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Disease Narrative for Tuberculosis

For Information **For Review and Advice** **For Decision**

Table of Contents

Executive Summary	3
1 Analysis of disease context	7
1.1 Disease introduction.....	7
1.2 Global goals and associated strategy.....	7
1.3 Tools to diagnose, treat and prevent TB, and associated unmet needs and commodity access gaps.....	10
1.3.1 Diagnostics.....	10
1.3.2 Treatment	10
1.3.3 Prevention.....	11
1.4 The importance of BRICS and engagement with countries.....	12
1.5 The role of private sector care-providers	12
1.6 Innovation expected to accelerate the pace of change in the coming years	13
2 Partner landscape in TB.....	14
3 Challenges threatening progress towards global goals.....	17
4 Priority challenges to be addressed by UNITAID	20
4.1 Challenge prioritization process.....	20
4.1.1 UNITAID's expertise: focus on challenges that are inherently commodity access issues.....	20
4.1.2 Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact	20
4.1.3 Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe.....	21
4.1.4 Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible.....	22
4.2 Overview of the priority challenges to be addressed by UNITAID in the next 24 months ..	22
5 APPENDIX: Description of challenges.....	24
5.1 Challenges related to integrated diagnosis and care.....	24
5.1.1 Treatment	24
5.1.2 Diagnostics.....	26
5.2 Challenges related to prevention.....	28
5.3 Cross-cutting challenges	28
5.3.1 Health systems	28
5.3.2 Social and environmental	30

Executive Summary

Significant progress has been made in the fight against TB in the past 25 years. TB prevalence was reduced by 42% between 1990 and 2014; TB deaths were cut by 47% in the same timeframe. Nevertheless, the burden of TB is still high, in 2014, 9.6 million people were estimated to have fallen ill with TB and 1.5 million were killed by the disease¹. Critical unmet needs persist, especially related to diagnosis, treatment of drug-resistant TB, and access to care for vulnerable groups such as children.

In May 2014 the World Health Assembly approved a new global TB strategy. The 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 TB². The End TB Strategy emphasizes the need for innovation to accelerate progress: that is, optimizing existing tools in the short-term, and introducing new, innovative tools in the longer term. While the pipeline promises new tools, change in diagnosing and treating TB has historically been slow. Archaic technologies and old drugs are still central to diagnosis and treatment. New medicines for drug-resistant TB have launched since 2012 – the first in 40 years – but adoption has been slow. UNITAID and others will need to proactively support innovation to realize the full potential of new tools in ending the TB epidemic.

The 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 cases³. That is, better diagnosis and treatment need to be complemented by prevention strategies, especially in people at the greatest risk of developing active TB.

UNITAID has identified a comprehensive list of challenges the response is facing to reach global goals. These challenges were identified through the following steps:

- Analysis of partners' strategies
- Review of relevant UNITAID's landscapes
- Engagement with partners

Based on this list UNITAID has identified potential Areas for Intervention (AfIs) using the following criteria:

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

Since the last Board meeting in November 2015, these potential AfIs have been refined through broad consultations with key partners. A consensus has been reached about the areas where UNITAID could be best positioned to fill gaps and overcome challenges to reach the global goals to end TB by 2035.

¹ WHO Global TB Report 2015

² In seeking diagnosis and care, the average TB patient in a low- or middle-income country faces costs and lost income of >50% of annual income. Catastrophic costs lead to profound social and health impact from TB and are thus a core part of the End TB Strategy. WHO. Eliminating the financial hardship of TB (factsheet). http://www.who.int/tb/publications/UHC_SP_factsheet.pdf [accessed 19 Feb 2016].

³ Preventing TB, through the treatment of latent TB infection, is a critical component of the End TB Strategy

During this process, all preliminary indications for potential AfIs were exhaustively discussed and validated with partners, with some potential areas reconsidered to reflect UNITAID's potential approach. Three potential AfIs have now been identified, as outlined below.

Proposed Areas for Intervention:

1. Better, shorter MDR-TB treatment

Current treatment for drug-resistant TB is complex, expensive, long, and can cause severe side-effects, such as deafness and psychiatric disorders. New 2016 WHO guidelines are expected to recommend shorter combinations of existing drugs to improve outcomes. In addition, new regimens leveraging novel drugs are in development (including the UNITAID-funded endTB project), and are expected to offer simpler, more effective treatment options in the coming 2-5 years. UNITAID may have a role to play in: improving effectiveness of treatment with existing medicines, including rapid scale-up of shorter regimens; preparing the market for new regimens; and fostering innovation in TB to further improve treatment.

Better treatment options would mean better outcomes and fewer deaths: even among people on treatment for drug-resistant TB, fewer than half are cured. Shorter, more effective treatment could also reduce costs, allowing resources to be optimized: drug-resistant TB accounts for only 5% of TB cases but 27% of costs.

Better diagnostic tools, integrated from the point at which patients first seek care throughout the treatment of MDR-TB, are needed to guide treatment to avoid further resistance and optimize outcomes of treatment.

2. Scale-up of better TB treatment in children

Although a top 10 cause of death in children, paediatric TB has long been neglected. The first new child-friendly formulations to be aligned with 2010 WHO guidelines were announced in 2015, as a direct result of UNITAID's intervention through TB Alliance. However, work is still needed to ensure an effective uptake and roll-out.

Regulatory approval, in-country product registrations, national guideline adaptation, procurement and supply management to replace current stock, among other activities, are necessary steps in ensuring that the new drug formulations reach the children who need them. Support may be needed, initially to displace current, suboptimal medicines (including crushed or split adult pills), and eventually to reach more children in need, including those not currently receiving treatment.

Continued work in this particularly fragile area could therefore aim to speed adoption of the newly formulated medicines and foster continued innovation, including TB diagnostics better suited to children.

Better diagnostic tools, integration of childhood TB care within other child health services and optimized treatment of paediatric TB would reduce deaths of children from this curable disease: WHO reported 140,000 TB deaths in children in 2014⁴, but many more deaths go unreported.

3. Enabling preventive TB treatment in high-risk populations

Partner consultations highlighted the urgent need to improve prevention activities to accelerate progress in efforts to end TB. Global targets could be in jeopardy without innovative methods to prevent new TB infections and consequently new TB cases.

⁴ WHO Global TB Report 2015

Preventive therapy – i.e., treating people who are infected with TB but are clinical asymptomatic and not infectious (i.e., have latent TB), but who are at high risk of developing active disease – is recognized in the WHO End TB Strategy as an integral component of TB care, and among the highest impact interventions possible. However, country uptake of preventive therapy, even in high-risk populations, has been severely limited by the complexity of current treatment options and the lack of appropriate tools.

The possibility of shorter regimens for TB prevention may – for the first time – enable broader implementation of preventive TB therapy. Work in this area would complement efforts to improve diagnosis and treatment of active TB to accelerate progress towards ending the TB epidemic.

Summary of key changes since EB 23 in November 2015

Since November, consultations with key partners and stakeholders were continued to discuss and refine potential AfIs, with a particular focus on validating challenges, perceived gaps in the global response and UNITAID’s potential added value. The disease narrative proved its value as a ‘living document’ and tool for focusing these discussions, with key learnings incorporated to inform strategic priorities reflected in the proposed AfIs.

Two potential Areas to Consider, presented at EB 23 in November 2015, have been subsequently refined:

- 1) The importance of private-sector care-providers (i.e., non-state actors) in addressing TB is clear. However, there is a wide range of potential approaches to engage with the private sector, which is itself heterogeneous and diverse. Similarly, engagement with key middle-income countries – as partners to scale interventions to prevent, detect and treat TB – may be a condition to succeed or a means of working, rather than an end in itself. Relevant approaches may thus fit with the potential AfIs described above, rather than constituting an AfI in its own right.
- 2) Diagnostic needs have been embedded in each of the AfIs being proposed, reflecting the critical role of diagnostics *in context*, and the need for an integrated approach. This enables a more integrated way of considering diagnostics needs, which is essential for enabling a holistic approach that puts the person at the center of care.

A high-level approach to articulating the potential value for money has also been developed. This includes a proposed theory of change for each AfI, as a suggestion for how considerations related to value for money may be framed and considered.

For ease of review, the box below summarizes key changes in the TB disease narrative since November 2015.

Summary of key changes since November 2015

- Refined potential “Areas to consider” into proposed “Areas for Intervention” through consultation with partners;
- Revised challenge inventory based on input from partners;
- Included “Enable preventive TB treatment in high-risk populations” as a proposed Afi, reflecting support from partners during the consultation process and new innovations that may make implementation feasible at scale for the first time;
- Repositioned “Leverage private sector to improve TB diagnosis and care” as a means of operating, potentially relevant to all AfIs, rather than a standalone Afi at this time (NB: similar consideration for BRICS engagement);
- Noted recent changes in the diagnostics pipeline. Repositioned “Address unmet & evolving diagnostic needs in TB and MDR-TB” to reflect a more holistic approach, integrated with treatment and care and therefore with diagnostic components included and embedded in all other AfIs; and
- Developed potential value for money framework within each proposed Afi.

1 Analysis of disease context

1.1 Disease introduction

TB is a communicable, airborne disease caused by *Mycobacterium tuberculosis*. Transmission often leads to a latent TB infection that is non-infectious and asymptomatic; an estimated one-third of the world's total population has latent TB.⁵ However, approximately 5–15% of all latently infected individuals will develop active TB during their lifetime, with people living with HIV at considerably higher risk.⁶ If active TB is not diagnosed and treated, mortality is high and the infection can remain transmissible.

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 as new or improved tools to treat drug-resistant forms of the disease. However, many patients do not have access to effective diagnosis or appropriate TB medicines. As a result, there were an estimated 9.6 million new cases of TB in 2014, resulting in 1.5 million deaths.^{7, 8}

1.2 Global goals and associated strategy

Significant progress has been made in the fight against TB in the past 25 years. From 1990–2014, TB prevalence rate fell 42% and TB mortality rate (among HIV-negative people) fell by 47% in the same timeframe. Nevertheless, TB remains one of the world's deadliest communicable diseases, causing 1.5 million deaths in 2014. Of the estimated 9.6 million people who developed TB in 2014, 480 000 cases were resistant to first-line drugs⁹.

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, notably children, people living with HIV and other co-infections. TB is one of the top 10 causes of death in children, but the burden of TB in children is poorly understood. In late 2015, WHO revised its estimate of TB in children, from 550 000 cases in 2013 to 1 million in 2014.¹⁰ TB is the most common cause of death among people co-infected with HIV, accounting for one quarter of all HIV-related deaths.¹¹

In May 2014, the World Health Assembly approved a new global TB strategy. The End TB Strategy marks a critical shift from controlling TB to ending the epidemic. Ambitious targets include: reducing TB deaths by 95% and cutting new cases by 90% between 2015

⁵ WHO Tuberculosis fact sheet No. 104. Geneva: World Health Organization; 2015. <http://www.who.int/mediacentre/factsheets/fs104/en/index.html> [accessed 20 Oct 2015]

⁶ i.e., 20–37 times more likely than those who are HIV-negative to develop active TB in any given year. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin Infect Dis.* 2010;50(Suppl. 3):S201–S207.

⁷ WHO Global TB Report 2015

⁸ Section 1.1 adapted from UNITAID TB Medicines Technology and Market Landscape, 2014

⁹ WHO Global TB Report 2015

¹⁰ WHO Global TB Report 2015

¹¹ WHO Tuberculosis fact sheet No. 104. Geneva: World Health Organization; 2015. <http://www.who.int/mediacentre/factsheets/fs104/en/index.html> [accessed 20 Oct 2015]; Pawlowski A, Jansson M, Skold M, Rottenberg ME, Kallenius G. Tuberculosis and HIV co-infection. *PLoS Pathog.* 2012;8(2):e1002464

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 1.¹²

Figure 1. End TB Strategy milestones and targets

End TB Strategy				
	Milestones		Targets	
	2020	2025	SDG 2030	END TB 2035
Reduce # of TB deaths vs. 2015	35%	75%	90%	95%
Reduce TB case incidence rate vs. 2015	20%	50%	80%	90%
Families facing catastrophic costs due to TB	ZERO			

The three pillars of the End TB strategy are:

- Integrated, patient-centered TB care and prevention;
- Bold policies and supportive systems; and
- Intensified research and innovation.

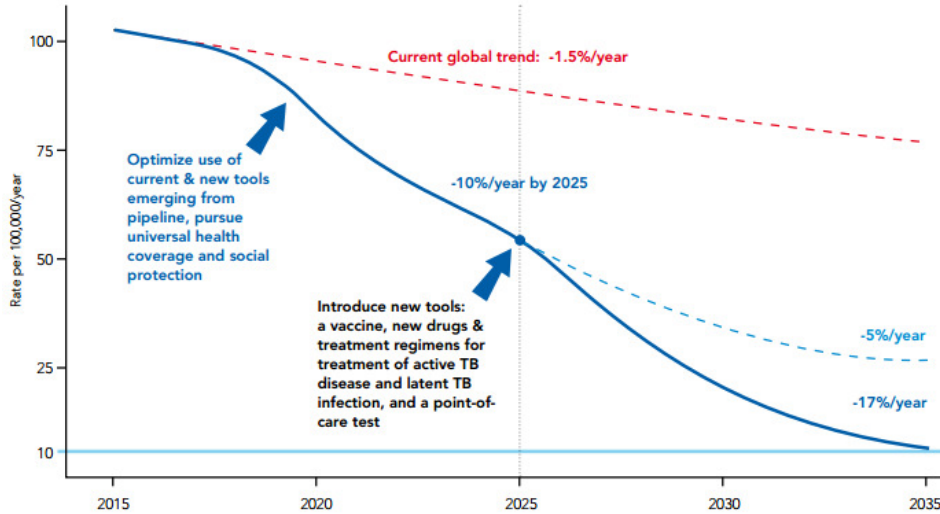
As shown in Figure 2, The End TB Strategy calls for acceleration of the global response by optimizing existing tools, health coverage and social protection in the short-term (from 2015), and introducing new, innovative tools in the longer term (from 2025):

“Reaching the targets ... requires effective use of existing tools to combat TB, complemented by universal health coverage and social protection.

Moving forward to the 2035 targets, the response must focus on ensuring availability of new tools from the research pipeline, in particular:

- *A new vaccine that is effective pre- and post-exposure;*
- *A safer and more effective treatment for latent TB infection;*
- *Better diagnostics, including new point of care tests;*
- *And safer and easier treatment including shorter drug regimens for TB disease.”*

¹²WHO End TB Strategy

Figure 2. Desired decline in global TB incidence rates to reach the 2035 targets

Source: WHO End TB Strategy

The End TB Strategy is complemented by the Stop TB Partnership's Global Plan 2016-20, 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.

Key messages:

- Significant progress has been made in the fight against TB, but the burden of TB is still high, with 9.6 million cases and 1.5 million deaths in 2014
- WHO's new End TB Strategy marks an important shift from TB control to ending the epidemic by 2035
- The End TB Strategy emphasizes innovation to meet ambitious targets: optimizing existing tools in the short-term (from 2016), and introducing new, innovative tools in the longer term (from 2025)
- An integrated approach is key to ending TB, with better diagnosis and treatment complemented by prevention strategies, especially in people at the greatest risk of developing active TB

1.3 Tools to diagnose, treat and prevent TB, and associated unmet needs and commodity access gaps

Application of existing tools has improved diagnosis and treatment of TB:

- Diagnosis of TB in adults increased from 1.5m in 2000 to 2.7m in 2014 – although relative figures have been stable.¹³
- Treatment of drug-sensitive TB in adults increased from 40% of those requiring treatment in 2000 to 63% in 2014; treatment of MDR-TB in adults increased from just 7% in 2009 to 23% in 2014.¹⁴

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

1.3.1 Diagnostics

Access to effective diagnosis is low, and needs continue to evolve. In 2014, only 63% of adults with TB were diagnosed and treated, according to official data (from national TB programmes) versus a global target of at least 90% by 2025.¹⁵ 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.¹⁶

Effective diagnosis and reporting – including from the private sector – is essential to reaching this ‘missing 3 million’ and curbing the epidemic. At the same time, better access to drug susceptibility testing – including new tools 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 12% of new bacteriologically confirmed TB cases and 58% of previously treated TB patients were tested for drug resistance in 2014.

Better diagnostics are also needed to identify more children with TB. In 2014, WHO estimated 1 million TB cases and 140 000 TB deaths in children, although these figures are highly uncertain.¹⁷ This market segment has long been neglected due to its small size and high uncertainty – problems exacerbated by the difficulty in diagnosing TB in children.

1.3.2 Treatment

Improved access to better MDR-TB treatment is key in combating the threat of resistance.¹⁸ 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 13% of TB deaths

¹³ i.e., 40% of all TB cases in 2000 vs. 43% of all TB cases in 2015. WHO Global TB Report 2015

¹⁴WHO Global TB Report 2015

¹⁵WHO End TB Strategy 2015

¹⁶ While a cure is possible in roughly 90% of patients who are diagnosed and treated, 70% of patients with untreated TB die. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural History of Tuberculosis: Duration and Fatality of Untreated Pulmonary Tuberculosis in HIV Negative Patients: A Systematic Review. Pai M, ed. *PLoS ONE*. 2011;6(4):e17601. doi:10.1371/journal.pone.0017601

¹⁷ WHO End TB Strategy 2015

¹⁸ As challenges in diagnosis and treatment are closely interlinked, an integrated approach is critical

and 27% of costs,¹⁹ pointing to low rates of diagnosis and treatment, poor outcomes (50% global cure rate²⁰) and high cost of treatment.

Resistance threatens overall progress in the fight against TB, with critical MDR-TB epidemics in key countries. 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.²¹ There was a 23% increase in notified MDR-TB cases between 2012-13, led by India, Ukraine, and Uzbekistan.²² Current MDR-TB regimens are complex, expensive (average cost of \$5240 vs. \$46 for DS-TB medicines),²³ long (20–24 months, including 8 months of injections), and can cause severe side-effects.

Poor access to commodities and limitations of current tools are central to this threat of resistance. Over 70% of all people estimated to have MDR TB were not detected in 2014, and only 23% received treatment. Even among people with a diagnosis of MDR TB, the coverage of drug-susceptibility testing (DST) to guide treatment was only 24% (with DST access much lower in some settings).²⁴

Of those who do receive treatment, only 50% are cured or successfully complete treatment. UNITAID's endTB project and other initiatives are expected to drastically improve MDR-TB treatment options, but work may be needed to improve MDR-TB care in parallel and in preparation for new regimens.

1.3.3 Prevention

Prevention is key to ending the TB epidemic, but an effective vaccine is not available. In the End TB strategy, WHO emphasizes innovation that is needed to reach ambitious new targets – in particular, a new vaccine that is effective pre- and post-exposure. While 12 vaccine candidates are in development, new products are not expected to be available before 2020-25.²⁵

Medicines to treat latent TB infection and prevent progression to active TB infection could 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, and children under age five). Although WHO already recommends preventive treatment for these target populations, even in low-income, high-burden settings,²⁶ uptake has been low – or not clearly supported by data due to recording and reporting gaps. For example, in 2014, only 10 of the 30 high HIV/TB burden countries reported initiating isoniazid preventative therapy in people living with HIV, reaching 875 000 people²⁷.

¹⁹ WHO Global TB Report 2014

²⁰ WHO Global TB Report 2015

²¹ NdjekaN, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. 2015, 19 (8):979-85 *Int. J. Tuberc. Lung Dis.*

²² WHO Global TB Report 2014

²³ WHO Global TB Report 2014

²⁴ WHO Global TB Report 2015

²⁵ WHO End TB Strategy 2015 and internal UNITAID landscape monitoring

²⁶ NB: For broader implementation of preventive therapy, WHO guidelines have focused on use in low TB burden, upper middle and high-income countries.

²⁷ WHO Global TB Report 2015

Shorter, innovative regimens that are currently in evaluation may – for the first time – enable meaningful scale-up in target populations for which preventive therapy could have the highest impact, including in low-income, high-burden countries. Other fixed-dose combinations, including isoniazid with co-trimoxazole for people living with HIV, as well as child-friendly combinations, may increase the uptake of preventive therapy.

Key messages:

Despite significant progress, critical needs persist:

- Better access to diagnosis and care, reaching the 1/3 of TB cases that are currently unreported
- Diagnose and treat multidrug-resistant (MDR) TB cases more effectively
- Improve diagnosis and scale up treatment of TB in children
- Enable preventive TB treatment in high-risk groups, including children and people living with HIV

1.4 The importance of BRICS and engagement with countries

Buyers of TB diagnostics and medicines are increasing in number and type. TB disproportionately affects middle-income countries, which bear approximately 70% of the global burden.²⁸ In 2014 almost 50% of all notified TB cases globally occurred in Brazil, Russian Federation, India, China and South Africa – the so-called BRICS countries²⁹. Furthermore, over half of all drug-resistant TB cases occurred in these countries. With many countries assuming greater responsibility for provision of TB care (i.e., funding, producing), and increasingly setting the agenda in accelerating uptake of new tools, there is a need to engage with governments to coordinate efforts and maximize impact on the global shape and scale of the TB epidemic.

1.5 The role of private sector care-providers

Effective engagement with the private-sector care-providers (i.e., non-state actors) is essential to ensuring impact of many interventions in tackling the global TB epidemic. Provision of TB medicines in the private sector is thought to be significant, especially in high-burden countries such as India, Indonesia, Pakistan and the Philippines (and China, in terms of absolute number of patients)³⁰ – recent estimates suggest over half of all patients in many countries initially seek care in the private sector.³¹ Associated challenges include the use of inappropriate tools, uncertain quality standards, and high out-of-pocket costs.

At the same time, there is high variation in the pathway each patient takes to access diagnosis and care. A patient may first seek care in the private sector before eventually seeking care in or getting

²⁸ WHO Global TB Report 2015

²⁹ WHO. Use of high-burden country lists for TB by WHO in the post-2015 era. Discussion paper; June 2015. http://www.who.int/tb/publications/global_report/high_tb_burden_country_lists_2016-2020.pdf [accessed 16 Feb 2016]

³⁰ Wells WA et al. Size and usage patterns of private TB drug markets in the high burden countries. PLoS One. 2011;6(5):e18964

³¹ Pablos-Mendez A, editor. Leveraging the economic transition in health to improve private and public sector TB care. Washington DC: Public Private Mix (PPM) Models for the Sustainability of Successful TB Control Initiatives; May 2014

referred to the public sector – resulting in delayed diagnosis or treatment, missed cases, and discontinued or interrupted treatment, all factors increasing the risk of drug resistance.

Moreover, visibility on the private-sector market segment is poor: market size, treatment patterns and other dynamics are very poorly understood in low-income countries.³² Better coordination is needed between public- and private-sector care-providers to foster meaningful uptake and scale-up of new tools. As scalable models are developed for better TB diagnosis and care, engagement with the private healthcare sector will help reach many of the ‘missing 3m’ people with TB who currently do not get diagnosed or treated – including many of the world’s most disenfranchised people. Engagement with not-for-profit and non-governmental organizations’ community health workers and volunteers can also be a powerful tool to find these missing cases and reduce the delay in diagnosis.³³

1.6 Innovation expected to accelerate the pace of change in the coming years

Diagnosis and treatment of TB has been conservative and slow to change. Archaic technologies such as sputum smear microscopy and old drugs discovered in the 1950s are still considered standard.

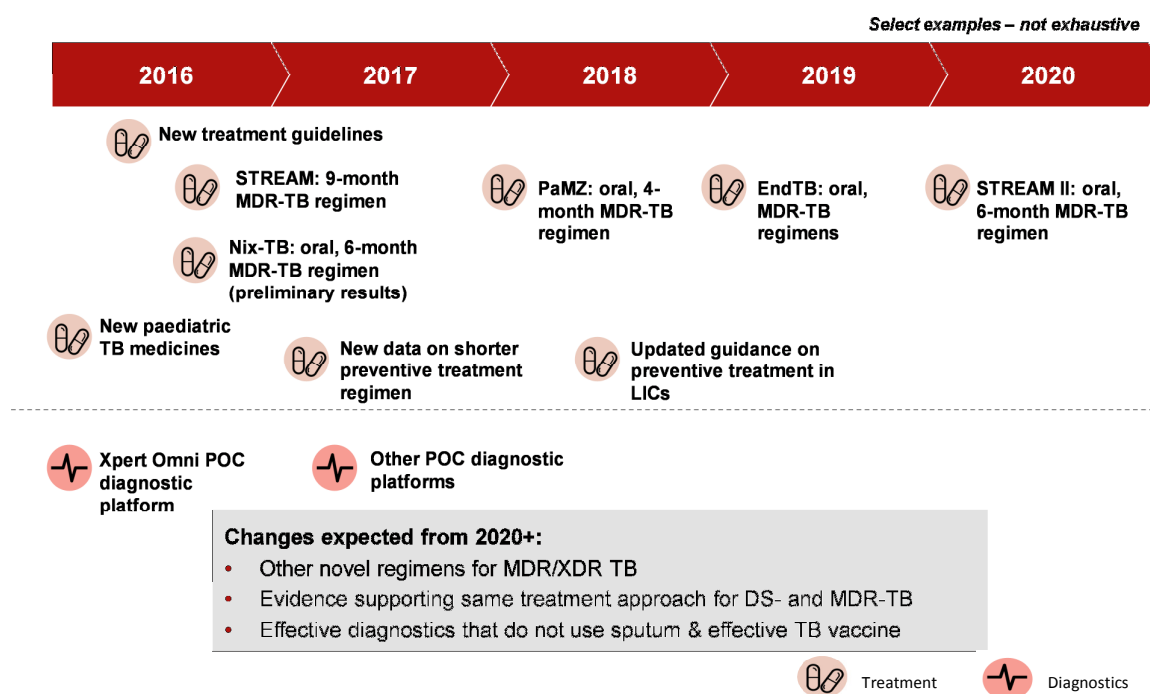
An innovative diagnostic (Xpert MTB/RIF, 2010) and two novel MDR-TB medicines (bedaquiline, 2012; delamanid, 2013) have recently entered the market, but further innovation is still urgently needed. Anticipation of new innovations is key to accelerating adoption in low-income countries, especially with the advent of new diagnostics and MDR-TB treatments – for which coordination and integration is increasingly important (e.g., new drug susceptibility tests need to be designed to test for resistance to novel drugs).

Key innovations expected within the next five years (as illustrated in Figure 3) include:

- New point-of-care diagnostics – though recent changes in the TB innovation pipeline suggest that breakthrough innovations will not be available in the timeframe required for action under a standalone Area for Intervention at this time;
- Shorter MDR-TB regimens comprising existing drugs, as well as novel MDR-TB treatment options (including regimens from UNITAID’s endTB project); and
- New, shorter regimens for preventive TB treatment, which could make implementation of WHO guidelines feasible in low-income countries for the first time.

³²UNITAID TB Medicines Technology and Market Landscape, 2014 (excerpt)

³³ WHO. ENGAGE-TB: Integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Geneva: 2012

Figure 3. Innovation pipeline**Key messages:**

- Historically, change in TB has been slow, with archaic technologies and old drugs still central to diagnosis and treatment
- New MDR-TB medicines have entered the market in the past 3 years – the first in 40 years – but adoption has been slow
- Anticipation of new innovations could accelerate change, especially with the advent of new MDR-TB and preventive treatments

2 Partner landscape in TB

Understanding the partner landscape is essential for identifying gaps that UNITAID could address to complement others' work and contribute to the global response.

Key partners support upstream innovation. For example, the Bill & Melinda Gates Foundation (Gates Foundation), US Government/USAID and other funders/bilaterals³⁴ prioritize support for TB research. Non-governmental organizations (NGOs), academics, and other actors are also active in this area, such as the European and Developing Countries Clinical Trial Partnership, the International Union Against Tuberculosis and Lung Disease (the Union), and Institut Pasteur.

³⁴The US Government invested more than \$2.8 billion between 2010-14 through USAID programmes in TB, PEPFAR programmes in TB/HIV, and Global Fund contributions; and in December 2015, launched the National Action Plan for Combating Multidrug-Resistant Tuberculosis. Other bilaterals and multilaterals play instrumental roles in the fight against TB, notably DFID (UK), Cooperation Française, Japan International Cooperation Agency, and the European Commission, among others

Figure 4. Partner mapping

Partners also play a crucial role downstream, delivering commodities to the patients who need them. Countries themselves are central: domestic resources cover 89%³⁵ of reported TB funding (total \$5.5B), and national TB programmes are a cornerstone of TB care provision. The Global Fund is the leading funder of TB commodities, and the US Government is the largest bilateral donor in TB, both with invaluable experience and insight from implementation and technical assistance in countries. Other groups that provide valuable perspectives allowing UNITAID to anticipate and respond to country needs include: civil society including representatives of communities living with the diseases; Stop TB Partnership and key advocacy groups; and NGOs and other actors with experience implementing large-scale projects in countries.^{36,37}

UNITAID has a strong value-added role to play between these two groups, ensuring that upstream innovations can be accessed by those in the downstream (illustrated in Figure 4). This is particularly relevant in ensuring that:

- The needs of people with TB 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).

³⁵NB: wide variation, from <10% domestic funds in some LICs to approx. 100% in BRICS

³⁶ e.g., KNCV, the International Union against TB and Lung Disease (Union), the Red Cross

³⁷ Actions aimed at accelerating the implementation of the End TB Strategy through community and NGO engagement can be found in the *Statement of Action*, WHO 2015.

http://apps.who.int/iris/bitstream/10665/199333/1/WHO_HTM_TB_2015.30_eng.pdf?ua=1&ua=1 [accessed 26 Feb 2016]

UNITAID also has a continuing role in highlighting where challenges are unresolved by market forces, ensuring innovation reaches the most vulnerable people. For example, UNITAID has long supported TB care for the relatively neglected paediatric population, with recent work including development of child-friendly formulations of TB medicines.³⁸

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

³⁸TB Alliance STEP-TB project

3 Challenges threatening progress towards global goals

UNITAID identified a comprehensive inventory of challenges that threaten achievement of global goals, as a framework for articulating and refining its focus in potential Areas for Intervention. This analysis was based on consultation with partners and input from multiple sources, as mentioned in the box at right.

Each input was checked, and partners consulted, to avoid missing potential opportunities. Many challenges are interlinked, and there may be many root causes contributing to a single challenge. In some cases, similar challenges have been merged to reach an inventory that can be used as a framework for action.

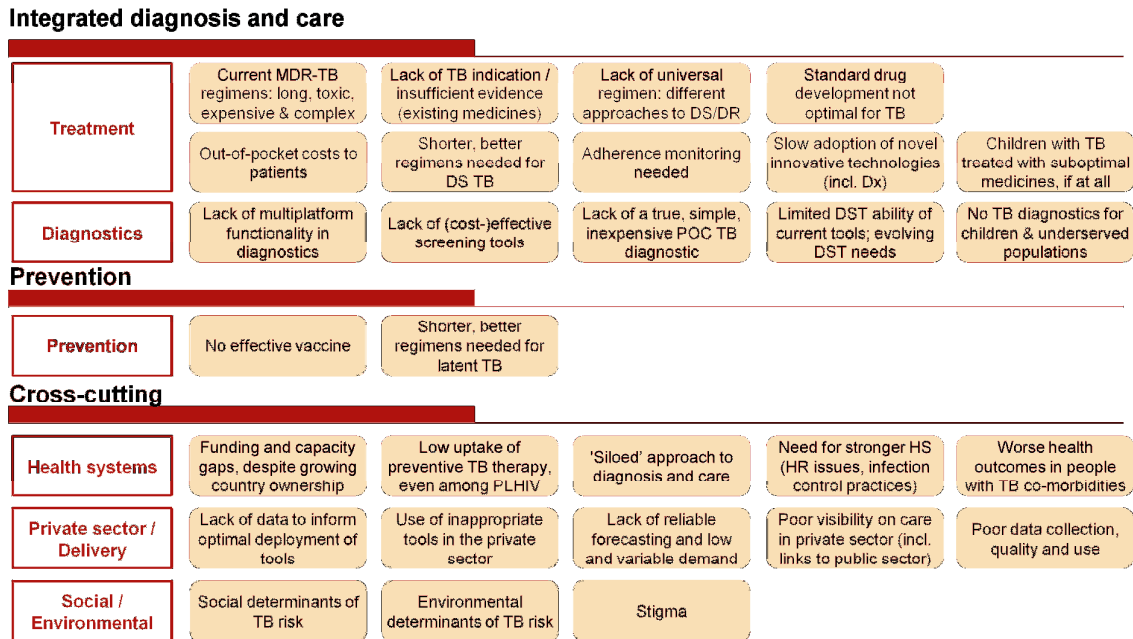
This comprehensive inventory of challenges was grouped according to three key categories:

- **Integrated diagnosis and care:** A holistic, patient-centered approach to diagnosis and care is essential to optimize individual patient outcomes and reach overall public health goals. Diagnosis and treatment are increasingly interdependent, requiring coordination and integration in innovation, development and delivery.
- **Prevention:** An effective vaccine would be a game-changer in the fight against TB, but is not expected to be available until 2020-25. Preventive therapy has so far been the main stay in TB prevention. Current regimens are long (6-36months) but new, shorter and more effective regimens are on the horizon.
- **Cross-cutting:** Challenges related to weak health systems, the need to improve care and visibility in the private sector, suboptimal delivery, and social or environmental factors are multifaceted and complex. They are important to consider for a balanced, comprehensive understanding of challenges facing the global goals. Given the focus of UNITAID on commodities, some may be partially or indirectly addressed through a UNITAID intervention.

List of sources used to develop list of challenges:

- UNITAID strategic insight and market intelligence resources (e.g. landscapes, dashboard)
- Countries' implementing strategies
- WHO End TB Strategy
- Stop TB Partnership's Global Plan to Stop TB 2016-20
- Global Fund's strategies and analyses
- Reach, Cure, Prevent: US Government TB Strategy
- Innovation pipelines of the private sector

The complete inventory of challenges is shown in Figure 5. Description of challenges is available in the appendix.

Figure 5. Challenges inventory

Four criteria were then applied to the inventory of challenges:

- UNITAID's expertise:** focus on challenges that are inherently commodity access issues
- Potential public health impact:** focus on challenges for which there is strong evidence of high potential public health impact
- Feasibility:** focus on challenges for which the necessary technology can be available in the relevant timeframe
- Optimized use of resources:** focus on challenges for which critical gaps exist in the global response and where scale up is possible

These criteria were used as filters to identify a shortlist of challenges that represent the highest potential for UNITAID intervention. This final list of challenges, following the filtering process described below (refer to Figure 6) provided the basis for the identification of Areas for Intervention for UNITAID.

Figure 6. Challenges inventory, following filtering process

Integrated diagnosis and care

Treatment	Current MDR-TB regimens: long, toxic, expensive & complex	Lack of TB indication / insufficient evidence (existing medicines)	Monitor Lack of universal regimen: different approaches to DS/DR	Standard drug development not optimal for TB	Children with TB treated with suboptimal medicines, if at all
	Partially Out-of-pocket costs to patients	Shorter, better regimens needed for DS TB	Monitor Adherence monitoring needed	Slow adoption of novel innovative technologies (incl. Dx)	
Diagnostics	Monitor Lack of multiplatform functionality in diagnostics	Monitor Lack of (cost-)effective screening tools	Monitor Lack of a true, simple, inexpensive POC TB diagnostic	Monitor Limited DST ability of current tools; evolving DST needs	Monitor No TB diagnostics for children & underserved populations

Prevention

Prevention	No effective vaccine	Shorter, better regimens needed for latent TB
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Cross-cutting

Health systems	Funding and capacity gaps, despite growing country ownership	Low uptake of preventive TB therapy, even among PLHIV	Partially 'Siloed' approach to diagnosis and care	Need for stronger HS (HR issues, infection control practices)	Partially Worse health outcomes in people with TB co-morbidities
	Private sector / Delivery	Lack of data to inform optimal deployment of tools	Partially Use of inappropriate tools in the private sector	Lack of reliable forecasting and low and variable demand	Partially Poor visibility on care in private sector (incl. links to public sector)
Social / Environmental		Social determinants of TB risk	Environmental determinants of TB risk	Stigma	

Notes: Grey denotes challenges removed through prioritization process detailed in Section 4.1. 'Partially' refers to cases where there may be potential for a market-based approach, but further exploration is needed. 'Monitor' refers to challenges flagged for monitoring or further attention.

4 Priority challenges to be addressed by UNITAID

The objective of this section is to describe the results of the filtering process through which challenges were prioritized as potential focus areas for UNITAID, leading to potential Areas for Intervention.

4.1 Challenge prioritization process

4.1.1 UNITAID's expertise: focus on challenges that are inherently commodity access issues

This first criterion is designed to ensure UNITAID focuses on areas where it has expertise and strength in addressing gaps in access to products used to test, treat, and prevent disease. By doing that, UNITAID will leverage its market-shaping experience.

This criterion filters out those challenges that, to resolve, require skills or a mandate that is not consistent with UNITAID's business model. These include critical challenges that threaten the global TB response, but are multifaceted issues or systemic challenges requiring action beyond better access to products used to test, treat, and prevent disease. For example:

- Social determinants of TB risk
- Environmental determinants of TB risks
- Stigma
- Funding and capacity gaps, despite growing country ownership
- Need for stronger health systems (human resource issues, infection control practices)
- Standard drug development not optimal for TB

In some cases, there is potential for a market-based approach to partially address a challenge, but further exploration is needed – e.g., to identify scalable models for impact, or models that emphasize access to innovative commodities. These challenges may be alleviated *in part* with innovative tools or delivery models, but also relate to health coverage, social protection, care-seeking behaviour, and other factors. For example:

- Out-of-pocket costs to patients
- Worse health outcomes in people with TB co-morbidities
- 'Siloed' approach to diagnosis and care
- Poor visibility on care in private sector (including links to public sector)
- Use of inappropriate tools in the private sector

4.1.2 Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact

The second criterion is designed to focus UNITAID on those areas where its action will have the greatest impact on the global response.

This criterion filters out those challenges for which there is limited or conflicting evidence of public health impact. For example:

- Lack of TB indication / insufficient evidence: existing medicines (Some older TB medicines lack a formal label indication in TB, but use is based on decades of experience. It is not clear if securing a formal indication in TB for these drugs would – in itself – change clinical practice and therefore public health outcomes.)
- Shorter, better regimens needed for drug-sensitive TB (There is some debate on the public health impact of improving DS-TB treatment regimens – e.g., by reducing treatment

duration or improving efficacy – since existing treatment can achieve a cure in 90% of patients.)

In considering potential for public health impact and needs for intervention, UNITAID will continue to monitor closely:

- Adherence monitoring needed

4.1.3 **Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe**

The third criterion is largely pragmatic, focusing UNITAID intervention on challenges for which the necessary technology is available, or can be expected to be available, in the timeframe needed. This filters out those challenges where action would not yet be feasible. For example:

- No effective vaccine (an effective, preventive TB vaccine is expected only in 2020-25)

In some areas, much-needed technologies are not expected to be available in the short term. Cepheid's Xpert remains the only rapid molecular diagnostic tool, with new platform Omni enabling use as a point-of-care option. Unfortunately the pipeline is not yet delivering technologies to compete with Xpert, or to meet the priorities for TB diagnostics recently identified by WHO and other TB experts.³⁹ Other stopgap measures such as digital chest X-ray are under careful monitoring, but questions on feasibility of implementation – including whether and how this fits with diagnostic algorithms – remain challenges. However, UNITAID will continue to monitor these areas to enable quick action if data supporting promising innovations with capacity to scale do emerge:

- No TB diagnostics for children & underserved populations (These are much-needed technologies, but there are no promising technologies in late-stage development.)
- Lack of multiplatform functionality in diagnostics; lack of a true, simple, inexpensive point-of-care TB diagnostic (No TB competitors to Xpert are anticipated in the short term, while new point-of-care platforms are becoming available for HIV viral load and early infant diagnosis.)
- Lack of (cost-) effective screening tools. (As described above, stopgap measures exist, but questions on feasibility of implementation limit use.)
- Limited drug-susceptibility testing ability of current tools; evolving needs (Technical requirements are evolving as new drugs and regimens emerge; integrated with treatment opportunity)
- Lack of universal regimen: different approaches to drug-sensitive/drug-resistant TB treatment (This has high potential to revolutionize TB care, if successful, but is not expected before 2020+.)

In November 2015, the preliminary disease narrative included on this 'watch list' shorter, better regimens for latent TB (i.e., preventive therapy). Partner consultations have since highlighted the promise of an innovative regimen: new data expected in early 2017 may, for the first time, enable appropriate use in low-income, high-burden countries. The new global End TB Strategy proposes that preventive actions, together with better diagnosis and care, could accelerate progress to make it possible to end the epidemic by 2035.

³⁹High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

4.1.4 **Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible**

The fourth and final criterion is the most critical in ensuring UNITAID's added value in the global response. Under this criterion, the ongoing/planned activities of partners (including UNITAID's projects) are evaluated to see whether the landscape either a) leaves limited opportunities for UNITAID, or conversely, b) provides opportunities for UNITAID to leverage and build upon the activities of others.

Challenges that would have been removed with this final criterion had been removed with previous filters – e.g., lack of (cost-)effective screening tools or an effective vaccine. While no additional challenges were removed with this criterion, it served to validate the process and resulting proposed focus areas. Ongoing partner consultation will also aid in the monitoring required to reassess periodically the critical gaps and opportunities for UNITAID.

The validation of the first three filters and completion of the fourth, including accommodation of key changes, highlights the utility of the disease narrative methodology. The disease narrative, with revisions since EB 23 in November 2015, serves as an effective tool to assess challenges and monitor opportunities in a rapidly evolving technology and partner landscape.

4.2 **Overview of the priority challenges to be addressed by UNITAID in the next 24 months**

Based on the filtering exercise undertaken by the Secretariat and validated with key partners, themes in the above challenges have informed three Areas for Intervention, high priorities for the next 24 months:

Speed access to better, shorter MDR-TB treatment: This Afi will speed access to shorter, simpler treatments for MDR TB. More effective regimens with fewer side effects will allow for better adherence and patient outcomes at the individual level, including for more vulnerable populations such as children and people living with HIV. In aggregate, better tools for MDR TB will accelerate progress to end TB and could realize vast savings in lives and costs. Integration of diagnostics will be vital in ensuring a holistic approach to TB care and treatment, in particular detecting drug resistance and guiding optimal treatment.

Work in this area would aim to amplify the impact of upstream research and development (including UNITAID's endTB project) by speeding uptake of emerging treatment options and consolidating the market around fewer priority regimens. In addition, there are more immediate opportunities to shorten or improve treatment, for example with shorter combinations of current medicines, or novel drugs.

Scale up TB treatment in children: This Afi aims to accelerate access and adoption of new child-friendly medicines for TB, launched in November 2015 as a direct result of UNITAD's intervention. In-country work is now required to ensure uptake of these new medicines to reach the children who need them. This will enable children to receive suitable medicines in the right doses and free carers from crushing and splitting medicines. As more children receive better treatment, broader benefits include reduction in resistance (with more accurate dosing and better adherence), and stabilization of this neglected and fragile market niche. Increased awareness and better treatment of children with TB will also stimulate further innovation, including much-needed TB diagnostics better suited to children.

Approaches in this area may require integration of TB care into other child health services (e.g., child-welfare clinics, immunization clinics, community-based delivery, private-sector care-providers), and leveraging the influence and reach of critical advocacy partners in civil society.

Enable preventive TB treatment in high-risk populations: This Afi focuses on preventive strategies in TB, complementing efforts to improve diagnosis and treatment of active TB, to

accelerate progress in ending the TB epidemic. Specifically, this AfI aims to speed access to innovative tools for TB prevention in high-risk populations in limited-resource settings. In particular, children under age five and people living with HIV are among the most vulnerable, with the greatest risk of developing active TB infection and the worst health outcomes. The potential impact of preventive strategies is recognized, but uptake has been low in limited-resource settings. Emerging tools may offer the first viable option for broader use, but work may be needed to inform the most cost-effective use in these settings. As with the previous AfI, approaches in this area will require an integrated approach (e.g., considering diagnostic needs in the context of preventive treatment; leveraging HIV and child health services for delivery and scale).

Related to the scope of these AfIs, other challenges and opportunities will be monitored for relevance beyond this 24-month period (e.g., new disruptive technologies or approaches relevant to TB as part of broader antimicrobial resistance efforts).

The following sections of this report describe each proposed AfI in greater detail. If these AfIs are endorsed, the UNITAID Secretariat will, over the next 24 months, launch Calls for relevant proposals in each of these areas.

5 APPENDIX: Description of challenges

5.1 Challenges related to integrated diagnosis and care

5.1.1 Treatment

Current MDR-TB regimens: long, toxic, expensive & complex

MDR-TB regimens are complex, expensive (average cost of \$5240 vs. \$46 for DS-TB medicines),⁴⁰ long (20–24 months, including 8 months of injections), and can cause severe side-effects, including deafness and psychiatric disorders. Even among people on MDR-TB treatment, fewer than half currently achieve a cure (48% global cure rate).⁴¹

The complexity of MDR-TB treatment fragments an already small market and reduces commercial incentives for manufacturers to engage. Many medicines, each with many formulations and packaging options, currently exist. Even within WHO guidelines, over 50 regimens, or combinations of medicines, can be used to treat MDR TB. More evidence is needed to streamline treatment options in a rational way that optimizes treatment outcomes – part of the rationale for the UNITAID-funded endTB project with Partners in Health, MSF and Interactive Research & Development.

Lack of TB indication / insufficient evidence (existing medicines)

Commonly used TB medicines include some without formal indications in TB, such as linezolid and clofazimine – the latter primarily a leprosy drug. WHO guidelines classify these as ‘group 5’ medicines – i.e., agents with limited data on efficacy and/or long-term safety on the treatment of drug-resistant MDR-TB. However, several studies^{42,43} have examined current clinical applications and future prospects for these drugs, and in November 2015, a WHO guidelines development group is expected to consider new data from the STREAM trial, which studied clofazimine as part of a shortened nine-month MDR-TB regimen.

Access has been challenged by: Novartis’ tendency to restrict clofazimine supply to the licensed indication of leprosy; and Pfizer’s high price and patents (until 2014) preventing availability of cheaper, generic linezolid.⁴⁴ However, it is unclear the degree to which the lack of a formal TB indication has – in itself – limited access: demand for clofazimine has reportedly already been increasing on the basis of operational research for shortened regimens and inclusion in the STREAM trial.

⁴⁰ WHO Global TB Report 2014

⁴¹ WHO Global TB Report 2014

⁴²Cholo MC, Steel HC, Fourie PB, Germishuizen WA, Anderson R. Clofazimine: current status and future prospects. *J. Antimicrob. Chemother.* (2011) doi: 10.1093/jac/dkr444

⁴³Hwang TJ, et al. Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies. *BMJ Open.* 2014;4(1):e004143. doi:10.1136/bmjopen-2013-004143.

⁴⁴MSF Access Campaign. Ready, Set, Slow down: New and promising DR-TB drugs are grabbing headlines but not reaching patients. https://www.msfacecess.org/sites/default/files/MSF_assets/TB/Docs/DR-TB%20DRUGS%20FACT%20SHEET_FINAL_ENG_OCT24.pdf

Lack of universal regimen: different approaches to DS/DR

Diagnosis and treatment of TB is complicated by the need for tailored approaches depending on an individual patient's resistance profile. That is, low access to sophisticated (and evolving) drug susceptibility testing remains a constraint to effective treatment. This leads to delays and suboptimal treatment outcomes.

More broadly, the lack of a universal regimen limits the ability of the global response to be unified and high-impact among all patients. That is, different approaches to DS- and DR TB fragment the market, and the high volume of DS cases cannot be used to leverage price reductions or assure market stability for DR-TB medicines.

Standard drug development not optimal for TB

The typical approach to TB drug development—one medicine at a time—means that development of entirely novel regimens is long and challenging. According to the Critical Path to TB Drug Regimens (CPTR), *'Standard drug development has traditionally required that each new drug be evaluated and approved separately before it is tested in combination with other new compounds. Using this approach, obtaining regulatory approval for a new three- or four-drug combination TB therapy could take more than 20 years.'*⁴⁵ Innovative mechanisms and partnerships (including CPTR) may facilitate progress through activities such as collaboratively testing TB drug candidates in combination early in development, but underlying reform of regulatory systems may also be needed.

Slow adoption of novel innovative technologies (incl. Dx)

A new drug or diagnostic may receive marketing authorization on the basis of demonstrated efficacy and safety, but launch with very limited evidence to inform its use. There may be questions on optimal use of a new drug as part of complex regimens, or how a new diagnostic should be integrated into existing algorithms. This can translate into slow adoption of new technologies in low-income countries, with 5- to 10-year delays common.⁴⁶

Children with TB treated with suboptimal medicines, if at all

Paediatric TB has long been neglected. In 2010, WHO issued revised guidelines for treating children with TB, recommending higher dosages. The small and uncertain market for paediatric TB medicines – reduced further by the difficulty of diagnosing TB in children – meant that manufacturers were reluctant to invest in development of the new products aligned with the revised guidelines. As a result, there were no correctly dosed, properly formulated, affordable, high-quality TB medicines for children, and children with TB were treated with suboptimal medicines (e.g., split or crushed pills). New formulations will launch soon as the result of the UNITAID-funded STEP-TB project with TB Alliance.

The difficulty in diagnosing TB in children also contributes to poor access to medicines. ***See also: No TB diagnostics for children & underserved populations (Section 5.1.2).***

Shorter, better regimens needed for DS TB

Regimens in development could lead to a 4-month or even 2-month treatment course. While certainly an improvement over the six months currently required, recent modelling⁴⁷ suggested that minimal impact on TB incidence may be expected by reducing treatment time to four months.⁴⁸

⁴⁵Critical Path to TB Drug Regimens (CPTR).Statement of Principles.http://www.tballiance.org/downloads/misc/STATEMENT_OF_PRINCIPLES.pdf

⁴⁶ ARV example cited in Burrone E, Perry G. Affordability of new HIV treatments. *Lancet*, 2014 (384).[http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(14\)61484-7.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)61484-7.pdf)

⁴⁷Fofana MO, Knight GM, Gomez GB, White RG, Dowdy DW. Population-level impact of shortercourse regimens for tuberculosis: a model-based analysis. *PLoS One*. 2014;9(5):e96389.

⁴⁸UNITAID 2014 TB Medicines Technology and Market Landscape (excerpt).

Out-of-pocket costs to patients

TB is often a cause *and* effect of poverty, with devastating economic consequences for many affected families (average 50% reduction of annual income and aggravation of existing inequality).⁴⁹ Out-of-pocket costs can be particularly high for patients seeking care in the largely unregulated private sector.

This challenge threatens global goals and – while linked to high cost of current commodities – is also rooted in systemic social protection. In recognition of this, the End TB Strategy calls for elimination of catastrophic costs for TB patients and their families by 2020, through more accessible care but also financial protection schemes to minimize medical and non-medical costs and lost income.⁵⁰

Shorter, better regimens needed for latent TB

Recent WHO guidelines⁵¹ for managing latent TB infection (LTBI) recommend several shortened regimens for treating LTBI, in addition to six or nine months of isoniazid: three months of once-weekly isoniazid and rifapentine, three to four months of isoniazid and rifampicin, or three to four months of rifampicin alone.⁵² Although, these guidelines have been initially focused on high-income, low-incidence settings, since the approval of the End TB Strategy, they have changed into a broader strategy for at high risk population in countries where the preventive therapy of LTBI could be feasible and cost-effective.

Adherence monitoring needed

Treatment adherence is a complex issue, and a particular challenge in TB given the long duration and many side effects associated with treatment. Potential approaches to improve adherence vary widely and may include innovations in both technology and delivery – for example: better management of side effects (or less toxic treatment options); more holistic support (nutritional, psychosocial, counselling); technological innovations (e.g., monitoring boxes); social protection/vouchers; simplified packaging; etc.⁵³

5.1.2 Diagnostics

Lack of (cost-) effective screening tools

An effective screening tool, or triage test, is among the four highest priority TB diagnostics recently identified by WHO and other TB experts.⁵⁴ A triage test – especially a simple, low-cost test that allows community health workers at the lowest levels of care to rule out TB – could help narrow the population that needs costlier confirmatory testing. In this way, such a test could be a critical part of reaching the ‘missing 3 million’ people with undiagnosed TB in a cost-effective way.

⁴⁹WHO calls on the world to “Gear up to End TB”. 19 Mar 2015.
<http://www.who.int/mediacentre/news/releases/2015/end-tb/en/>

⁵⁰WHO End TB Strategy 2015

⁵¹Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1).

⁵²UNITAID 2014 TB Medicines Technology and Market Landscape (excerpt).

⁵³Stop TB Partnership. The Global Plan to Stop TB 2016-20. Bending the Curve: A Global Investment Framework to Win the Fight against TB. 2015

⁵⁴High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014.
http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

Lack of a true, simple, inexpensive POC TB diagnostic

A rapid, sensitive, point-of-care test that can replace smear-microscopy is also among the four highest priority TB diagnostics recently identified by WHO and other TB experts.⁵⁵ Such a test would reduce delays in diagnosis and treatment initiation, and thus morbidity at the individual level. In addition, a POC TB diagnostic would increase TB diagnosis and reduce transmission overall, reaching more of the ‘missing 3 million’ and impacting the trajectory of the epidemic.

Lack of multiplatform functionality in diagnostics

Multiplatform functionality – or the ability to test for more than one disease – could facilitate more integrated, patient-centered care and leverage other programmes’ reach.

Limited DST ability of current tools; evolving DST needs

Even among people with a diagnosis of MDR TB, fewer than 17% had access to drug-susceptibility testing (DST) to guide effective treatment, with access much lower in some settings.⁵⁶ This leads to delays and suboptimal treatment outcomes, increasing the threat that resistance undermines overall progress in the fight against TB.

Better tools are needed – indeed, a tool capable of rapid DST at the microscopy center level is among the four highest priority TB diagnostics recently identified by WHO and other TB experts.⁵⁷ Even with a defined target product profile, however, specific technological requirements are evolving as new drugs and regimens emerge. An integrated approach to development of new medicines and diagnostics is therefore essential.

No TB diagnostics for children & underserved populations

In 2013, WHO estimated 550 000 TB cases and 80 000 TB deaths in children, although these figures are highly uncertain⁵⁸. This market segment has long been neglected due to its small size and high uncertainty – problems exacerbated by the difficulty in diagnosing TB in children.

Current TB diagnostics are not appropriate for children and other underserved populations. Sputum is often difficult to collect in children and people living with HIV. In addition, children tend to have low levels of bacteria in sputum: 90% of TB in children is smear-negative, and children are prone to extrapulmonary forms of TB.⁵⁹

Accordingly, a point-of-care, non-sputum-based, biomarker TB test is among the four highest priority TB diagnostics recently identified by WHO and other TB experts.⁶⁰ Such a test should ideally use an easily accessible sample (e.g., urine, blood, or breath condensate).

⁵⁵High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

⁵⁶UNITAID Market Dynamics dashboard

⁵⁷High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

⁵⁸ WHO Global TB Report 2014

⁵⁹UNITAID 2014 TB Medicines Technology and Market Landscape (excerpt)

⁶⁰High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland: meeting report. Geneva: World Health Organization; 2014. http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

5.2 Challenges related to prevention

No effective vaccine

The absence of a safe and effective vaccine to prevent active infection of TB continues to be a significant obstacle to ending the epidemic. Bacille Calmette Guerin (BCG) is the only TB vaccine presently on the market and has been used for almost 100 years with limited effectiveness. BCG protects against severe forms of TB in children (TB meningitis and miliary TB) but does not protect against pulmonary TB, the most common form of the disease in adolescents and adults. In addition, BCG use is unsafe in HIV-positive and other individuals with compromised immune systems.⁶¹ Although there are other, potentially more effective, vaccines currently in various stages of clinical development, such products are not expected to be commercially available until 2020-25.^{62,63}

See also: Low uptake of preventive TB therapy (Section 5.3.1).

5.3 Cross-cutting challenges

5.3.1 Health systems

'Siloed' approach to diagnosis and care

The WHO End TB Strategy 2015 emphasizes the need for integrated, patient-centered care as one of three central pillars. Diagnosis and treatment are increasingly interdependent, so coordination and integration in development and delivery are key (e.g., new drug susceptibility tests need to be designed to test for resistance to novel drugs). In a similar vein, services to detect and treat TB and HIV are often separate and better coordination could improve outcomes for both diseases.

Funding and capacity gaps, despite growing country ownership

WHO reports that available funding for TB prevention, diagnosis and treatment doubled from 2006-14, reaching US\$ 6.3 billion in 2014. About 89% is from countries' domestic resources, but with wide variation between countries. Generally, BRICS and UMICs meet the vast majority of TB funding needs with domestic resources, while donor funding dominates in high-burden countries that are not BRICS and in LICs (up to 90% in some LICs). An estimated \$8b is needed annually for a full response to the global TB epidemic in low- and middle-income countries (excluding R&D), leaving a \$2b gap.⁶⁴

Funding requirements are expected to increase in the immediate future as accelerated progress and intensified R&D efforts are needed to secure longer-term gains. Needs may subsequently taper as prevention, diagnosis and treatment interventions realize gains through reach broader coverage.⁶⁵

⁶¹Stop TB Partnership. The Global Plan to Stop TB 2011-2015: Transforming the Fight Towards the Elimination of Tuberculosis. 2010.

⁶²Kaufmann, SH. Fact and fiction in tuberculosis vaccine research: 10 years later. *Lancet Inf Dis.* 2011; 6:33-40.

⁶³UNITAID 2014 TB Preventives Technology and Market Landscape (internal document) (excerpt)

⁶⁴ WHO Global TB Report 2014

⁶⁵ WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

Low uptake of preventive TB therapy, even among people at highest risk of progression to active TB (including children and people living with HIV)

Recent WHO guidelines⁶⁶ for preventive TB therapy focus on high-income, low-incidence settings. For isoniazid preventive therapy (IPT), the global coverage target is 100%, yet access to IPT remains fragmented and largely limited to high-income countries.^{67,68}

Need for stronger health systems (including human resource issues, infection control practices)

The WHO End TB Strategy 2015 notes: “Inadequate coverage and weak performance of health services limit access to high-quality TB care. ... Regulatory mechanisms essential to ensure effective infection control, rational use of tuberculosis diagnostics and medicines, mandatory disease notification, functioning vital registration systems, and protection of the legal rights of people with TB remain weak.”⁶⁹

Worse health outcomes in people with TB co-morbidities

The WHO End TB Strategy 2015 notes: “Risk-factors such as diabetes, tobacco-smoking, silicosis, alcohol and drug misuse, and undernutrition hamper TB control, especially in LMICs. The increasing prevalence of noncommunicable diseases also changes the profile of TB co-morbidities, complicating clinical management and worsening health outcomes. Few links currently exist between health services for communicable and noncommunicable diseases.”⁷⁰

5.3.1.1 Private sector and delivery

Poor visibility on care in private sector (incl. links to public sector)

The private sector plays an important role in provision of TB care (especially in India, Indonesia, Pakistan and the Philippines, and China, in terms of absolute number of patients).⁷¹ Recent estimates suggest over half of all patients in many countries initially seek care in the private sector.⁷² However, visibility on this market segment is poor. Market size, treatment patterns and other dynamics have been characterized to some extent in middle-income countries, but are very poorly understood in low-income countries.⁷³

In addition, the WHO End TB Strategy 2015 notes the problem of poor referrals and linkages between many public and private health providers from national tuberculosis control efforts.⁷⁴

⁶⁶ Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2014 (http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf?ua=1&ua=1).

⁶⁷ WHO Global TB Report 2013

⁶⁸ UNITAID 2014 TB Preventives Technology and Market Landscape (internal document) (excerpt)

⁶⁹ WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

⁷⁰ WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

⁷¹ Wells WA et al. Size and usage patterns of private TB drug markets in the high burden countries. PLoS One. 2011;6(5):e18964.

⁷² Pablos-Mendez A, editor. Leveraging the economic transition in health to improve private and public sector TB care. Washington DC: Public Private Mix (PPM) Models for the Sustainability of Successful TB Control Initiatives; May 2014

⁷³ UNITAID TB Medicines Technology and Market Landscape, 2014.

⁷⁴ WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

Use of inappropriate tools in the private sector

Inappropriate selection and use can occur in the private sector (e.g., inappropriate prescribing by private-sector physicians), in part due to the lack of access to a full range of quality-assured tools and lack of enforced quality standards.⁷⁵

Lack of reliable forecasting and low and variable demand

Better forecasting and procurement could alleviate TB medicine shortages. The small and fragmented MDR-TB medicines market is particularly affected, with access to QA drugs under continuing threat. Supply disruptions are a symptom of low and variable demand, unreliable projections and few suppliers. More accurate forecasts improve supplier confidence and production planning and assure timely payment.⁷⁶

Lack of data to inform optimal deployment of tools

Evidence is needed to speed adoption of new innovative tools, including informing use of a new drug as part of complex regimens, or optimizing integration of a new diagnostic into existing algorithms.⁷⁷

Poor data collection, quality and use

The WHO End TB Strategy 2015 emphasizes the need to improve data collection, quality and use at all levels – and to address the weaknesses in health systems that limit linkages required for progress.⁷⁸

5.3.2 Social and environmental***Social and environmental determinants of TB risk***

Underlying factors that contribute to TB risk include poverty and inequity; food insecurity and under-/malnutrition; ageing, chronic diseases and other comorbidities; other adverse living and working conditions; population movements and emergencies.⁷⁹

Stigma

TB is stigmatized, in part due to associations with poverty and HIV. People may not seek care for fear of job loss, eviction, or isolation in the case of a TB diagnosis. Tackling deep-rooted stigma is essential to success in improving TB care.⁸⁰

⁷⁵UNITAID TB Medicines Technology and Market Landscape, 2014 (excerpt)

⁷⁶UNITAID TB Medicines Technology and Market Landscape, 2014 (excerpt describing key outcomes of UNITAID 2013 TB Market Forum)

⁷⁷UNITAID TB Medicines Technology and Market Landscape, 2014 (excerpt describing key outcomes of UNITAID 2013 TB Market Forum)

⁷⁸WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

⁷⁹WHO End TB Strategy 2015 (excerpt from WHO report on the proposed post-2015 TB Strategy and targets)

⁸⁰Stop TB Partnership. The Global Plan to Stop TB 2016-20. Bending the Curve: A Global Investment Framework to Win the Fight against TB. 2015