diagnostics will allow opportunities in COVID-19 to be leveraged for direct application for TB. As such, Unitaid is uniquely well placed to support diagnostics for TB in the new context of COVID-19, continuing to address the HIV and TB co-pandemics, and implementing solutions that can be leveraged for potential future pandemics.

For TB LAM tests and for some newer molecular tests, specific interventions could build on Unitaid's existing work to enable point-of-care diagnostics and access to tools for care of advanced HIV disease

These interventions and others could pave the way for the introduction and adoption of even better innovative point-of-care test that will emerge in the pipeline. Demonstration studies and operational research could help drive adoption of newer TB detection tools that better meet target product profiles and leverage the innovation in COVID-19.

5. Potential opportunities for Unitaid

For the first time in many years, possibilities for effective point-of-care diagnostic solutions that can be applied to TB are promising especially given the opportunities that have emerged due to COVID-19. The global priorities for TB detection to consider in determining the best solutions to bring forward include:

1. Finding missed cases and linking to care;
2. Addressing diversion of TB laboratory capacity and ramping up testing to above pre-COVID-19 levels;
3. Engagement and incentivization of diagnostic companies to continue TB R&D;
4. Evolution of TB policies incorporating integrated testing services to increase case notifications in both public and private sectors; and
5. Intervening to ensure adequate diagnostic production and supply.

The key opportunities presented address these priorities, taking into account the fit with Unitaid's mandate and scope and the readiness of the technology.

5.1. Potential short-term opportunities (1-2 years)

To complement Unitaid's TB portfolio, investments for the next 12 months should include diagnostic solutions already available on the market or close to market entry. Of those already on the market, improvements in sensitivity or affordability may be necessary to expand the target population and increase adoption.

The most promising short-term opportunities address these challenges with the diagnosis of TB at the primary and community health care level and focus on integration in two categories: **1) enabling non-sputum-based and integrated TB diagnostic solutions** and **2) adapting and leveraging COVID-19-specific diagnostic and case detection solutions for TB detection.**

5.1.1. Enabling non-sputum-based and integrated TB diagnostic solutions

There are several diagnostic tests available or emerging that could be used at the lower levels of health care and overcome some of the challenges with the current sputum-based tests while also being harnessed for a variety of other important conditions. Among the top solutions are integrated molecular testing which allows for molecular detection of TB and drug-resistant cases, faster and more cost-effectively than culture. Many of these platforms can sequentially or simultaneously test for multiple infectious agents, pathogen variation and AMR. To enable these tests to be used at the point of care, there needs to be a greater expansion of these machines to process other samples (i.e., urine, stool, blood), more affordable pricing to accommodate higher testing volumes, and technical improvements adapted for rural and low-resource settings. These tests could allow for more integrated or bidirectional case detection and policies that include TB and other diseases.

In addition, the rapid evolution of TB lipoarabinomannan (LAM) tests, antigen (Ag) detection tests which detect the LAM antigen in urine (and potentially blood), offer another alternative to sputum sampling which has hindered TB diagnosis. Currently, TB LAM is used only in people with advanced HIV disease. These tests could be used as point-of-care tests for TB more broadly if there are improvements in concentration of the sample, amplification of the signal in the assay, and/or detection sensitivity for TB.

Also, the deployment of portable chest x-ray with computer-aided design and further advancements in its portability could offer an additional diagnostic solution that could further improve TB detection with added benefit to COVID-19 policies and other respiratory infections.

Example: integrating multi-disease molecular platforms for greater TB detection and related diseases

Of the WHO endorsed TB molecular technologies, Xpert® using the MTB/RIF Ultra test kits, LAMP (loop-mediated isothermal amplification) using the Loopamp™ MTBC LAMP assay, and Truelab® using the TrueNAT® MTB Plus and MTB-RIF test kits can be adapted at the lowest health care levels given the turn-around times, their high sensitivity and specificity over microscopy, and their ability to integrate testing for other pathogens.

Currently, these three WHO-endorsed technologies have the potential to be used for both TB and other priority diseases (i.e., HIV, COVID-19, STIs). Leveraging existing multi-disease NAAT platforms for both TB and other testing could be an effective integrated or bidirectional testing strategy. It will be important to validate molecular platforms for simultaneous testing using different samples for TB and for other conditions.

Example: higher sensitivity, next-generation urine LAM assays

In 2019, the guidelines for Alere-LAM were updated to indicate the increased strength of the recommendation for Alere-LAM in hospitalized HIV-positive patients with CD4+ counts ≤ 200 cells/µl, or who are seriously ill regardless of CD4+ cell count; in this setting, the test is recommended also now more clearly for children and adolescents. With respect to ambulatory settings, Alere-LAM testing is conditionally recommended for severely ill HIV-positive outpatients of all ages with CD4+ counts ≤ 100 cells/µl regardless of signs and symptoms, or any outpatient with TB symptoms. A Cochrane systematic review commissioned for the WHO update found the pooled sensitivity of Alere-LAM was 42% and pooled specificity was 91%. In hospitalized in-patients, pooled sensitivity was 52% versus 29% among outpatients.

Despite the positive WHO recommendations and evidence demonstrating that Alere-LAM testing reduces mortality in the intended use population, data show Alere-LAM use remains low among high TB/HIV burden countries.[21] The most commonly cited constraint to adoption and implementation was budget limitations. Additional barriers to Alere-LAM implementation included lack of country-specific data and piloting, regulatory approval, lack of coordination between TB and HIV programs, and small perceived patient population.

Effort is being made to develop urine-based LAM assays with higher sensitivity. An example is Fujifilm SILVAMP TB LAM test ("FujiLAM"; Fujifilm, Tokyo, Japan), a well-advanced next-generation LAM test (CE-marked). FujiLAM offers greater sensitivity than AlereLAM and is therefore likely to extend the indication of TB LAM testing beyond seriously ill HIV-positive patients.

SILVAMP is an instrument-free diagnostic test for TB that produces results in under one hour, allowing it to be deployed at low levels of healthcare systems where patients first present for care. It also has a step that enhances the visibility of the test result lines; this allows SILVAMP to detect LAM at substantially lower concentrations in the urine than the current lateral flow urinary LAM assay. These improvements that would allow for device-free testing even by health care workers in the community has the potential for both more accurate case detection and dramatically simplified care for TB.

To take sensitivity to an even higher level, several groups are working on various approaches, including use of monoclonal antibodies, sample concentration and incubation methods, and ultra-sensitive detection methods.

Example: portable, lower-cost digital X-rays and CAD-based solutions for both TB & COVID-19

There are now several ultra-portable digital x-ray hardware options. Along with the computer-aided-design-based (CAD-based) software options, it is now possible to use this combination as a powerful way of screening for TB at the community level.

While CAD solutions are getting better and better, a key rate limiting factor of widespread use of digital x-rays is the high cost of hardware (which can be US$ 50,000 – 100,000).

A 2019 systematic review concluded that CAD-based programs are promising, but the majority of work thus far had been on development rather than clinical evaluation.[22] Subsequently, in a large, multi-country study, all three deep-learning automated reading systems outperformed experienced human readers in differentiating people with bacteriologically confirmed TB and those without.[23] Another large study in Pakistan compared qXR and CAD4TBv6 in a HIV-negative population. Both these software solutions met WHO-recommended minimal accuracy for pulmonary TB triage tests.[24] In 2020, WHO organized a meeting to review the evidence, and a policy statement is expected shortly.

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[21] Adoption and uptake of the lateral flow urine LAM test in countries with high tuberculosis and HIV/AIDS burden: current landscape and barriers. Gates Open Research 2020. https://gatesopenresearch.org/articles/4-24

[22] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0221339
[23] https://www.nature.com/articles/s41598-019-51503-3
[24] https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30221-1/fulltext

5.1.2. Adapting and leveraging COVID-19-specific diagnostic and case detection solutions for TB detection

Innovation for the detection of COVID-19 has occurred at a rapid pace and given its synergies with TB, many of the tools that have been developed could be adapted for use in TB or integrated to allow for bidirectional case detection.

New efficient contact tracing approaches and applications could help improve the historically low implementation of one of the most effective means of detecting a person at risk for TB. There are rapid diagnostic tests that could be set up for both COVID-19 and TB detection allowing for efficiencies with tackling both pandemics.

Example: innovative contact tracing and case-finding

Mobile apps & services (e.g. using Whatsapp & chatbots) are being widely used for public education on COVID-19, for risk or self-assessment, screening and linkage to testing, for contact tracing and mapping.

For example, South Africa, building on its success with MomConnect, has reached over 7 million people using a suite of digital tools (e.g. COVID-19 HealthAlert & COVID-19 HealthCheck) – these are now being repurposed for TB.[25,26] India's open-source Aarogya Setu mobile app has been downloaded by over 150 million individuals.[27] If these apps can enhance TB contact tracing, there is significant potential for impact, since contact investigation is an effective but underused intervention in many high TB burden countries.

Since there are hundreds of COVID-19 apps being widely used in many countries, there is the opportunity to add a TB component to them, or to develop TB apps that work in similar ways. Millions of people have downloaded COVID-19 apps and therefore this approach offers potential for scale. The app can be used for symptom screening and risk assessment for TB (and COVID-19). This could then trigger care seeking and could facilitate linkage to a nearby TB testing centre. In South Africa, platforms such as *MomConnect* has proven to be useful, and were repurposed for COVID-19. There is no reason why such work cannot be extended to include TB.

Once TB test results are obtained and entered into the app, it could be used to facilitate contact tracing as well as notification to the National TB Program. This, in turn, could be used to collect real-time data on TB notifications and allow geospatial mapping on dashboards. Equity, privacy, data protection concerns would need to be addressed for responsible deployment of these tools.

Example: innovative sample collection and diagnosis

Innovative community-based (decentralized) testing and enhanced case finding can be lessons learned from COVID-19 and scaled up for TB. The demand for rapid and simpler COVID-19 testing has pushed companies and health systems to innovate around what samples to collect, where to collect them, and how to make testing easier to access. For example, samples such as saliva, rinse and gargle, oral swabs, and even sampling of face masks are being actively explored.

[25] https://www.praekelt.org/momconnect

[26] https://www.praekelt.org/healthconnect

[27] https://www.mygov.in/aarogya-Setu-app/

Tremendous effort is being made to develop home-based, self-tests for COVID-19. Mobile testing sites, drive-through testing, and sample collection via community health workers, neighbourhood pharmacies, schools and workplaces are all happening. Simple self-sampling (e.g. from face masks) is being tried out – and in combination with cutting-edge molecular detection assays like CRISPR, this could pave the way for testing closer to homes.[28,29]

Currently, TB testing is highly reliant on sputum, a sample that is not easy to collect and process. TB testing is also not easily accessible at the primary care level. So, if some of the innovative approaches around COVID-19 sample collection & near-patient access can be applied to TB, this might help reduce the massive diagnostic gap in TB.

6. Theory of Change and expected impact

The global gap in TB detection is not only sizable (2.9 million unnotified TB cases in 2019), but also deadly. Without diagnosis and proper treatment, 45% of HIV-negative people with TB and nearly all HIV-positive people with TB will die.[30] Not only do undiagnosed cases contribute significantly to the global death toll from TB, but also drive onward transmission as individuals unknowingly spread the infection to others. For these reasons, the proposed Area for Intervention *Accelerating tools to drive TB detection* offers the potential for significant impact. As described in previous sections of this document, several promising opportunities have emerged that offer real potential to dramatically increase access to TB screening and diagnosis in the coming years with several key areas of impact.

Increasing TB detection and reducing the number of missing TB cases

A primary objective of this AfI is to improve and expand TB case finding and screening approaches to support the detection of the millions of missing TB cases. All components of the AfI will support this objective (see outputs outlined in the Theory of Change below). The COVID-19 pandemic brings opportunities to leverage innovative case finding and integrated diagnostics to significantly expand and scale improved TB detection activities.

Impacting the most vulnerable and reducing inequalities

The existing systems for case detection and screening are disproportionately missing key vulnerable groups such as PLHIV, children, those with poor access to health services, stigmatized groups and people living in poverty. This AfI aims to reduce these inequities by leveraging innovative detection approaches that are decentralized and better suited for lower levels of the health system to reach these populations. People living with HIV, specifically would benefit from a more sensitive 3rd generation TB LAM test.

Allowing faster diagnosis and treatment initiation

This AfI aims to introduce near point-of-care tools (integrated diagnostics, TB LAM test, computer-assisted x-ray, etc.) that allow for same-day diagnosis and treatment initiation. Shortening the time to diagnosis and treatment initiation results in better treatment outcomes and shorter infectious periods.

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[28] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30707-8/fulltext
[29] https://www.tandfonline.com/doi/full/10.1080/22221751.2019.1664939
[30] https://www.who.int/news-room/fact-sheets/detail/tuberculosis#:~:text=Key%20facts,(above%20HIV%2FAIDS).

Increasing proportion of bacteriologically confirmed cases

Globally, only 57% of notified TB cases are bacteriologically confirmed. The remaining cases are diagnosed based on clinical criteria and without drug susceptibility testing, resulting in an increased risk of incorrect TB diagnosis, non-detection of resistant cases, and unnecessary or incorrect treatment. Through the introduction in improved and more sensitive screening tools, Unitaid is seeking to increase the proportion of notified cases with a bacteriological confirmation.

The following Figure 5 describes the changes that can be expected through the Accelerating tools to drive TB detection AfI. Further work to qualify impact can be undertaken at the level of specific projects.

Figure 5. Theory of Change for TB decentralized diagnostics

Problem

Public health need

- Only 70% of estimated 10 million annual TB cases were notified last year. The "missing" 3 million cases account for a large amount TB-related mortality, morbidity and onward transmission. The COVID-19 pandemic is expected to further increase this detection gap with many countries already seeing dramatic decreases in TB notifications.
- Globally, only 57% of notified TB cases are bacteriologically confirmed while the remaining are clinically diagnosed with a higher likelihood of incorrect diagnosis, which can lead to inappropriate or unnecessary treatment.

Access barriers

- **Innovation & availability**: Many of the diagnostic tools endorsed by the WHO do not sufficiently meet the needs of people at risk of TB or of health systems in terms of accuracy, time to results, and appropriateness for use at the decentralized level
- **Demand & adoption**: Country programs and providers struggling with challenges of introducing individual tools for multiple simultaneous disease epidemics. Increased adoption of integrated testing approaches could increase TB case detection.
- **Affordability:** The costs of available tests inhibit high-throughput screening for triage testing and scale-up of diagnosis including drug-sensitivity testing, contributing to the large gap in TB detection.
- **Supply & delivery**: Complex procurement and supply chains for individual diagnostic tools are burdensome to health systems.

Conceptual pathway

Input	Output	Outcome	Impact
Unitaid Funding	Integrated diagnostic platforms for primary and community levels using novel sampling methods and processing	Availability of better tools and approaches to detect TB at first contact with the healthy system	Reduction in number of missing TB cases
Product developers' contributions	Second generation TB LAM expanding use case in HIV+ and children	Adoption of new tools and integrated approaches that improves case detection for TB and one or more other priority disease	Additional TB-related deaths averted
Country's health system (e.g. capital cost, HR)	Chest X-ray with computer aided design for triage	Increased access of screening and diagnostic services for TB	Additional TB-related morbidity averted
	Adapting innovative COVID-19 contact tracing for TB		Reduced transmission of TB
	Adapting innovative sample collection tools for TB		Reduction in incorrect diagnosis and treatment of non-TB cases

Key assumptions /risks

Examples of Risks (non-exhaustive):

- Implementation – Impact of new tools limited by weaknesses in health systems needed for integrated, end-to-end care
- Sustainability/Scalability - Limited funding is available from donors and countries, introductions of multiple tools across the health system leading to low uptake and scale-up of any one tool

Assumptions

There is strong political willingness across TB endemic countries to adopt interventions for TB that integrate and simplify care

7. Fit with Unitaid's portfolio

Unitaid has a portfolio rich in diagnostic innovations. Within the current Unitaid TB portfolio there is work supporting diagnostics and care for children and for MDR-TB. The CAP-TB project, led by Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), is promoting better integration among TB and HIV, mother and child care, nutrition and others paediatric services; while the TB-Speed project, led by University of Bordeaux, is increasing paediatric TB detection by validating new diagnostic algorithms and introducing new type of samples, including the use of stool samples, to be used in molecular tests. For MDR-TB, Unitaid is funding a grant in target next-generation sequencing for clinical decision making for better care management in LMICs. This project, the Seq&Treat, led by the FIND, aims to accelerate the introduction and global adoption of commercial targeted gene sequencing for affordable, scalable and rapid drug-susceptibility test (DST) for clinical decision-making. In addition, Unitaid has key investments in digital technology including the Adherence Support Coalition to End TB (ASCENT) project, led by KNCV, which is one of the most significant of these investments with the objective to catalyze global adoption and scale up of new digital adherence technologies to improve treatment outcomes.

In addition, Unitaid has been extensively involved in fostering and supporting rational implementation and adoption of integrated diagnostic tools and simplified care with examples including the HIV portfolio with the grants on POC testing, HIV self-testing, and TB LAM for advanced HIV disease; the Hepatitis C portfolio with grants to develop and enable better diagnostics and care; and the cervical cancer portfolio which is enabling integrated diagnostics. Unitaid is involved with an integrated diagnostic network comprised of partners across global health to maximize and ensure effective adoption and uptake in this area. Recently, work on diagnostics for COVID-19 builds on our current work on integrated diagnostics as well as presents opportunities to inform future opportunities and work. Therefore, further work in diagnostics could complement and leverage this significant portfolio.