DISEASE NARRATIVE FOR TUBERCULOSIS

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Unitaid
Innovation in Global Health

EXECUTIVE SUMMARY

This *Disease Narrative for Tuberculosis* provides an overview of Unitaid's strategic approach to maximize the effectiveness of its contribution to the tuberculosis (TB) response. The scope of the report is focused on the challenges and opportunities in innovation related to TB. Through a systematic analysis that included consultation with key stakeholders, short- and longer-term opportunities have been identified for Unitaid to actively explore ways to support accelerated progress towards achieving the global TB targets.

From 1990 until 2015, the global efforts to meet the Millenium Development Goals (MDGs) resulted in significant progress in the fight against TB with a 42% reduction in prevalence and a 47% reduction in TB deaths. Despite progress, TB is currently the deadliest communicable disease globally and the leading cause of death among people living with HIV (PLHIV), surpassing AIDS as the most lethal communicable disease of modern times.[1]

In 2018, 10 million people were estimated to have fallen ill with TB and 1.5 million died because of the disease (including 251,000 people co-infected with TB/HIV). From the total number of TB cases, roughly 70% were detected and reported to WHO, with 3 million people with TB still missed leading to continued spread of the disease.[2]

Drug-resistant tuberculosis (DR-TB), considered a global health crisis by WHO, is a growing problem. Multi-drug-resistant TB (MDR-TB) is the most prevalent among diseases with antimicrobial resistance (AMR), responsible for one-third of all deaths caused by AMR.[3] In 2018, less than 18% of DR-TB cases were cured.[4]

Succeeding the MDGs era, in May 2014, the World Health Assembly approved a new global TB strategy. The *WHO-End TB Strategy* marks a critical shift from controlling TB to ending the epidemic by 2035, and includes clear and ambitious targets to coordinate the global response. These include a 95% reduction in TB deaths and 90% reduction in new cases from 2015 to 2035, and a commitment to eliminate catastrophic expenses due to TB.[5] The *WHO End TB Strategy* emphasizes the need for innovation to accelerate progress: that is, optimizing existing tools and new tools emerging from the pipeline in the short-term, and introducing newer, innovative tools in the longer term.

The WHO End TB Strategy also emphasizes the importance of an integrated approach to reach global goals – for example, detecting and treating active TB disease, as well as, preventing future cases.[6] That is, better diagnosis and treatment need to be complemented by prevention strategies, especially in people at the greatest risk of developing active TB.

Additional efforts are needed to address access barriers to TB tools, and to support innovations

Critical unmet needs for new tools persist, especially related to diagnostics at the point of care; drug susceptibility tests for effective MDR-TB treatment; shorter, less toxic regimens for all forms of TB, better treatment and diagnostics for latent TB infection (LTBI); a new

and effective vaccine; and accelerated development and access of new tools for vulnerable groups such as children.

While the development pipeline, for first time in many decades, is bringing new tools and promising others for the near future, there is a risk of repeating the historically slow adoption and scale-up of new treatments and diagnostics. Archaic technologies and old drugs are still used to diagnose and treat. New medicines for drug-resistant TB launched in 2012 – the first in 40 years – using conservative estimates, were only used by roughly 20% of patients requiring these novel drug agents between 2016 and 2019.[7]

The slow pace of progress against TB is evident and the 2020 milestones are off track and will not be reached given the modest decreases in mortality, incidence, and catastrophic costs in recent years.

In light of this urgent need for faster progress, better access to key health products is critical

Unitaid and others will need to proactively support innovation to realize the full potential of new tools in ending the TB epidemic. Understanding the partner landscape is essential for identifying gaps that Unitaid could address to complement others' work and contribute to the global response. In this context, Unitaid consults partners to articulate its work and ensure a coordinated contribution to the global TB fight.

Within a dynamic partner landscape, Unitaid has a clear role in supporting the use of innovative tools and approaches by advancing R&D and innovation, supporting evidence generation to inform normative guidance and product quality, catalyzing product introduction, and addressing delivery challenges. Unitaid works in close cooperation with partners at different stages of the value chain to ensure that innovative tools are brought to market and scaled-up.

Unitaid is responding to key TB challenges through a rich portfolio of projects

As part of the Unitaid's ongoing assessment of the TB landscape and global priorities, several key challenges were identified around treatment, diagnosis, prevention and adherence to treatment that are being addressed in part within our TB portfolio of active grants. The current portfolio centers around three strategic priorities that aim:

- to accelerate access and adoption of new child-friendly medicines for TB by identifying more children with TB and reaching children outside of TB services;
- to increase uptake of better, shorter preventive treatment for people living with HIV and household contacts of people with active TB;
- to expand access to simpler, more optimal treatment regimens for MDR-TB for both adults and children and to enable better diagnosis of MDR-TB.

The TB pipeline holds a range of promising new tools

The R&D pipelines for TB drugs, diagnostics, and vaccines hold a range of promising new tools, particularly in the medium- to longer-term. In the short-term, the focus will be on improved screening tests for TB such as TB LAM and implementing multi-disease diagnostic platforms to better detect TB and other related conditions to support more integrated approaches to health. Also, with the greater uptake of bedaquiline and delamanid and the entry of pretomanid, the treatment of XDR-TB and intolerant MDR-TB has evolved

considerably and there will need to be increased efforts to ensure adoption and access. By 2025, R&D pipelines are likely to yield new true point of care diagnostics and long-acting preventive therapy. In addition, the results of ongoing clinical trials will be available that could lead to better shorter MDR-TB and preventive therapy regimens and better treatment outcomes for patients. Beyond 2025, there is promise of a subunit TB vaccine that can be used in a broader population than BCG. As we advance the drug development pipeline, the possibility of having a shorter regimen less than 2 months is becoming a closer reality for those with drug-sensitive TB.

Unitaid has identified opportunities to address key challenges in the short term

Having considered the existing portfolio and applied the challenges identified above, potential opportunities have been identified by the Secretariat for consideration as new potential areas for intervention, or strategic opportunities. In addition, each of these areas are reviewed regularly to determine if additional work is warranted. Expanding existing areas of intervention can occur where there are opportunities that could meet the objectives of our strategic priorities. For example, Unitaid is investing in preventive treatment of susceptible TB, but new tools to prevent MDR-TB are still needed. New potential areas for intervention on the horizon include diagnostics that can be utilized at the primary and community level of the health system.

With this document, Unitaid intends to inform its current strategic approach to fight TB, its portfolio of grants, and potential investment opportunities in the near future, which will enable better alignment and coordination with global partners, that will allow Unitaid to add the best efforts of its mandate to contribute to the achievement of the global goal of ending TB.

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ABBREVIATIONS

AfI	Area for Intervention
AMR	Antimicrobial resistance
BPaL	Bedaquiline, pretomanid and linezolid
DR-TB	Drug-resistant TB
DS-TB	Drug sensitive/susceptible TB
DST	Drug-susceptibility testing
FDC	Fixed-Dose Combinations
HIV	Human Immunodeficiency Virus
IGRA	Interferon gamma release assay
IPC	Infection prevention and control
LF-LAM	Lateral Flow lipoarabinomannan (LAM) antigen
IPT	Isoniazid preventive therapy
LMICs	Low-and-Middle Income Countries
LTBI	Latent tuberculosis infection
MDGs	Millenium Development Goals
M. tuberculosis	Mycobacterium tuberculosis
MDR-TB	Multi-Drug resistant TB
MPP	Medicines Patent Pool
PCR	Polymerase chain reaction
PLHIV	People living with HIV
PoC	Point-of-Care
RDT	Rapid Diagnostic Tests
SDGs	Sustainable Development Goals
TB	Tuberculosis
TST	Tuberculin skin test
UN HLM	UN High-Level Meeting
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB

1 ANALYSIS OF THE DISEASE CONTEXT

1.1 *Disease Narrative* introduction

This *Disease Narrative for Tuberculosis* is intended to communicate Unitaid's strategic approach to TB, its portfolio of grants, and potential opportunities that will contribute to the global health response aimed at achieving the goal of ending TB by 2035. This document builds on Unitaid's 2016 *Disease Narrative for Tuberculosis* by providing updates on global progress against the goals set out in the *WHO End TB* Strategy, challenges impeding the TB response, and Unitaid's activities in TB.

The Secretariat is constantly scanning and monitoring the pipeline of products and technologies through continuous landscaping and partner engagement. This starts with an analysis of the disease characteristics (including burden, key commodities), gaps to the global goals and associated strategies, challenges identified by partners to reach the goals, actions of partners to reach the goals, and finally, opportunities for intervention for Unitaid. From the disease narrative and consultation with partners, Unitaid identifies areas for intervention (AfI), which are then proposed to the Board for endorsement. Unitaid then identifies specific interventions to conduct within each area and launches calls for proposals.

The disease narrative is not intended to be a full-fledged strategy but rather, a living document that provides directional visibility on the context and focus areas that will be relevant as future strategy is developed. The disease narrative stops short of detailing specific calls for proposals or the estimated amount to be invested in each intervention; these areas are detailed in the AfI and investment plan.

1.2 Disease introduction

TB is a communicable, airborne disease caused by *Mycobacterium tuberculosis.* Transmission often leads to a latent TB infection (LTBI) that is non-infectious and asymptomatic; an estimated 1.7 billion people, 23% of the world's total population, has latent TB.[8] Approximately 5–15% of all latently infected individuals will develop active TB during their lifetime, with people living with HIV at considerably higher risk.[9]

If active TB is not diagnosed and treated, mortality is high and the infection can remain transmissible. In 2018, there were an estimated 10 million new cases of TB, resulting in 1.5 million deaths. From the total number of TB cases, 7 million were detected and reported to WHO, with 3 million remaining cases missed.[10]

TB disproportionately affects – and kills – the world's poorest and most vulnerable, including children, people co-infected with HIV, migrants, miners, and individuals without access to healthcare. Effective diagnosis – critical for ensuring treatment success – is most difficult in many of these most vulnerable groups. In 2017, an estimated 1 million children[11] fell sick with TB with only about half of them identified and treated. Children accounted for 10% of total estimate TB cases and 15% of TB deaths, making TB one of the top 10 causes of death in children and suggesting poorer access to diagnosis and treatment. During 2018, beyond the estimated 1.2 million TB deaths among HIV-negative people, an additional 251,000 deaths among people living with HIV (PLHIV) were due to TB, making it the leading killer in this group.[12]

Exacerbating the TB pandemic, drug-resistant tuberculosis (DR-TB) is considered a global health crisis by WHO and is a growing problem with 484,000 cases estimated in 2018. Less than one-third of these cases were enrolled on treatment with a second-line regimen and only 56% of those were cured.[13] Multi-drug-resistant TB (MDR-TB) is the most prevalent among diseases with antimicrobial resistance (AMR), responsible for one-third of all deaths caused by AMR.[14]

Currently available medicines can cure most cases of TB in six months, and advances in technology – including novel and repurposed medicines and regimens – hold promise to treat drug-resistant forms of the disease. However, many patients do not have access to effective diagnosis or appropriate TB medicines.[15]

From 1990 until 2015, the global efforts to meet the Millenium Development Goals (MDGs) resulted in significant progress in the fight against TB with a 42% reduction in prevalence and a 47% reduction in TB deaths. Despite the progress, TB is currently the deadliest communicable disease globally, surpassing AIDS as the most lethal communicable disease of modern times.[16]

1.3 Global goals and current status

In 2014, the World Health Assembly approved a new global TB strategy, the End TB Strategy, that marked a critical shift from controlling TB to ending the epidemic. Ambitious targets in the strategy include: reducing TB deaths by 95% and cutting new cases by 90% between 2015 and 2035, and ensuring that no family is burdened with catastrophic expenses due to TB. It also sets interim milestones for 2020, 2025, and 2030 as shown in **Figure 1** below.[17]

FIGURE 1: End TB Strategy milestones and targets

Indicators with baseline values for 2015	Milestones			Targets
	2020	2025	2030	2035
Percentage reduction in deaths due to tuberculosis (projected 2015 baseline: 1.3 million deaths)	35%	75%	90%	95%
Percentage and absolute reduction in tuberculosis incidence rate (projected 2015 baseline 1101 J 00 000)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
Percentage of affected families facing catastrophic costs due to tuberculosis (projected 2015 baseline: not yet available)	Zéro	Zéro	Zéro	Zéro

The End TB Strategy emphasizes the need for innovation to accelerate progress: that is, optimizing existing tools and new tools entering the market in the short-term, and introducing newer more innovative tools in the longer term. While the development pipeline has changed and new tools are finally becoming or close to becoming available, there is a risk of repeating the historically slow adoption and scale-up of new treatments and diagnostics. Archaic technologies and old drugs are still used for diagnosis and

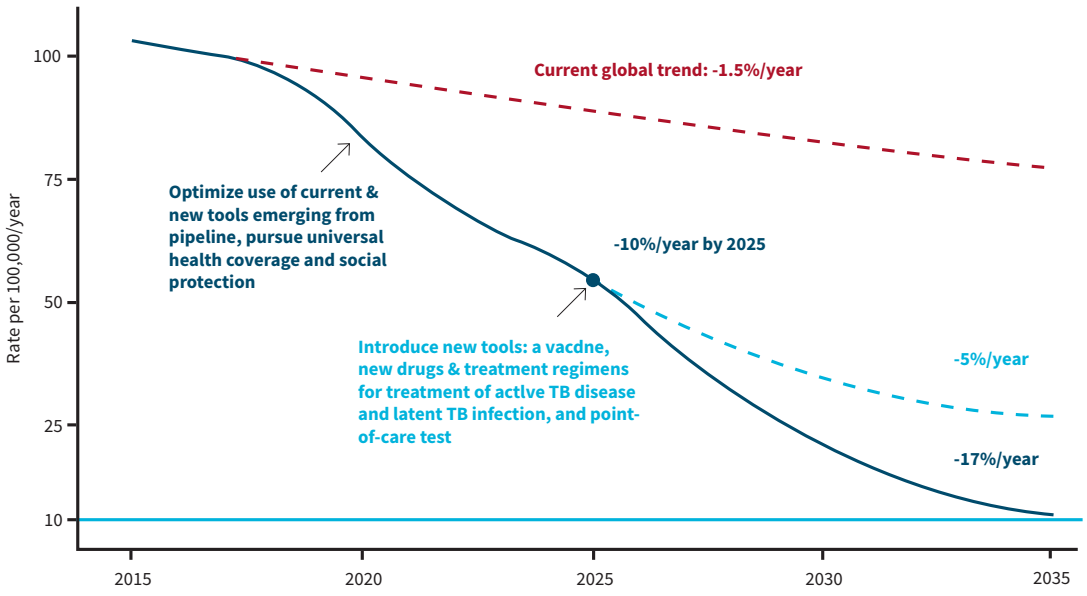
treatment. New medicines for drug-resistant TB launched in 2012 – the first in 40 years – are used in less than 10% of eligible patients.[18]

The tracking of the End TB 2020 milestones make it clear that the global health response is advancing slower than expected. The decline in mortality and incidence rates are far from the bold targets set and the monitoring of TB-affected families facing catastrophic costs is not yet widely done.

The End TB Strategy also stresses the importance of an integrated approach to reach global goals – for example, detecting and treating active TB disease as well as preventing future cases.[19] That is, better diagnosis and treatment need to be complemented by prevention strategies, especially in people at the greatest risk of developing active TB.

As shown in **Figure 2**, the End TB Strategy calls for acceleration of the global response by optimizing existing tools and those emerging from the pipeline, health coverage and social protection in the short-term (from 2015), and introducing newer, innovative tools in the longer term (from 2025).[20]

FIGURE 2: Desired decline in global TB incidence rates to reach the 2035 targets



Source: WHO End TB Strategy

In 2015, the United Nations lauched the Sustainable Development Goals (SDGs), which include similar, but even bolder targets aiming to reduce the number of TB deaths by 90% and the TB incidence rate by 80% by 2030.[21]

The End TB Strategy and the SDGs are complemented by the Stop TB Partnership's Global Plan to End TB 2016-20[22], which recommends additional people-centered '90-(90)-90' targets for 2025, as follows:

- Find at least 90% of all people with TB who require treatment and place them on appropriate therapy (first-line, second-line, and preventive);

- Make a special effort to reach at least 90% of key population groups – the most vulnerable, underserved, at-risk populations in countries; and

- Reach at least 90% treatment success through affordable treatment services, promoting adherence and social support.

In support of the global targets set for ending TB, the WHO organized a Global Ministerial Conference in November 2017 where 80 ministers agreed to the Moscow Declaration to End Tuberculosis increasing the global political commitment to multisectoral action.[23] This global commitment led to the 2018 UN High-Level Meeting (UN HLM) where heads of States and Governments stated their commitment to build the global response to end TB.

Aligned with and building on previous targets, the UN HLM targets are bold (see **Figure 3**). One year after the UN HLM, there is hope to see unprecedented progress in key areas, with countries implementing their commitments, dedicating more domestic funds, moving quickly to achieve universal health coverage, and consequently detecting more TB cases and expanding treatment. However, multisectoral accountability continues to lag toward availability of new tools to diagnose, treat, and prevent TB.

FIGURE 3: UNHLM on TB Key Targets for 2022

1.
COMMIT TO PROVIDE **DIAGNOSIS AND TREATMENT** with the aim of successfully treating 40 million people with tuberculosis by 2022.

2.
COMMIT TO PROVIDE **DIAGNOSIS AND TREATMENT** with the aim of successfully treating 35 million children with tuberculosis by 2022.

3.
COMMIT TO PROVIDE **DIAGNOSIS AND TREATMENT** with the aim of successfully treating 1.5 million people with drug-resistant tuberculosis, including 115000 children with drug-resistant tuberculosis by 2022.

4.
COMMIT TO PROVIDE **PREVENT TUBERCULOSIS** for those most at risk of falling ill so that at least 30 milllon people, including 4 million children under five years of age. 20 million other household contacts of people affected by tuberculosis, and 6 million people living with HIV, receive preventive treatment by 2022.

5.
COMMIT TO MOBILIZE **SUFFICIENT AND SUSTAINABLE FINANCING** for universal access to quality prevention, diagnosis, treatment and care of tuberculosis, from all sources. with the aim of increasing overall global Investments for ending tuberculosis reaching at least US$13 billion a year by 2022.

6.
COMMIT TO MOBILIZE **SUFFICIENT AND SUSTAINABLE FINANCING FOR R&D** With the aim of increasing overall global investments to US$2 billion. In order to close the estimated US$ 1.3 billion gap in funding annually for tuberculosis research. ensuring all countries contribute appropriately to research and development.

7.
PROMOTE AND **SUPPORT AN END TO STIGMA AND ALL FORMS OF DISCRIMINATION,** including by removing discriminatory laws, policies and programmes against people with tuberculosis, and through the protection and promotion of human rights and dignity.

Recognize the various sociocultural barriers to tuberculosis prevention. diagnosis and treatment services. especially for those who are vulnerable or in vulnerable situations. and the need to develop integrated, people-centred, community-based and gender-responsive health services based on human rights.

8.
COMMIT TO DELIVERING. **AS SOON AS POSSIBLE. NEW, SAFE, EFFECTIVE, EQUITABLE. AFFORDABLE, AVAILABLE VACCINES,** point-of-care and child-friendly diagnostics, drug susceptibility tests and safer and more effective drugs and shorter treatment regimens for adults, adolescents and children for all forms of tuberculosis and infection, as well as innovation to strengthen health systems such as information and communication tools and delivery systems for new and existing technologies to enable Integrated people-centred prevention, diagnosis. treatment and care of tuberculosis.

9.
REQUEST THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION TO **CONTINUE TO DEVELOP THE MULTISECTORAL ACCOUNTABILITY FRAMEWORK** and ensure its timely implementation no later than 2019.

10.
FURTHER REQUEST THE SECRETARY GENERAL WITH THE SUPPORT OF THE WORLD HEALTH ORCANIZATION. TO **PROVIDE A PROGRESS REPORT IN 2020** on global and national progress, across sectors, in accelerating efforts to achieve agreed tuberculosis goals, which will serve to inform preparations for a comprehensive review by Heads of State and Government at a high-level meeting in 2023.

Source : Stop TB Partnership[24]

To achieve these targets, the fight against TB needs to accelerate in pace. The global response must be faster and more effective. The diagnostic pipeline is prolific with potential candidate products covering identification of antigens, antibodies, biomarkers, cellular response and molecular biology for TB detection, and culture-based and molecular biology for drug-susceptibility testing. Despite this rich pipeline, the availability and introduction of innovative TB diagnostics has been conservative and slow.

Most of the pipeline is at an early stage of development with a slow progression of new tools to late-stage development, market authorization and WHO evaluation. Further stunting innovation in TB is the challenge of timely adoption and scale-up of available new tools in the countries that most need them. The reality for the treatment pipeline and access is not much different. Archaic diagnostic technologies such as sputum smear microscopy and old drugs discovered in the 1950s are still considered standard of care.

A new diagnostic (Xpert MTB/RIF, 2010) and two novel MDR-TB medicines (bedaquiline, 2012; delamanid, 2013) have entered the market in the last decade, but adoption and uptake have been unacceptably slow, notably for the new drugs. The performance of Xpert MTB/RIF has been improved with new versions of its catridges (Xpert Ultra) and new point of care machines -- Edge (2018) and Omni (launch to be confirmed), but the new products that are available remain underutilized or are utilized by only a few target patients at high risk. Using conservative estimates, only about 20% of patients requiring novel drug agents received them from 2016-2019.[25]

More specific latent TB infection screening tests are urgently needed that can reliably identify latent infection and predict the likelihood of latent infection progressing to active disease. In this regard, there are some promising tests in the development pipeline, but they are in early stages.

Anticipating the upcoming new innovations is key to accelerating adoption in low-income countries, especially with the advent of new diagnostics and MDR-TB treatments – for which coordination and integration is increasingly important (e.g., better drug susceptibility tests need to be designed and rolled out to test for resistance to novel drugs).

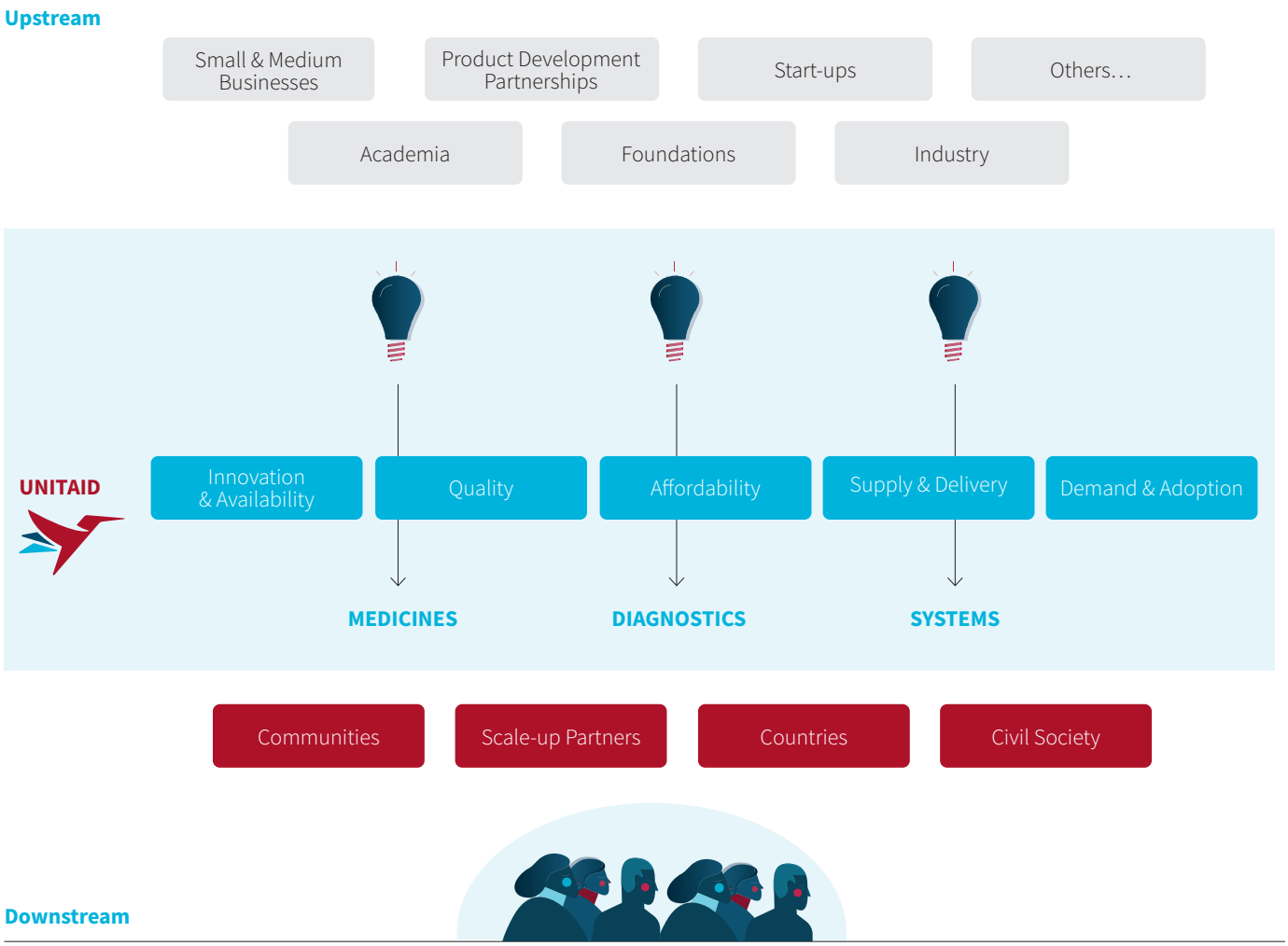
However, critical needs related to commodity access persist, especially in diagnosis, MDR-TB, and in vulnerable groups such as children. Prevention efforts will also be key to ending TB. While an effective vaccine is not yet available, new regimens may soon make preventive treatment of latent TB more feasible in high-burden settings.

1.4 Collective action and the partner landscape

Understanding the partner landscape is essential for identifying gaps that Unitaid could address to complement others' work and contribute to the global response. In this sense, Unitaid has performed frequent consultation with partners to articulate and coordinate the global TB fight.

Figure 4 shows where Unitaid sits in the global response vis-a-vis other partners. Within a dynamic partner landscape, Unitaid has a clear role in supporting the use of innovative tools and approaches by advancing R&D and innovation, supporting normative guidance and product quality, catalyzing product introduction, and addressing delivery challenges. Unitaid works in close cooperation with partners at different stages of the value chain to ensure that innovative tools are brought to market and scaled-up.

FIGURE 4: Unitaid's role in global health – connecting the upstream with the downstream to unlock access



Complementing the role of WHO in setting normative guidance, many key partners support upstream innovation through product development to market entry. For example, the Bill & Melinda Gates Foundation (Gates Foundation), US Government/USAID, the Stop TB Partnership's TB REACH, the European and Developing Countries Clinical Trial Partnership (EDCTP), and other funders/bilaterals prioritize support for TB research. Non-governmental organizations (NGOs), product development partnerships, academics, industry, and other actors are also active in this area, such as, the International Union Against Tuberculosis and Lung Disease (the Union), and Institut Pasteur.

Partners also play a crucial role downstream, implementing projects, creating demand, and promoting adoption or scale-up of innovative health commodities. Countries themselves are central: domestic resources cover 87% of reported TB funding (totaling $6.9 billion)[26], and national TB programmes are a cornerstone of TB care provision. The Global Fund is the leading funder of TB commodities utilizing largely the Stop TB Partnerships' Global Drug Facility, the largest global provider of quality-assured TB medicines, diagnostics, and laboratory supplies to the public sector. The U.S. government is the largest bilateral donor in TB, with extensive experience and insight from both the implementation and technical assistance perspective in countries. Other groups that provide valuable perspectives

allowing Unitaid to anticipate and respond to country needs include: civil society and representatives from communities affected by TB and related comorbities; Stop TB Partnership and key advocacy groups; and NGOs and other actors with experience in implementing large-scale projects in countries.[27]

This is particularly relevant in ensuring that needs of people with TB, especially the most vulnerable, are met (e.g., more effective regimens, new tools for unmet and evolving diagnostic needs), and adoption is not delayed (e.g., accelerated uptake of new medicines and diagnostics, leverage of country partners and private-sector care providers, as applicable).

2 PROGRESS, INTERVENTION COVERAGE AND REMAINING GAPS IN THE RESPONSE

2.1 The challenge map

As a starting point for identifying potential future Areas for Intervention (AfIs), Unitaid compiles an inventory of challenges that threaten the achievement of the global goals for TB. As part of the first publication of the TB disease narrative in March 2016, an extensive challenge inventory was systematized, which included a wide range of challenges, most of them did not fit into Unitaid's mandate or business model, or had limited potential public health impact or had no technology available to solve the problem. The challenge inventory has been updated to reflect changes in the global landscape (**Figure 5**). Next, a filtering process was undertaken by the Secretariat and validated with key partners through which challenges were prioritized as potential focus areas for Unitaid.

In development of proposed AfIs, particular emphasis is placed on ensuring readiness to scale up to ensure sustainability, through discussions with countries, WHO, the Global Fund, US Government/USAID, the Gates Foundation, other funders/bilaterals, and other key actors.

Many challenges are interlinked, and there may be multiple root causes contributing to a single challenge. In some cases, similar or related challenges have been merged to reach an inventory that can be used as a workable framework for considering corresponding opportunities.

To account for interdependent or overlapping challenges, the challenges have been grouped into four thematic areas representing an integrated diagnosis and care approach:

- **Diagnostics**: challenges related to diagnostic strengthening is key to achieve the global goals to end TB. It includes all types of TB, under all forms of presentation, sensitive, resistant and latent TB.
- **Treatment:** challenges reflecting the need to have a holistic, patient-centered approach to diagnosis and care to optimize individual patient outcomes and reach overall public health goals and including challenges related to not having an optimal regimen to address the need of a short, effective, safe and affordable

regimen for the majority of TB cases. Diagnosis and treatment are increasingly interdependent, requiring coordination and integration in innovation, development and delivery.

- **Prevention:** challenges related to not having an effective vaccine, to lack of uptake of current preventive therapies, and to lack of a preventive therapy for MDR-TB.
- **Cross-cutting:** challenges related to weak health systems, inadequate treatment completion and cure rates, the need to improve care and visibility in the private sector, suboptimal delivery, and social or environmental factors are multifaceted and complex. These are important to consider for a balanced, comprehensive understanding of challenges facing the global goals.

FIGURE 5: Challenges inventory* threating progress towards global goals

Integrated diagnosis and care					
TREATMENT AND DIAGNOSTICS	Suboptimal or missing child-friendly medicines	MDR-TB regimens long, toxic, expensive & complex	Lack of response to paediatric MDR-TB	Lack of a true, simple and inexpensive TB PoC diagnostic	Lack of a multi-disease diagnostic platform
	No TB diagnostics for children & underserved populations	Limited DST ability of current tools; evolving DST needs	Lack of a cost-effective screening tool	Lack of TB universal regimen (DS/DR)	Immunotherapeutic tools needed for resistance prevention
Prevention					
PREVENTION	Shorter, better regimens needed for latent TB	Low uptake of preventive TB therapy, even among PLHIV	Latent MDR-TB	No effective TB vaccine	
Cross-cutting areas					
ADHERENCE TECHNOLOGIES	Adherence support needed	Burden of pills	Monitor drugs in urine and/or blood		
SERVICE INTEGRATION	Lack of Integrated approach to diagnosis and care	Poor health outcomes in people with TB comorbidities	Suboptimal sample transport tools	Need for better reporting Dx and Tx (elm-health)	Lack of reliable forecasting and low/variable demand
DELIVERY & IMPLEMENTATION	Lack of data to inform optimal deployment of tools	Slow scale-up of existing tools	Slow adoption of novel innovative tools	Poor data collection, quality and use	

To monitor Unitaid past and active grants

**Challenges being addressed in part through our past or existing portfolio (in blue), for illustration, the IMPAACT4TB project is working to help address "shorter, better regimens needed for latent TB" and the endTB project is working to help address the challenge "MDR-TB regimes that are long, toxic, expensive and complex"; Challenges to be monitored for opportunities for innovation in TB (in gray).*

2.1.1. Diagnostics

The progress and the gaps

Effective diagnosis and reporting – including from the private sector – is essential to reaching the 3 million missing cases and curbing the epidemic. At the same time, better access to drug susceptibility testing – including new tools, such as next-generation sequencing, for emerging drugs and regimens – is needed to inform appropriate treatment of MDR-TB cases. Despite major progress in coverage of drug susceptibility testing (DST) in the last years, only 31% of the 7 million TB cases notified globally were tested for resistance to rifampicin; from those bacteriologically confirmed, 46% of new TB cases and 83% of previously treated TB patients.[28]

Access to effective diagnosis is low, and needs to continue to improve. In 2018, only 70% of estimate people with TB were diagnosed and treated, according to official data (from national TB programmes) versus a global target of at least 90% by 2025.[29] This translates to up to 3 million TB cases that were not properly notified and may not be diagnosed and treated appropriately, many continuing to spread the infection and dying of an essentially curable disease. While a cure is possible in roughly 90% of patients who are diagnosed and treated, 70% of patients with untreated TB die.[30]

Also, without further addressing latent TB infection, the targets of End TB strategy will not be achieved. Although the WHO guidelines recommend that preventive treatment may not be constrained by lack of diagnostics, especially for PLHIV and household contacts of a TB index case, broader scale up of preventive treatment will only reach its full potential with better diagnostic tools. Better screening tests are urgently needed to identify LTBI and predict the likelihood of progressing to active disease. If latent infection can be accurately identified and differentiated from active disease, the most effective treatment can be given to the patient.

Better diagnostics are also needed for children. Diagnosis of TB in chidren is poor with only half of the estimated 1.1 million yearly cases being identified.[31] This market segment has long been neglected due to its small size and lack of understanding and awareness of the unique needs of children.

Biomarkers are another promising diagnostic tool. Biomarkers may be used to identify risks or detect infections, diseases, likelihood of cure, and acquired protection against active disease. There are several biomarkers under development in the diagnostic pipeline, using technologies as different as analysis of blood, urine, sputum, sounds or imaging, those available or close to the market will be discussed below.

The Tools

The pipeline for TB diagnostics is promising, although many candidates are still in early stages of development. There are some potential game-changing innovations that are nearer to market and warrant close monitoring over the next few years. Detection of mycobacterial glycan antigen lipoarabinomannan (LAM) in the urine has advanced significantly over the past year as an option for point-of-care testing for people living with HIV. In the past, this technology has been challenged by suboptimal sensitivity, and limited to use in HIV-positive patients with severe immunodeficiency (blood CD4 count below 100 cells per µL). However, now the technology behind the LAM assay is evolving and becoming more sensitive with promise for expanding the test for use in seronegative patients (i.e., those without HIV). Other promising technologies to detect TB using artificial intelligence

are emerging (e.g., digital applications that can interpret cough sounds to determine the risk of TB; or imaging technology such as digital chest X-rays, repositioning X-ray as an important triage test and diagnostic aid).

Some of these tools are under Unitaid's analysis for potential investment in the near future, as it will be seen later in this document.

Global action and Unitaid investments

There is a broad consensus in the global community for the need of new diagnostic tools to decrease the large gap between the 7 million new TB cases reported versus the 10 million estimated number of cases in 2018. To address the need to find and identify these missing cases, stakeholders such as the Global Fund, WHO and Stop TB Partnership launched a strategic initiative FIND.TREAT.ALL in 2018, aiming to improve TB detection and treatment in 13 high-burden countries. The goal is to find an additional 1.5 million people with TB between 2018 and 2020.

The Global Plan to End TB 2016-2020 addresses the main tools to improve TB detection: a rapid and affordable non-sputum-based diagnostic test, an accurate drug susceptibility test for critical medicines, and better tools for detecting infection and testing for risk of progression to active disease. Also, a part of reaching the targets commited to at the UN HLM is increasing global investments in better tools to detect TB and latent TB infection.

Countries have intensified efforts to improve TB diagnosis and treatment and close the gap between incidence and notification. Donors are investing more funds to develop new diagnostic tools, consequently, the diagnostic pipeline has an unprecedented number of products in all stages of development.

There is consensus among stakeholders for the need for a new user-friendly, affordable, non-sputum rapid test for diagnosing TB in the first patient visit at the lowest health care facilities' level. This is the biggest gap to reach the 3 million missing TB cases.

Unitaid is supporting work in this area that addresses paediatric and MDR-TB care and diagnostics. The two projects build on the STEP-TB project, which brought the new TB paediatric formulation into the market, and aim to increase TB detection among children so they can be effectively treated. 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 other 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 approved a new grant in targeted next-generation sequencing for clinical decision making for better care management in LMICs. This project, the Seq&Treat project, led by the Foundation for Innovative New Diagnostics (FIND), aims to accelerate the introduction and global adoption of commercial targeted gene sequencing for affordable, scalable and rapid drug susceptibility test for clinical decision-making.

2.1.2 Treatment

The progress and the gaps

Improved access to better MDR-TB treatment is key in combating the threat of drug resistance.[32] Following increased evidence on the use and safety of the newest drugs for

TB -- bedaquiline and delamanid, WHO took an important step towards recommending more patient-friendly all-oral MDR-TB regimens, by issuing consolidated guidelines on DR-TB treatment in March 2019. The updated guidelines reprioritized the drugs to be used in treatment regimens recommending all-oral regimens that include bedaquiline as a key drug and only indicating injectables when demonstrated by drug-susceptibility testing and when adequate measures to monitor for adverse reactions can be ensured.

Although most cases of TB can be cured with a standard regimen of first-line drugs, drug-resistant cases are much more difficult to treat. MDR TB accounts for 5% of TB cases but 14% of TB deaths and 32% of costs,[33] pointing to low rates of diagnosis and treatment, poor outcomes (56% global cure rate[34]) and high treatment costs.

Critical MDR-TB epidemics in key countries threaten overall progress in the fight against TB. For example, from 2009 to 2013, South Africa saw a 19% reduction in drug-sensitive TB cases, but the number of resistant cases enrolled on treatment more than doubled in the same time period.[35] There was a 23% increase in notified MDR-TB cases between 2012 and 2013, led by India, Ukraine, and Uzbekistan.[36]

Poor access to commodities and limitations of current tools are central to this threat of drug resistance. Over 60% of all people estimated to have MDR-TB were not detected in 2018, and only 32% received treatment. Even among people with a diagnosis of MDR-TB, the coverage of drug-susceptibility testing to guide treatment was only 51% (with DST access much lower in some settings).[37] Of those who do receive treatment, only 56% are cured or successfully complete treatment.

The Tools

The pipeline for new drugs is progressing. One promising new second-line TB drug is pretomanid has been developed by TB Alliance. Pretomanid, in combination with bedaquiline and linezolid in a 6-month regimen (known as BPaL), received FDA approval in August 2019, and will bring a new alternative to people with intolerant MDR-TB and XDR-TB.

For drug-sensitive TB, several trials are ongoing, with some of them including high-dosed rifamycins, rifampicin and rifapentine, and paediatric trials that aim to shorten treatment time to less than 4 months.

Global action and Unitaid investments

Aligned with other priorities, the global TB community has indicated that improving TB treatment is one of the key actions to end TB. As with diagnostics, the FIND.TREAT.ALL initiative has treatment and cure as the ultimate goal once cases are found. Along these lines, the UN HLM stated priorities, supported by the TB community, that include treatment for all the 40 million people with TB that are expected to be found from now until 2022.

Given the achievement of the initial target for treatment that was to be achieved by 2018, there is increased hope and momentum to continue this upward progress. There was an increase in detection and treatment from 6.4 million in 2017 to 7 million in 2018, the largest number reported of people with TB put on treatment in a single year. This likely reflects countries' increased commitment and intensified efforts to improve TB diagnosis and treatment.

Under this area, Unitaid is supporting the response to MDR-TB through its endTB Project, which is contributing to the evidence through observational and clinical trials of MDR-TB regimens using the new drugs. Data resulting from the endTB project was a key source of

evidence to inform WHO policies on MDR-TB and fed into the most recent WHO guideline review in November 2019.

Recently Unitaid approved projects aiming to bring new formulations of second-line drugs with increased importance in new regimens recommended by WHO and child-friendly formulations of second-line drugs, as clofazimine, linezolid, fluoroquinolones, and bedaquiline. Better Access to Treatment for Paediatric MDR-TB (BENEFIT Kids project), led by Stellenbosch University, aims to perform studies of pharmacokinetics (PK), safety, and acceptability of novel child-friendly 2nd-line TB generic drug formulations of key TB drugs for children of all ages with MDR-TB.

Beyond new formulations and regimens for DR-TB, Unitaid is investing in innovative approaches using digital technologies to support adherence to TB treatment for better patient outcomes. This will be further discussed in the cross-cutting section.

2.1.3 Prevention

The Progress and the gaps

The risk of progressing to active TB disease depends on several factors, the most important being immunological status. The management of latent TB infection should also address a different set of interventions. The first and main challenge is to identify and differentiate those infected from those with incipient TB disease. The next step is to deliver an effective, safe and affordable treatment.

According to the latest data on TB infection, 23% of the global population (1.7 billion people) is estimated to be infected with the *M. tuberculosis* and an average 5-10% of those who are infected will develop active TB disease over their lifetime. [38] To achieve the global targets to end TB epidemic, preventing TB infection is key, but an effective vaccine is not available yet. In the End TB strategy, WHO emphasizes the need for innovation to reach ambitious new targets – in particular, a new vaccine that is effective pre- and post-exposure. While 13 vaccine candidates are in development, new products are not expected to be available before 2025.[39]

In addition to efforts to develop a new and more effective TB vaccine, the global response to TB prevention has focused on the management of LTBI, especially in priority high-risk groups, such as PLHIV, children under 5 and household contacts of a person living with TB.

Although recent data have shown an increase in the number of people receiving preventive therapy for LTBI, primarily isoniazid preventive treatment (IPT), the coverage and completion of treatment have been disappointing, except for in a few countries.[40]

The main challenges for adoption have been the length, the burden of pills and the cost of new preventive treatment. To overcome these challenges, WHO recommended several shorter preventive treatment options besides 6 months of IPT, which include: rifampicin plus isoniazid daily for 3 months, rifampicin alone for 3 to 4 months, and rifapentine and isoniazid weekly for 3 months.[41]

Recently, another option for TB preventive therapy with the shortest duration seen to date, rifapentine plus isoniazid for 1 month (1HP), was recommended by WHO for PLHIV. This treatment may become a game-changer in preventive therapy once evidence becomes available for people that are HIV negative.

The Tools

An experimental TB vaccine candidate (M72/AS01E) was found to have significant efficacy against TB in a Phase IIb trial conducted in Kenya, South Africa and Zambia, in individuals with evidence of latent TB infection. The point estimate of vaccine efficacy was 54%, with approximately two years of follow-up.[42] These results, unprecedented in decades of TB vaccine research, constitute a major scientific breakthrough as the first time a subunit vaccine has shown significant protection. Key questions on this candidate remain to be answered, such as whether the vaccine will provide protection against TB among HIV uninfected people, or in other geographical areas beyond where it has been tested. Effectiveness trials are needed to allow a more accurate assessment. Even if successful, market entry is still some years away.

One unique use for vaccines that could be demonstrated in a shorter time frame is as treatment coadjuvants, helping to protect regimens and guarding against development of drug resistance. Also, revaccination with BCG has shown to offer significant protection in adolescents and adults and could be implemented as a short-term strategy.

Medicines to treat latent TB infection and prevent progression to active TB are expected to have significant impact on the course of the epidemic, with the highest impact in populations at high-risk of developing active TB (e.g., people living with HIV, children, and household contacts). Although WHO recommends preventive treatment for these high-risk populations, in low-income and/or high-burden settings that would benefit most,[43] uptake has been low and recording and reporting gaps remain. Despite the increase in administration of TB preventive therapy with isoniazid in recent years, only 27% of estimated eligible children receive the treatment. Coverage has increased more significantly among people living with HIV.[44]

Global action and Unitaid investments

Since the launch of the *WHO End TB Strategy* in 2015, prevention and, more specifically, preventive therapy of latent TB infection is recognized as an important tool to ensure the elimination of TB. The search continues for the shortest possible preventive therapy that would allow maximum global scale-up.

In support of exisiting short course preventive therapy, the WHO has revised and issued new LTBI guidelines in 2018. The Global Plan to end TB included shortening treatment for LTBI among its R&D priorities. The UN HLM on TB has set as one of its targets to reach at least 30 million people with TB preventive treatment in the next 5 years, 6 million of those being PLHIV and 24 million being household contacts, including 4 million children aged under 5 years. Globally in 2018, 65 countries reported initiating TB preventive treatment for 1.8 million PLHIV (61% in South Africa), suggesting that the targets are achievable and on track in this population. The efforts around household contacts are lagging and require greater attention in order to meet the targets by 2022.[45]

Responding to this emerging priority, Unitaid is contributing to the response in the prevention field. Through several funded projects including the IMPAACT4TB project, led by the Aurum Institute, Unitaid has been able to help change and catalyze the prevention market through a reduction of price for rifapentine, a key drug in the innovative shorter treatment for LTBI. This agreement achieved in collaboration with the Global Fund and the pharmaceutical company Sanofi will increase access for rifapentine-based preventive therapy globally. The new affordable price will allow countries to quickly adopt and scale-up efforts to replace the current six months regimen of isoniazid with the newer and effective 12 doses, once weekly combination of rifapentine plus isoniazid (3HP).

In addition to 3HP, Unitaid is considering the potential of a one-month 1HP regimen, among other options for preventive therapy.

Also, regarding rifapentine-containing regimens, following initial investment by the U.S. Centers for Disease Control and Prevention (CDC), Unitaid is co-funding an additional site to accelerate the completion of the study TBTC 35, an evaluation of rifapentine safety and pharmacokinetics in HIV-infected and uninfected children 0-12 years of age, and identifying dosage of water-dispersible tablet fixed-dosed combination (FDC) required for children under 2 years old; supporting DOLPHIN, a drug-drug interaction study, to demonstrate the feasibility of simultaneous use of rifapentine and dolutegravir for PLHIV; and potentially investing in the investigation of a long-acting formulation of rifapentine and isoniazid for preventive TB therapy.

Beyond rifapentine-containing regimens, Unitaid is also supporting CaP-TB project, catalyzing paediatric TB innovations, which include the delivery of a shorter preventive regimen composed of 3 months of rifampicin plus isoniazid (3RH) for children utilizing the innovative child-friendly fixed-dosed combination developed by Unitaid; and investing in MDR-TB prevention for children through the TB CHAMP project which is evaluating the role of levofloxacin in the prevention of MDR-TB in children.

2.1.4 Cross-cutting areas

The Progress and the gaps

Recently, extensive analyses have been published concerning how and where patients with TB encounter the health care system including their access to available diagnostics and treatment. These patient pathway analyses (PPAs) identified various gaps, including the need for access to quality and timely diagnosis; the need for efficient and clear linkages to treatment; and the need for affordable, simplified and more effective treatment. In order to address these gaps, more effective solutions are needed to improve linkages and integration in other disease programs and with the private sector. In addition, with the advent of innovative technologies (i.e., digital, long-acting) and multi-disease platforms, there are opportunities to bring far-reaching solutions including addressing antimicrobial resistance (AMR) for which TB accounts for almost a third of the global numbers.

The Tools

Digital technologies and use of machine learning algorithms/artificial intelligence are emerging across treatment managment and diagnositics that can be integrated into TB care and scaled for programmatic use. These new technologies have important applications across disease areas.

Long-acting formulations, such as long-acting injectables, removable or biodegradable implants, rings, or patches, hold great promise to improve adherence to treatment and preventive care, improving outcomes and reducing the risk of drug resistance (i.e., AMR). Long-acting formulations, that could be applied to treatment and prevention of main drivers of morbidity and mortality in low- and middle-income countries, could potentially lead to a paradigm change in the way diseases are managed.

There may be potential in new diagnostic technologies for early diagnosis and/or multi-disease diagnosis. Diagnostics, in particular nucleic acid testing, also offer an opportunity to facilitate integration across different diseases and populations, and to reinforce prevention, detection and management of drug-resistant pathogens.

Global action and Unitaid investments

Underlying the key priorities to achieve the goal of ending TB, there is a recognition of other areas of intervention that could play supportive roles in achieving the stated targets. Recent results from clinical trials of new drugs/regimens have indicated that improvements in adherence and care of patients can lead to high cure rates, irrespective of treatment regimens. There are also key targets around reducing castastrophic costs for patients due to TB care and one way is to reduce the amount of visits required.

Among Unitaid's investments in digital technology, the Adherence Support Coalition to End TB (ASCENT) project, led by KNCV, is one of the most significant with the objective to catalyse global adoption and scale up of new digital adherence technologies to improve treatment outcomes.

Unitaid has explored the opportunities in long-acting technologies and will support late-stage development of different technologies or delivery systems, as well as accelerate introduction, access and early adoption of products emerging from the pipeline. This will build on the other endorsed areas for intervention in TB and Unitaid's other priority diseases.

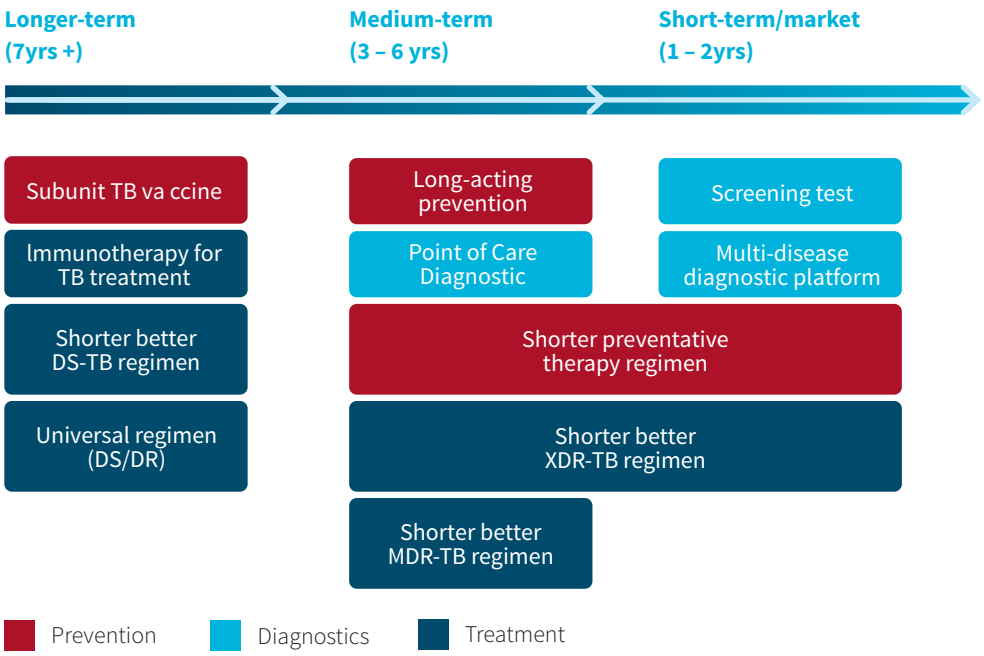
2.2 TB Innovation Pipeline

To reiterate, the R&D pipelines for TB drugs, diagnostics, and vaccines hold a range of promising new tools, particularly in the medium- to longer-term. In the short-term, the focus will be on improved screening tests for TB such as TB LAM and implementing multi-disease diagnostic platforms to better detect TB and other related conditions to support more integrated approaches to health. Also, with the greater uptake of bedaquiline and delamanid and the entry of pretomanid, the treatment of XDR-TB and intolerant MDR-TB has evolved considerably and there will need to be increased efforts to ensure adoption and access. The focus on adoption of new shorter preventive regimens will be important for both the short and medium terms.

By 2025, R&D pipelines are likely to yield new true point-of-care diagnostics and long-acting preventive therapy. In addition, the results of ongoing clinical trials will become available that could lead to better shorter MDR-TB and preventive therapy regimens and better treatment outcomes for patients.

Beyond 2025, there is promise of a subunit TB vaccine that can be used in a broader population than BCG. As we advance the drug development pipeline, the possibility of having a shorter regimen less than 2 months is becoming a closer reality for those with drug-sensitive TB. There is continued interest and research on developing a regimen or group of drugs that can be combined to treat all forms of TB. Lastly, immunotherapy is an emerging field that could help enhance the effectiveness of treatment and guard against the development of drug resistance.

FIGURE 6: Pipeline of TB innovations 2020 - 2030



3 POTENTIAL OPPORTUNITIES FOR UNITAID'S INTERVENTION

Unitaid is assessing all opportunities using a step-wise filtering methodology that is applied to a validated inventory of challenges threatening the achievement of the global TB goals. The filters applied to identified challenges are:

a. Unitaid's expertise: challenges that are inherently commodity access issues.
b. Potential public health impact: challenges for which there is strong evidence of potential for high public health impact.
c. Feasibility: challenges for which the necessary innovation will be available in the relevant timeframe for Unitaid interventions.
d. Optimized use of resources: challenges for which critical gaps exist in the global response and where scale-up is possible.

As discussed in section 3, these criteria were used as filters to identify a shortlist of challenges that represent the highest potential for Unitaid intervention (**Figure 5**) and that will be further investigated over the next 6 to 12 months. Some opportunities were identified for active exploration for longer-term consideration. It should be noted that these opportunities are subject to change in light of the dynamic nature of commodity markets, changes in partner activities, or other factors. In addition, Unitaid has several new grants in the TB portfolio which are in early- or mid-stages of implementation. As these investments mature, they will inform future opportunities in related areas.

Before discussing the priority opportunities, the following section provides an overview of Unitaid's currently endorsed areas for interventions and TB portfolio as of September 2019.

FIGURE 7: Overview of outcomes* of Unitaid's filtering process

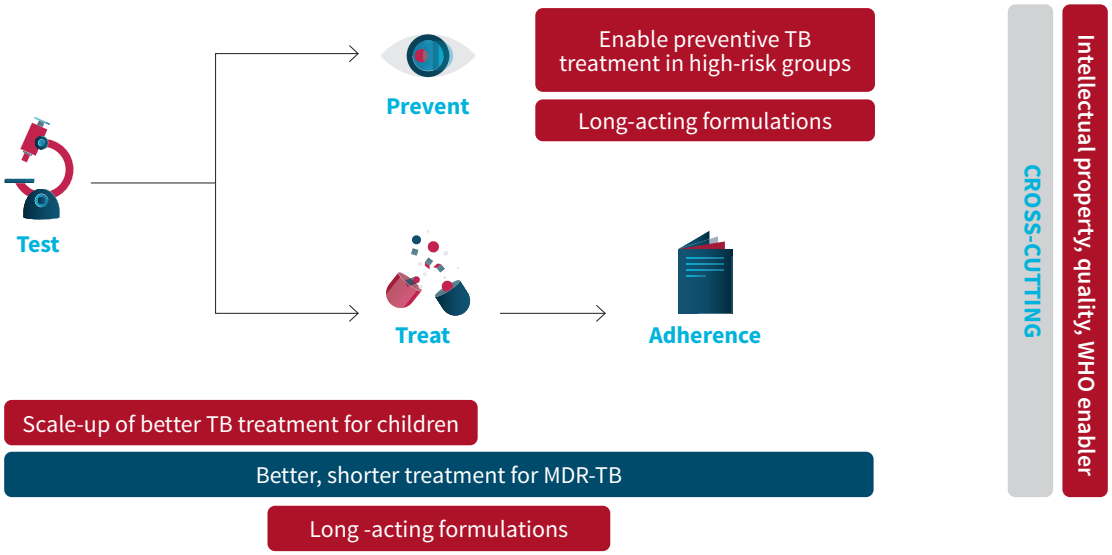
Integrated diagnosis and care					
TREATMENT AND DIAGNOSTICS		MDR-TB regimens long, toxic, expensive	Lack of response to paediatric MDR-TB	Lack of a true, simple and inexpensive TB PoC diagnostic	Lack of a multi-disease diagnostic platform
	No TB diagnostics for children & underserved populations	Limited DST ability of current tools; evolving DST needs	Lack of a cost-effective screening tool		Immunotherapeutic tools needed for resistance prevention
Prevention					
PREVENTION		Low uptake of preventive TB therapy, even among PLHIV	Latent MDR-TB	No effective TB vaccine	
Cross-cutting areas					
ADHERENCE TECHNOLOGIES		Burden of pills	Monitor drugs in urine and/or blood		
SERVICE INTEGRATION					
DELIVERY & IMPLEMENTATION	Slow adoption of novel innovative tools				

To monitor Unitaid past and active grants Potential opportunities

**Challenges being addressed in part through our past or existing portfolio (in blue); Challenges considered not included in existing portfolio of grants but are near term opportunities for innovation in TB (in pink); Challenges to be monitored for opportunities for innovation in TB (in gray).*

3.1 Overview of currently endorsed Areas for interventions and TB portfolio

FIGURE 8: Overview of Unitaid's current tuberculosis portfolio



3.2 Potential opportunities in the next 12 months

Having considered existing portfolio and applied the challenges identified above, potential opportunities have been identified by the Secretariat for consideration as new potential areas for intervention. In addition, each of the currently endorsed area for interventions are reviewed regularly to determine if additional work is warranted. Expanding endorsed AfIs can occur in areas where there are existing or emerging opportunities that could meet the objectives of the strategic priority. For example, Unitaid is investing in preventive treatment of susceptible TB, but new tools to prevent MDR-TB are still needed. Besides the expansion of endorsed areas for interventions, there is near term opportunities in diagnostics that may warrant a new strategic priority in which Unitaid plans to invest.

Preventive treatment in high-risk groups (expansion):

Unitaid has invested heavily in operational research to support optimization of preventive therapy as previously indicated. Beyond investigating the role of 1HP for preventive therapy, there is a further assessment of priorities and outcomes from implementation of current therapies to determine the potential for greater intervention in this area in the context of the number of Unitaid investments in prevention.

With the spread of drug resistance and the advent of newer drugs, preventive therapy of MDR-TB is an increasing priority. Unitiad is already funding the TB CHAMP project, an intervention to evaluate levofloxacin as a preventive drug for MDR-TB infection in children. A few clinical trials using new (e.g. delamanid, bedaquiline) or repurposed drugs for prevention are currently ongoing. Depending on outcomes from these studies, prevention of MDR-TB infection may be an opportunity for Unitaid to include interventions in this area across age and high-risk groups.

Better, shorter treatment for resistant forms of TB (i.e., DR-TB, MDR-TB, XDR-TB) (expansion):

Unitaid is supporting endTB project, which is conducting one of the major operational studies including regimens with bedaquiline and delamanid. With the FDA approval of BPaL regimen and the update of the WHO DR-TB guidelines following the guidelines review meeting in November 2019, the landscape of treatment options in this area is rapidly changing. Possible interventions in this area will be investigated to determine how Unitaid can contribute to ensuring access and scale-up of these innovations in MDR-TB treatment.

Diagnostics (new):

Unitaid recognizes the need for better, connected diagnostics to detect TB and guide treatment. Despite improvements, an estimate 3 million cases of TB were 'missed' in 2018 – i.e., not reported to national authorities and WHO.

For the first time in many years, TB diagnostic pipeline is promising with several products close to coming to market in 2 to 3 years. Some of the tests in late-stage development or under evaluation for policy are -- triage tests (breath tests such as e-Nose and RBS), new molecular point-of-care tests (TrueNAT MTB Molbio; Blink Dx; Xpert Omni; Xpert XDR-TB; QuantuMDx molecular Q-POC; Bioneer MDx POC), urine point-of-care tests (Alere LAM; FujiFilm TB LAM), or use of alternative samples for devices already available (e.g. stool testing for GeneXpert machines) and other technologies, such as computer-aided X-ray machines, digital stethoscopes, cough apps, handheld digital ultrasounds, etc.

Given the TB diagnostic pipeline, there is an opportunity in the near term in the area of TB rapid diagnostic test for point-of-care. With the advancements in Lipoarabinomannan (LAM)

rapid diagnostic test for PLHIV (urine test), more evidence is needed to support its use case and expansion into broader populations (see case study below). With real time molecular test (PCR amplification), demonstration projects in different primary and community care levels in different geographies in LMICs could significantly impact and increase identification and numbers of people put on treatment for TB.

Case study – Urine lateral flow lipoarabinomannan (LF-LAM) test

TB continues to be the leading cause of death among PLHIV; TB killed 300,000 people living with HIV in 2017[46] and 250,000 in 2018[47]. Few countries are on track to meet the target of reducing TB deaths among PLHIV and will be in danger of not meeting the target if governments do not adopt new technologies and new activities to help reduce these avoidable deaths.

Diagnosing TB in PLHIV is difficult due to the presentation of the disease in this population where many do not produce sputum, or their sputum has low bacillary burden.

A rapid, true point-of-care urine-based TB test (Alere Determine™ TB LAM Ag) is available, but it only addresses PLHIV with very low CD4 count, and has suboptimal sensitivity (43.3% overall, 57.3% among patients with CD4 counts under 100 cells per copy[48]). The test thus precludes broad adoption as a screening tool.

New lateral flow urine lipoarabinomannan (LF-LAM) assays in the pipeline could offer better performance than the currently available test. The Fujifilm SILVAMP TB LAM (FujiLAM) urine-based test is one example, which has recently received CE marking. Its sensitivity was demonstrated to be significantly higher than Alere TB LAM. FujiLAM's sensitivity and specificity was estimated to be 70.4% and 90.8%, respectively. FujiLAM's increased sensitivity was observed across all ranges of CD4 counts, indicating the possibility to expand use for this new test to detect TB in all PLHIV, including children, allowing the recommendations for TB LAM to move beyond use in patients with very severe immunodeficiency.

The target population

Considering the size of the population living with HIV, estimated by UNAIDS to be almost 38 million people, and the improvements in sensitivity, this diagnostic if implemented programmatically in a test-and-treat approach could lead to significant impact on TB morbidity and mortality among this high-risk population.

If this approach proves applicable to HIV seronegative based on new evidence, this tool could lead to major decreases needed to eliminate TB.

LF-LAM use case

According to the last two WHO Global TB Reports, in 2017 and 2018, more than a half million PLHIV died due to tuberculosis. The reduction in deaths from 2017 to 2018 were mainly observed in countries where the TB preventive treatment has been broadly implemented, especially in South Africa, which averted approximately 16,000 deaths in this period.

A demonstration project in LMICs with high burden of TB and HIV, aiming to improve TB detection among PLHIV at the lower levels of the health system, could include the LF-LAM

technology into the diagnostic algorithm to test TB among PLHIV, and evaluate the yield in case detection and cost-effectiveness of implementation of rapid LF-LAM test as a routine in HIV services.

Given 2019 WHO updated policy for the use of urine LF-LAM for diagnosing active tuberculosis in PLHIV, the potential market for the improved product is significant, but affordability could still be a barrier to uptake, despite potential cost savings.

Possible Unitaid intervention in this area - for example, to address evidence gaps, affordability, or other barriers to uptake - would be fully aligned to other projects in the Unitaid portfolio, especially the IMPAACT4TB and advanced HIV disease projects, as PLHIV without active TB would be candidates for TB preventive therapy and those who were detected with TB would benefit from early treatment, improving health outcomes.

Programmatic adoption of LF-LAM assay could open the door for further expansion of this technology for use in a wider population including children and HIV-negative people as evidence supports.

3.3 Further innovative areas for exploration

There are some other areas in diagnostics that will be monitored, including screening tests to differentiate TB infection from TB disease and predictive tests allowing health professionals to evaluate the risk of LTBI developing into active TB. Possible options include blood tests that use TB immune cells following pathogen-specific stimulation with the examples of Lophius RTT TB; Qiagen QFT-Plus and Qiagen QFT-Predict.

Given the advances in TB vaccines, this area will be further explored to delineate further opportunites that could fit within Unitaid's mandate and operating model. The progress of the new TB vaccine M72 AS01 will be closely monitored and also other proposed vaccination strategies such as revaccination with BCG. The use of vaccines as immunotherapy (including other host-directed therapy strategies) will also be explored to see if there are near term opportunities to enhance new regimens and guard them against drug resistance.

An additional area for exploration that would support effective treatment could be in the area of drug monitoring using urine or blood samples. This could ensure that the proper concentration of drug is achieved for cure and would allow for adjustments as needed bringing treatment closer to the more patient-centered approach.

PLEASE NOTE: Further analysis and partner consultation is needed before these exploratory areas can be presented to the Board of Unitaid for funding-decisions.

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