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Abbreviations and acronyms

AMK	amikacin
BDQ	bedaquiline
BPaL	bedaquiline, pretomanid and linezolid
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
CFZ	clofazimine
DCS	D-cycloserine
DLM	delamanid
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
EMB	ethambutol
ETO	ethionamide
FQ	fluoroquinolone
HIV	human immunodeficiency virus
Hr-TB	isoniazid-resistant, rifampicin-susceptible tuberculosis
INH	isoniazid
LF-LAM	lateral-flow urine lipoarabinomannan assay
LFX	levofloxacin
LMIC	low- and middle-income countries
LZD	linezolid
M. tuberculosis	*Mycobacterium tuberculosis*
MDR/RR-TB	multidrug-resistant or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
MXF	moxifloxacin
NAAT	nucleic acid amplification test
NGS	next-generation sequencing
Pa	pretomanid
PHC	primary health care
POC	point of care
PPV	positive predictive value
pre-XDR-TB	pre-extensively drug-resistant tuberculosis
PZA	pyrazinamide
RIF	rifampicin
R&D	research and development
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
TPP	target product profile
USA	United States of America
WHO	World Health Organization
WRD	WHO-recommended rapid diagnostic
XDR-TB	extensively drug-resistant tuberculosis

Terminology and definitions

Drug resistance

Drug-susceptibility testing (DST) refers to in vitro testing of a strain of *Mycobacterium tuberculosis* complex using either molecular or genotypic techniques to detect resistance-conferring mutations; or using phenotypic methods to determine susceptibility to a medicine.

Isoniazid-resistant, rifampicin-susceptible tuberculosis (Hr-TB) refers to strains of *M. tuberculosis* complex that are resistant to isoniazid (INH) but susceptible to rifampicin (RIF).

Rifampicin-resistant tuberculosis (RR-TB) is caused by strains of *M. tuberculosis* complex that are resistant to RIF. These strains may be susceptible or resistant to INH (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB, and they are eligible for treatment with MDR-TB regimens.

Multidrug-resistant tuberculosis (MDR-TB) is caused by strains of *M. tuberculosis* complex that are resistant to at least RIF and INH.

Pre-extensively drug-resistant tuberculosis (pre-XDR-TB) is caused by strains of *M. tuberculosis* complex that fulfil the definition of MDR/RR-TB and that are also resistant to at least one fluoroquinolone (FQ), either levofloxacin (LFX) or moxifloxacin (MXF).

Extensively drug-resistant tuberculosis (XDR-TB) is caused by strains of *M. tuberculosis* complex that fulfil the definition of MDR/RR-TB and are also resistant to at least one FQ (LFX or MXF) and at least one additional Group A drug (bedaquiline [BDQ] or linezolid [LZD]).

Types of tests based on accessibility in peripheral settings

Peripheral setting refers (within the scope of this document) not to central or reference settings but instead to health care closer to where patients live (e.g. community centres, health clinics and microscopy centres). In these settings, point-of-care, near point-of-care and low-complexity tests can be performed, whereas more centralized, reference-type diagnostic tests cannot be performed.

Point-of-care (POC) tests refer to tests that do not require an instrument or any particular infrastructure in terms of electricity, equipment or cold chain and thus can be used in health care settings that do not have laboratories. Also, no special skills are needed to perform these tests. Some POC tests may require small ancillary devices such as mobile phone applications (apps) or compact portable readers. Examples of POC tests are dipstick or lateral-flow formats.

Near-POC tests can be instrument based, with the instrument preferably being battery operated and thus not requiring any special infrastructure. As with POC tests, these tests can be placed in health clinics that do not have laboratories, and they can be performed by health care workers with basic technical skills (e.g. basic pipetting) because they do not require precision. An example of a near-POC test is a portable nucleic acid amplification test (NAAT) platform.

Low-complexity tests are instrument based; thus, they are placed in peripheral laboratories (e.g. microscopy centres) and in some cases in health clinics that have basic laboratory infrastructure and staff with basic technical skills. An example of a low-complexity assay is a cartridge-based NAAT.

Executive summary

Tuberculosis (TB) remains one of the deadliest infectious diseases worldwide. Although there has been a positive trajectory in the number of diagnosed and treated cases, as reported in 2022 *(1)*, global TB targets remain unmet. The latest estimates highlight that, among the 10.6 million people estimated to have developed TB in 2022, only 7.5 million people were diagnosed; and although this is the highest reported number in nearly three decades, there is still a significant gap between the estimated number of people who develop TB each year and those who are actually diagnosed *(1)*. Action has been taken to narrow current gaps; however, there is still a need for increased development of innovative tools, including novel diagnostics to enhance case identification, improve the detection of drug resistance and guide the initiation of treatment.

In an effort to inform the priorities for research and development of TB diagnostics, the World Health Organization (WHO) published its first high-priority target product profiles (TPPs) for new TB diagnostics in April 2014 *(2)*. At that time, there were broader diagnostic needs *(2)*; however, four high-priority TPPs were identified and agreed upon by key stakeholders (**Box A**).

These high-priority TPPs for TB diagnosis provided detailed technical specifications and operational characteristics that are important to end users. Hence, they aimed to further inform and help to expedite the development of products addressing the greatest and most urgent public health needs at the time.

Box A. High-priority TPPs for new TB diagnostics released in 2014

- A rapid, biomarker-based, non-sputum-based test for detecting TB
- A community-based triage or referral test to identify people suspected of having TB
- A rapid, sputum-based test for detecting TB at the microscopy-centre level of the health care system
- A next-generation drug-susceptibility test to be implemented at the peripheral level of the health care system, to inform decisions about first-line treatment regimens

Since the release of these TPPs, WHO has embarked on a process of updating these targets, to steer the development of new tools and technologies for TB diagnosis. This updating process is intrinsic to the development of TPPs; for example, updates are made to account for novel technologies transitioning from the research domain and clinical evaluations to country introduction, and for the evolving needs specific to people with TB and communities affected by TB. Moreover, the initial time horizon proposed by WHO for the validity of high-priority TPPs has been reached.

Through this updating process, the TPPs have not only been adjusted to the current context, tailoring the targets to meet the needs of end users, but they have also been aligned with WHO's overarching strategic priorities. This includes the End TB Strategy (2016–2035) *(3)*, the Triple Billion targets *(4)*, and additional considerations to support primary health care and universal health coverage targets.

The present document comprises two currently valid TPPs, a newly updated TPP for a rapid test for TB detection and a second one, released in 2021, on next-generation DST for *M. tuberculosis (5, 6),* both to be carried out at the peripheral level. The updated and consolidated TPPs introduce, for the first time, definitions of point-of-care (POC) tests and near-POC tests, and it relates these to the class of low-complexity diagnostic technologies currently recommended. The rapid diagnostic TPP does not distinguish between sputum-based and non-sputum-based tests, meaning that either option would be suitable as long as the diagnostic tool meets the required target. Additionally, this marks the first WHO TB diagnostic TPP development process where a model-based approach was used to inform discussions on the performance and cost per test of the new tests.

Efforts in updating these TPPs brought together multidisciplinary professionals and stakeholders who contributed to this work through participation in Delphi consultation processes, public open calls to increase public engagement and consultations with technical experts. Stakeholder consultation meetings were convened for experts to objectively discuss and share their experience and views on these revised targets.

Box B below highlights some of the key changes that resulted from multiple levels of engagement with stakeholders during the revision and finalization of these TPPs.

Box B. Overview of changes discussed in updated TPPs for TB diagnostics

TPP on a diagnostic test to detect pulmonary TB at the peripheral level (the current 2024 update)

- prioritizes technology classes that can be accessible at the peripheral settings
- opens up the potential for a variety of technologies to develop solutions, either sputum or non-sputum, NAAT based or non-NAAT based (e.g. lateral-flow urine lipoarabinomannan assay [LF-LAM] biomarker)
- provides aspirational but realistic targets informed by modelling.

TPP on next-generation drug-susceptibility testing (DST) (2021 update) *(6)*

- the priority for testing of anti-TB agents now includes resistance testing of fluoroquinolones (FQs) and other Group A agents such as bedaquiline (BDQ)
- the target population is more inclusive, covering individuals of all ages who require drug-resistance assessment
- sample types have been revised to include other clinically relevant specimens for TB
- there are new considerations for time-to-result linked to treatment decisions.

WHO expects that these revisions will help to inform and guide stakeholders involved in developing TB diagnostics, including diagnostics manufacturers, product development partnerships, academics, funding agencies and other stakeholders.

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1. Introduction

The World Health Organization (WHO) estimates that more than 10 million people fall ill with tuberculosis (TB) each year *(1)*. The global incidence of TB is steadily declining and diagnosis is improving, with the number of bacteriologically confirmed TB cases having increased; however, there is still a large gap between estimated TB incidence and the number of cases newly diagnosed, with about 30% of cases being missed. TB diagnostic coverage has also increased in recent years, but only 47% of the 7.5 million people newly diagnosed in 2022 underwent testing with WHO-recommended rapid diagnostics (WRDs) used as the initial tests. Among people bacteriologically confirmed as having pulmonary TB in 2022, 73% (2.9/4.0 million) underwent further testing to determine rifampicin (RIF) resistance, an increase from 69% (2.4/3.5 million) in 2021 *(1)*. To compound the problem, drug resistance continues to be an additional threat owing to misdiagnosis and mismanagement, which, in turn, result in inadequate treatment regimens. In addition, interruptions in drug supply or poor treatment adherence are further amplifying drug-resistance patterns in *Mycobacterium tuberculosis* and the ongoing cycle of transmission. In 2022, for example, only 43% of people estimated to have developed multidrug-resistant or RIF-resistant TB (MDR/RR-TB) were diagnosed and enrolled on treatment *(1)*.

Realizing the vision of "a world free of TB" requires timely TB diagnosis to guide treatment and thus interrupt transmission. However, progress in the development of newer and better tests has been slower than expected, as has uptake of existing WRDs; for example, in some settings in low- and middle-income countries (LMIC), sputum smear microscopy remains the primary tool for TB diagnosis. Also, although the TB diagnostic pipeline has expanded considerably, there is still an urgent need to accelerate the global response by optimizing existing tools and intensifying research and development (R&D), as noted in the first TB diagnostic target product profiles (TPPs) released in April 2014 *(2)*, and as prompted by the End TB Strategy *(3)*. In this context, WHO has closely worked with key stakeholders in the identification of R&D priorities for TB diagnostics, and in the development and update of these global TPPs. The WHO TPPs can drive innovation by providing funders and developers with information that clarifies public health and programmatic perspectives on the performance and operational characteristics of therapeutics, vaccines, diagnostic products and other devices. In turn, this helps the global TB community to align R&D efforts with the needs of TB communities and government, global targets and priorities *(3, 4),* to rapidly detect *M. tuberculosis* and drug resistance at the most basic levels of care. Additionally, the TPPs help to improve collaboration and coordination in the development of novel diagnostic approaches.

The present document supersedes the 2014 high-priority TPPs for new TB diagnostics *(2)* and incorporates the chapter on next-generation drug-susceptibility testing (DST) at peripheral centres that was released in 2021 *(6)*. Moreover, these consolidated TPPs are intended to guide the next 5 years of development and move the field of TB diagnostics forward.

1.1 Objective and target audience

WHO TPPs are strategic reference documents that are intended to facilitate and accelerate the development of medical products and devices that address the greatest and most urgent public health needs. Therefore, the overall objective of these TPPs is to align the performance and operational characteristics of TB diagnostic tests at the peripheral level of the health care system with the needs of users.

The target audience comprises test developers and manufacturers interested in entering the TB diagnostic market, regulatory agencies, academia, research institutions, product development partnerships, nongovernmental organizations (NGOs), civil society organizations and donors.

1.2 Background

Rapid, more sensitive and accurate diagnostics that are used close to or at the point of care (POC) are a mainstay of modern medicine. For decades, diagnostic tests for the detection of *M. tuberculosis* generally performed poorly; however, in recent years, the field of TB diagnostics has seen advances in the form of new molecular tests. Although more sensitive diagnostics – especially nucleic acid amplification tests (NAATs) of low and moderate complexity – have emerged as a replacement for conventional microbiological methods *(7)*, these technologies are generally not suited for universal use at the peripheral level, such as primary health care (PHC) facilities. Diagnostic tests that are more responsive to the evolving needs of patient-centred care are needed; such tools include tests that are intended to be deployed at the most decentralized levels of care (i.e. where people first have contact with the health system), and that are affordable and accessible.

Rapid diagnostic tests for malaria emerged in the early 1990s *(8)*, and for HIV infection in the early 2000s *(9)*; in contrast, rapid diagnostic options for all presumed TB cases, at the peripheral level, are not yet available. In 2015, WHO recommended the use of the lateral-flow urine lipoarabinomannan assay (LF-LAM) to assist in the diagnosis of TB disease among individuals with HIV, under specific provisions *(10, 11).* Although LF-LAM gained high relevance as the first biomarker-based POC test for TB, because of its suboptimal sensitivity in other subpopulations, its use has been limited to HIV-positive individuals with signs and symptoms of TB, or with advanced HIV disease, or who are seriously ill *(7, 10, 11).*

The advancement of novel TB diagnostics faces many challenges, from the inherent nature of *M. tuberculosis* (i.e. its slow growth), to the challenges of TB diagnosis in various subpopulations (e.g. extrapulmonary, paediatric TB patients and individuals living with HIV, as well as people with drug-resistant forms of TB). In relation to the latter, accurate detection of drug resistance carries its own challenges, from the complex innate and acquired resistance mechanisms of *M. tuberculosis* to clinical reference points and reliable DST methods, particularly for the novel compounds and new treatment regimens. In addition, specific contextual factors further exacerbate diagnostic gaps; for example, in resource-constrained settings where there is a lack of infrastructure, trained personnel and access to diagnostic tools.

In envisioning novel and rapid diagnostic tests for TB, their design should consider the need to reduce loss to follow-up during the first encounter with health services, and during the time between diagnosis and initiation of TB treatment. Therefore, the optimum would be tests that detect *M. tuberculosis* and drug resistance to further support adequate treatment initiation. Such tests could improve TB programmes and patient care in two ways: first, they would increase the number of patients who are diagnosed and treated effectively, and thus reduce transmission; and second, they would reduce morbidity and mortality because patients would be diagnosed and treated earlier.

Although the level of complexity is only one of the elements that should guide R&D and subsequent deployment and implementation of a test, because of the conditions that prevail in high-burden settings, the simpler, easier to perform, more portable and more durable a test is, the more likely it is to be implemented in peripheral settings. Such tests also need easy sample preparation, minimal operational and maintenance requirements, and results that are easy to interpret, in a timely manner (to reduce turnaround time and thus help to decrease loss to follow-up).

1.2.1 Considerations for the update of the TPP for rapid diagnostic tests for TB in peripheral settings

Much has changed since 2014; hence, an update to the TB detection TPP was needed, taking into account the surge in new diagnostic technologies, sample types, portable instruments and innovative sampling strategies.

Worldwide, about 40% of pulmonary TB cases have not been bacteriologically confirmed,[1] highlighting a worrying overreliance on clinical diagnosis at the expense of providing targeted, timely and effective treatment regimens. This underscores the urgency of the need for rapid tests, especially in peripheral settings and hard-to-reach populations where there is little or no access to WRDs, referral mechanisms are inconsistent and health care providers mainly depend on clinical diagnosis.

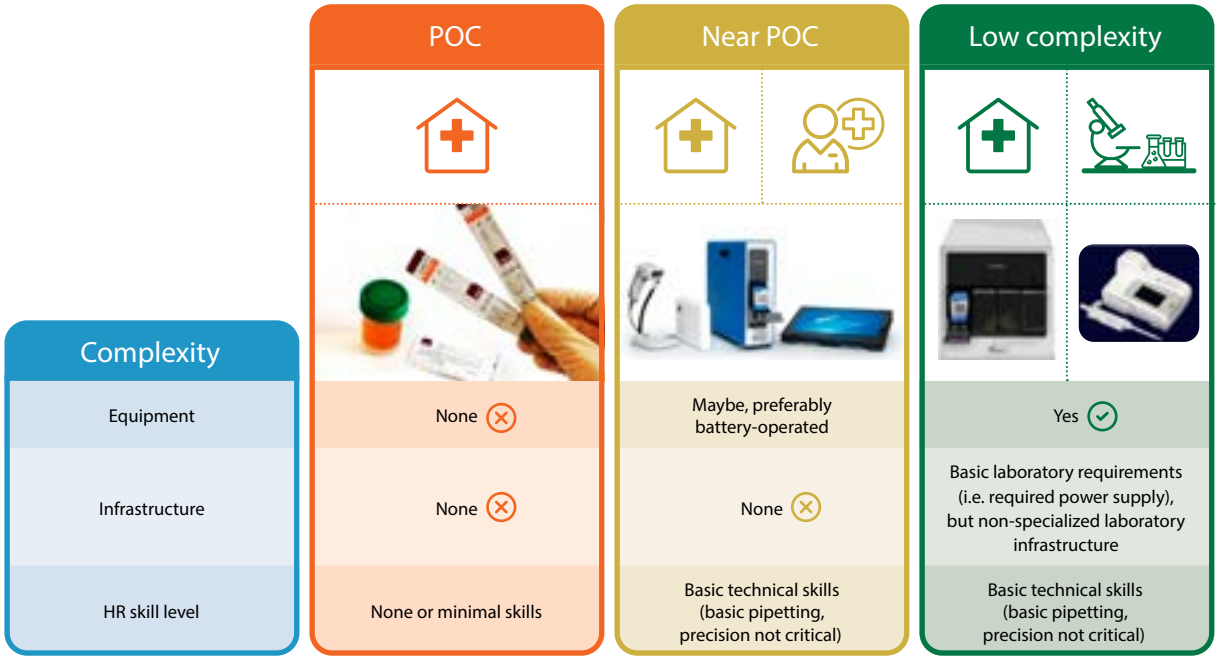
This updated TPP goes beyond the current TB diagnostic landscape, moving mainly laboratory-based sputum testing to non-laboratory-based testing using alternative sample types and technologies that are less sensitive but more accessible.

In 2023, WHO issued a standard on universal access to rapid TB diagnostics, providing 12 benchmarks across the diagnostic cascade to be adopted and tracked *(12)*. The standard emphasized the need to reach all individuals in need of testing, provide PHC access to testing with timely and quality-assured services, and achieve universal DST.

An important barrier to access, despite the availability of low-complexity assays, has been the design characteristics and costs of such technologies to be deployed at scale in PHC facilities where electricity may be unstable and environmental conditions are uncontrolled. This TPP has introduced, for the first time, POC and near-POC diagnostic definitions, relating them to the existing low-complexity diagnostic class. Ideally, what is needed is a test that can be used close to where those in need live; either a simple true POC test, akin to the rapid test used for HIV or, at the very least, a near-POC test that would be battery operated and would have sufficient throughput to meet the expected demand, while remaining affordable (**Fig. 1.1**).

[1] Of the 6.2 million people diagnosed with pulmonary TB worldwide in 2022, 63% were bacteriologically confirmed.

Fig. 1.1. TB diagnostic tests – proximity to health care and complexity



HR: human resource; POC: point of care.

[a] None or minimal skills refers to the minimal steps required for testing. Ideally, any person who has not done any test before can perform these tests and interpret the results. Examples of such tests include a urine pregnancy test and a self-test for COVID-19.

An additional barrier to TB testing, at the peripheral level, is sample collection. Testing for TB has typically been conducted using sputum; however, obtaining high-quality sputum samples, especially in certain patient groups (e.g. children, individuals with HIV infection or those with presumed extrapulmonary TB) has been challenging. Furthermore, the collection and processing of sputum or other respiratory samples (e.g. bronchoalveolar lavage) involves specific biosafety considerations for health care and laboratory staff, increasing the burden on health care infrastructure. Therefore, the performance of WRDs for detection of *M. tuberculosis* has been limited to their use on unprocessed (raw) or processed sputum samples, meaning that their diagnostic accuracy for non-sputum samples is limited.

Diagnostic tools such as Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Xpert Ultra) have been recommended for use in sputum (spontaneously expectorated or induced), nasopharyngeal aspirate or gastric aspirate samples; also, since 2021, stool specimens have been added to the list of samples for the diagnosis of TB in children *(13)*. The use of these tools represents substantial progress, but the use of a wider range of non-invasive or easily accessible samples would make testing more feasible in resource-constrained settings that lack sophisticated infrastructure. Simpler specimen collection (or, ideally, self-collectable specimens) would be more patient friendly, reducing discomfort, and improving accessibility, patient cooperation, and timely management and care in peripheral settings.

One additional consideration in developing novel TB diagnostics relates to extrapulmonary TB, which is estimated to account for about 17% of all TB cases worldwide *(14)*. Typically, extrapulmonary TB has been associated with diagnostic delays related to affected sites being inaccessible, the paucibacillary load in the biological specimens and increased long-term mortality.

1.2.2 Considerations for the update of the TPPs for next-generation DST for *M. tuberculosis* in peripheral settings

The landscape of TB treatment has changed dramatically over recent years, through the discovery of new TB drugs and newer combinations of drugs (sometimes including second-line drugs) that lead to more effective treatment regimens. Thus, there is an urgent need to prioritize R&D to address gaps in the detection of drug resistance.

In 2021, WHO evaluated a new regimen for the treatment of drug-susceptible TB. Instead of the usual 6-month regimen using RIF, isoniazid (INH), pyrazinamide (PZA) and ethambutol (EMB), the alternative is a 4-month combination regimen that includes a fluoroquinolone (FQ) *(15, 16).*

TB that is RIF-susceptible but INH-resistant (i.e. Hr-TB) is more common than MDR/RR-TB and is associated with poorer treatment outcomes *(17)*. However, Hr-TB goes largely undetected because of the lack of testing for INH resistance. In addition, Hr-TB requires treatment with an FQ; thus, there is an increasing need for upfront testing of resistance to RIF, INH and FQs *(18).*

Treatment regimens for drug-resistant TB (DR-TB) have changed markedly over the past 5 years, with the introduction of new medicines such as bedaquiline (BDQ), delamanid (DLM) and pretomanid (Pa), and the inclusion of repurposed medicines such as linezolid (LZD) and clofazimine (CFZ) *(18)*.

- A major advance in the management and care of DR-TB is the recommendation on the use of BPaL (BDQ, Pa and LZD) or BPaLM (BDQ, Pa, LZD and moxifloxacin [MXF]) as the first treatment option for all individuals with MDR/RR-TB who meet the eligibility criteria *(18)*. This all-oral 6-month regimen has shown excellent outcomes, even in people with pre-extensively drug-resistant TB (pre-XDR-TB), and is cost-effective. However, the introduction of new drugs and concerns over emerging drug resistance have made the development of rapid molecular tests more urgent.
- The 9-month regimen for MDR/RR-TB is still recommended for specific populations that currently do not meet the BPaL/BPaLM criteria. In this regimen, the injectable agent has been replaced by BDQ (used for 6 months), in combination with levofloxacin (LFX)/MXF, ethionamide (ETO), EMB, high-dose INH, PZA and CFZ for 4 months in the intensive phase. For those who are not eligible or for whom treatment was not successful on either the 6-month or 9-month regimen, an individualized regimen can be constructed, using all available drugs with known or presumed susceptibility *(18)*.

A next-generation drug-susceptibility test at the peripheral level will need to assist with regimen selection; hence, this TPP was updated to guide R&D and address relevant emerging needs. Novel diagnostic tests to be used at peripheral sites should ideally test for resistance to RIF, INH, FQs (MFX and LFX) and BDQ, to enable selection of the most appropriate treatment regimen. The prioritization of testing for these drugs is based on an assessment of the importance of each anti-TB agent in currently recommended regimens.

Changes in the treatment domain have been paralleled by rapid new developments in diagnostics technology. The first molecular tests that WHO has recommended for the rapid detection of drug resistance were based on reverse hybridization technologies; they provided accurate DST but required specialized infrastructure and skills. Since then, real-time molecular tests have been developed that can detect resistance to RIF and now to other drugs (e.g. INH and FQs). These tests can produce results in a matter of hours, are largely automated (thus requiring only basic skills) and do not require specialized laboratory infrastructure; hence, they can be placed at decentralized sites such as microscopy laboratories.

Ultimately, the detection of molecular drug resistance depends on a knowledge base of the mutations associated with drug resistance and their relative frequency in populations. To address this, WHO

has developed a catalogue of mutations and their association with resistance, by collating a large collection of isolate data with phenotypic DST and whole-genome sequencing results. The catalogue is aimed at developers and researchers, to allow new tests to be developed, and ensure consistent and robust interpretation of mutations for sequencing technologies *(19)*.

WHO now recommends targeted next-generation sequencing (NGS) methods that can provide comprehensive DST profiles covering multiple gene targets with nucleotide-level resistance information and are rapid enough to affect clinical decision-making. These products can detect resistance to the new and repurposed drugs, filling a major gap. NGS technologies vary in complexity and size, with some small enough to be handheld. However, further advances are required to simplify the testing procedures and the infrastructure needed.

As these treatment and diagnostic changes have evolved, WHO has revised the definition of extensively drug-resistant TB (XDR-TB) and introduced a new definition for pre-XDR-TB *(20)*. These changes were also driven by a change in the positioning of the second-line injectable agents, which are no longer considered core drugs for the treatment of DR-TB. Amikacin (AMK) was relegated to a Group C drug, whereas kanamycin (KAN) and capreomycin (CAP) are no longer recommended for use following an evidence review. The new definition was also updated to prioritize the Group A drugs that are now recommended as core drugs. The revised definitions are as follows:

- **pre-XDR-TB** is TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any FQ; and
- **XDR-TB** is TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any FQ and at least one additional Group A drug.

Those changes further support the need for an update of the TPP, because of the strong requirement for rapid and accurate testing for Group A medicines, and the relegation in the priority of injectable agents.

The prevalence of drug resistance in a population can vary owing to factors such as prior exposure, treatment practices in different regions, and the frequency of primary or acquired drug resistance. A study in five countries showed that the population-based point prevalence of FQ resistance was 4.4% or lower in four of the countries but 11.1% in the fifth *(21)*. In contrast, among people with RR-TB the point prevalence of FQ resistance was even higher, at 12.3–30.7%. Prior treatment history is also an important factor, with the prevalence of resistance to RIF and INH being higher among previously treated individuals than among those without a history of previous treatment. In addition, heteroresistance, which is uncommon for most drugs, is well-described for FQs and is therefore an important consideration for developers of drugs and diagnostics. Cross-resistance has also been observed; such resistance allows a single gene target to inform treatment-modifying decisions for more than one drug. Thus, for instance, mutations in the inhA promoter region are associated with resistance to ETO and INH, whereas mutations in the Rv0678 gene can lead to resistance to both BDQ and CFZ *(22, 23)*.

Another important consideration is the pre-existence of drug resistance to one or more drugs, because this can alter the likelihood of resistance to other drugs and affect test performance, depending on the population selected for testing. As an example, RIF is an indicator drug – if resistance to RIF is present, it is more likely that resistance to other anti-TB agents will be present. In a multicountry surveillance study, the point prevalence among cases with RR-TB was above 40% for PZA and above 65% for INH, but below 30% for FQs *(24)*.

Several factors make it essential to adopt appropriate and specific implementation strategies for any new TB assay being developed. These factors are the diversity of resources and needs in

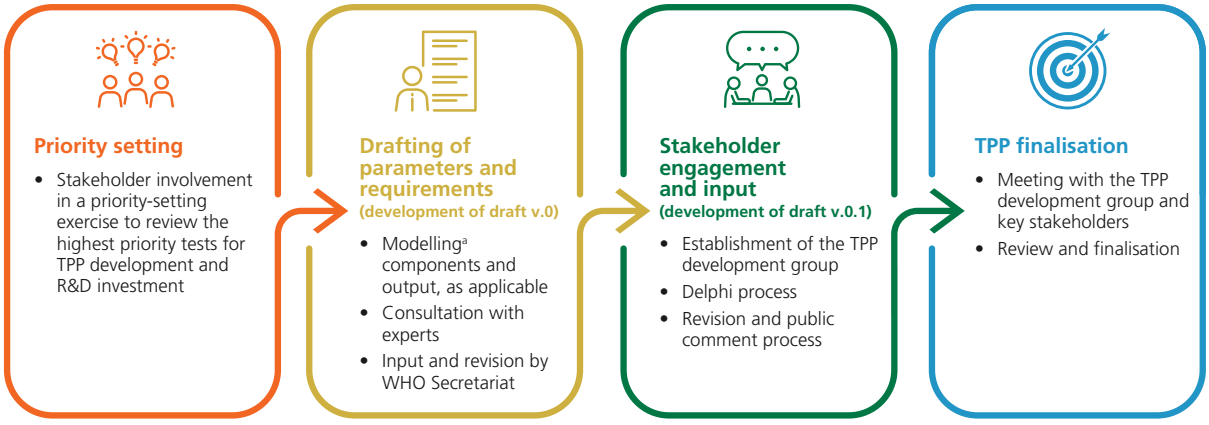
different countries; geographical variation in the epidemiology of TB and related comorbidities, and in DR-TB; and the specialized nature of the different technical procedures. Providing guidance for implementation strategies is beyond the scope of this document; however, the characteristics defined in the TPP should take into account the key steps in implementing and scaling up diagnostic tools *(25)*.

2. Methodology

This process of updating and consolidating advances the work conducted during the development of the first high-priority TPPs for new TB diagnostics *(2)*. Overall, these TPPs are the result of a consultative process among many stakeholders in the global health and scientific community . The methodology for the updating of the TPP on next-generation DST for *M. tuberculosis* has been published *(6)*; it is important to note that during the consolidation process, reformatting and minor editorial changes were made; however, the technical content of the TPP on next-generation DST remained unchanged. Additional processes for the development and updating of each TPP were employed where necessary; for example, in the current update for a diagnostic test for detecting *M. tuberculosis* in peripheral settings (**Fig. 2.1**), parameters related to performance and costs were informed through a modelling exercise.

The revised TPPs underwent a Delphi-like consultation and subsequent revision following several rounds of feedback and consultations. The draft TPPs were also made available for public comment on the WHO website before being finalized through a consultation that incorporated all of the feedback gathered throughout the process. More details are provided below.

Fig. 2.1. Overview of the process for developing and updating these TPPs



R&D: research and development; TPP: target product profile; WHO: World Health Organization.

[a] Of note, the modelling exercise was only implemented in the updating of the TPP for a rapid test for detecting *Mycobacterium tuberculosis* at the peripheral level.

2.1 Priority-setting process and drafting of the TPPs

Since the release of the TPPs in 2014, further work has been carried out to expand some of the earlier diagnostic needs *(26, 27)*; in addition, WHO has continued to engage diverse stakeholders and partners to gather feedback and keep diagnostic priorities up to date. For the current update,

various stakeholders were consulted on the current state of TB diagnostics and elements to be further prioritized, considering the main developments in the TB diagnostic pipeline and emerging needs noted earlier. The insights and expertise of professionals in TB diagnostics and clinical laboratory sciences were integral to the drafting phases, informing the delineation of the essential attributes within these TPPs.

2.2 Establishment of the Scientific TPP Development Group

A Scientific TPP Development Group was established for the updating[2] of the TPP on a rapid test for detecting *M. tuberculosis* at the peripheral level . The group comprised experts from high and low TB-burden settings, with experience in microbiology, mycobacteriology, molecular biology, health systems, pricing, procurement and regulation of medical devices, with balanced geographical and gender representation. It also included infectious disease specialists and scientists or researchers with a strong background and experience in TB diagnostics. In addition, to ensure that the perspectives and needs of TB patients and their communities were considered, representatives from civil society organizations participated in this process.

All members of the Scientific TPP Development Group participated in their individual capacity (i.e. they did not represent any external entity, authority or government). In compliance with the WHO standard procedures for declaration and assessment of interests, all members of the group were required to disclose any financial interests, relationships or activities that may be perceived as influencing their objectivity or decision-making in the context of the present work. All members therefore completed a WHO declaration of interest form and underwent an online background assessment to identify relevant matters that could give rise to an actual or ostensible conflict of interest, and that may have gone unnoticed or not reported during earlier assessments. Additionally, all experts were instructed to notify WHO of any change in relevant interests during the process. No significant conflicts of interest were noted for any of the members of the Scientific TPP Development Group.

2.3 Modelling of diagnosis accuracy estimates

A modelling exercise was carried out to evaluate and better inform the diagnostic accuracy estimates specified in the TPP for a rapid test for detecting *M. tuberculosis* at the peripheral level *(28)*.

The model was set to explore the nuanced trade-offs between enhanced testing accessibility and the variable accuracy of emerging diagnostic tools in the health care landscapes of India, Kenya and South Africa *(28)*. These countries were chosen because they have distinct patient pathways, diagnostic methodologies and population characteristics, making the modelling of new diagnostics across these diverse settings globally relevant. Three key diagnostic attributes – sample type (sputum versus non-sputum), testing site (POC, near-POC and settings with access to low-complexity testing) and result turnaround time – were integral components of the model. A baseline scenario traced the patient's journey from symptom onset to diagnosis, estimating required patient visits and potential attrition points from the health care system.

The results of this modelling exercise varied among the three countries because of differences in their patient pathways and existing standard of care (**Table 2.1**). The outputs indicated that novel POC tests, with minimum sensitivities of about 70% and 78% for non-sputum and sputum samples, respectively, could achieve comparable or superior case detection compared with the current standard

[2] For the update of the TPP on next-generation DST for *M. tuberculosis* at the peripheral level, WHO convened a group of about 70 experts from 25 countries during a stakeholder consultation in March 2021. Further details about the experts who participated in this process are available elsewhere *(6)*.

of care in each country *(28)*. The minimum acceptable test sensitivity values resulting from this model were considered during the Delphi-like consultation and public comment process, and were further discussed during the stakeholder consultation with the Scientific TPP Development Group (**Table 2.1**).

Table 2.1. Modelled estimates of the minimum acceptable sensitivity values

Countries	POC		Near-POC		Low-complexity assays	
	Sputum-based	Non-sputum-based	Sputum-based	Non-sputum-based	Sputum-based	Non-sputum-based
India	74%	70%	77%	71%	82%	77%
South Africa	78%	65%	86%	70%	91%	75%
Kenya	71%	59%	79%	65%	80%	66%
Proposed minimum	78%	70%	86%	71%	91%	77%

POC: point of care.

An approach of cost neutralization was used to formulate various pricing options, following initial input by stakeholders. The methodology involved using a preset budget envelope, or the total cost of testing a simulated cohort with a US$ 8 sputum-based low-complexity assay and a prevalence of TB in the tested population of 10%. The sensitivity estimates for each test type (sputum or non-sputum; and POC, near-POC or low-complexity assays) and the number of people that were expected to be reached with each different kind of diagnostic tool were derived from the information gathered through the modelling exercise *(28)*. Beginning with a baseline of US$ 8 for sputum-based, low-complexity tests – reflecting the currently available options – the analysis aimed to determine the threshold pricing for various scenarios to be cost-neutral, considering that some types of testing would increase the number of tests done. For optimal pricing, an aspirational stance was adopted, envisioning a future where costs for sputum-based, low-complexity tests would be lower. The baseline for sputum low-complexity tests was halved to US$ 4, serving as a starting point for further stratification based on different specimen types and health care settings. This approach was not intended to provide a definitive price point; rather, it was a starting point to facilitate informed discussions and decision-making. The goal was to understand the underlying principles of pricing, and seek a fair balance, considering diverse perspectives within the group.

Another analytical exercise involved maintaining the same budget envelope with the baseline case scenario using a US$ 8 price point for a sputum-based low-complexity assay, the same sensitivity estimates from the modelling, and the same underlying 10% prevalence of TB in the tested population, but increasing the detection rate by 30%. This increase in the detection rate was based on the assumption that the new tests will increase the amount of testing done while staying within the same budget envelope. In the earlier model, the focus was on simply changing the pricing for optimal scenarios by reducing it from US$ 8 to US$ 4, and then assessing the further stratification. However, using the budget neutralization approach and achieving a 30% increase in case detection, the optimal price indicated for a sputum-based low-complexity assay was US$ 4.90 (see **Annex 1** for further details).

2.4 Delphi-like consultation

Draft TPP documents were prepared to promote discussion between the different groups of stakeholders. Between 9 June and 10 July 2023, the draft document for the TPP for a rapid test for detecting *M. tuberculosis* at the peripheral level was shared through a Delphi-like consultation with experts from national TB programmes, reference TB laboratories, technical agencies

and researchers, implementers and clinicians, funding organizations, representatives from industry and patient advocates. The Delphi-like consultation for the TPP for next-generation DST was carried out from April to May 2019, with similar audiences.

For this process, the definition of consensus used was 80% agreement. Participants were asked to express their level of agreement on the proposed characteristics according to a predefined Likert scale ranging from 1 to 5 (1 – disagree, 2 – mostly disagree, 3 – neither agree nor disagree, 4 – mostly agree and 5 – strongly agree). An 80% cut-off was set as the threshold to indicate agreement with the parameters outlined in the TPP during the Delphi process. Participants were also asked to provide comments in support of their score (particularly when they did not agree and scored a characteristic at 3 or lower).

Overall, the outcomes of the Delphi process showed a high level of agreement for most of the attributes explored in these TPPs (see **Annex 1** and **Annex 2**). In the case of the TPP on next-generation DST, no (initial) agreement on either the minimal or optimal requirements was reached for the following characteristics: priority of anti-TB agents for testing, limit of detection for minor variants and indeterminate results during detection *(29)*. In addition, for the TPP on the rapid test, the most debated points were issues of pricing of individual tests and capital costs of the instrument, along with the initially proposed minimal time frame for time-to-result. However, consensus was achieved through successive iterations during the updating of these TPPs.

2.5 Public consultation and comment process

Proposed revised versions of the TPPs *(2)*, which incorporated changes made after the respective Delphi-like consultation, were shared online for public comment through the WHO DataForm. Draft version 0.1 of each of these TPPs was shared for at least[3] 28 days.

The intended audience included TB programme managers, laboratory specialists, clinical practitioners, implementers, researchers, representatives of civil society organizations and industry, and patient advocates. Comments were analysed quantitatively and grouped into themes when possible. Results of the public comment process are provided in **Annex 1** and **Annex 2**.

2.6 Scientific TPP Development Group consultation

A consultation of the Scientific TPP Development Group was organized on 13–14 September 2023. Feedback received through the online public comment process and the outcomes of the Delphi-like consultation were presented during the consultation for each TPP. The discussions involved a detailed analysis of public feedback and proposed revisions. This inclusive approach fostered information sharing, facilitated the exchange of perspectives, and allowed for clarification of various aspects, ensuring a comprehensive and well-informed decision-making process. Changes and suggestions made during the stakeholder consultation were incorporated into the final TPPs presented in **Section 3**.

2.7 Parameters used in the TPPs and trade-offs

Diagnostic manufacturers require TPPs at an early stage of the development process, so that they can be informed of the targets, technical specifications and diagnostic performance of the products. These parameters are set by a series of processes and consensus of stakeholders, keeping in mind

[3] The online public consultation for the TPP on a rapid test for detecting *M. tuberculosis* at the peripheral level was carried out from 31 July to 31 August 2023. The consultation for the TPP on next-generation DST at the peripheral level was carried out from 6 January to 4 February 2021.

the objective of the TPPs and their feasibility and utility for the end user. Each TPP has specific characteristics that refer to the measurable requirement or specification (e.g. diagnostic specificity, biosafety aspects, data interpretability and storage).

This document also provides both the "minimal" and the "optimal" outputs for each characteristic in the TPPs (**Table 2.2**). The minimal requirements are the lowest acceptable output for that characteristic, whereas the optimal requirements are more aspirational, but a realistically achievable output for that characteristic. The optimal and minimal characteristics define a range. Ideally, products should meet all of the minimal characteristics and as many of the optimal characteristics as possible.

Table 2.2. TPP definitions for "minimal" and "optimal" characteristics

Terms[a]	Definitions
Characteristic	A specific requirement or specification that is measurable.
Minimal	For a specific characteristic, "minimal" refers to the lowest acceptable output for that characteristic. To be acceptable, solutions must meet the minimal characteristic. However, a test may still be acceptable if shortcomings pertain to soft targets and if specific hard targets (marked with an asterisk) are missed only marginally.
Optimal	For a specific characteristic, "optimal" provides the ideal output that is believed to be realistically achievable. Meeting the optimal characteristics will provide the greatest impact for end users, clinicians and patients. Ideally, developers would design and develop their solutions to meet the optimal requirements for all characteristics.

TPP: target product profile.

[a] The optimal and minimal requirements and characteristics define a range.

It is expected that potential diagnostic products will meet all of the minimal requirements of the present TPPs, and as many of the optimal requirements as possible. However, potential trade-offs on performance, cost, impact and operational characteristics need to be considered for WHO policy; thus, the criteria or requirements outlined are indicative rather than absolute.

3. Target product profiles

3.1 TPP on a rapid test for detecting *M. tuberculosis* at the peripheral level

Table 3.1 provides the TPP for a rapid test for detecting *M. tuberculosis* at the peripheral level. In advancing the TB diagnostic pipeline, novel long-awaited tests are intended to be delivered at the most decentralized levels of care, where patients initially engage with the health system and within the community. These tests should utilize easily accessible samples and yield results within minutes or hours during a single clinical encounter, facilitating swift treatment decisions and mitigating the risk of patient loss to follow-up.

Table 3.1. TPP on a rapid test for detecting *M. tuberculosis* at the peripheral level

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Scope				
Intended purpose	A diagnostic test to detect pulmonary TB, at the peripheral level, to support initiation of TB therapy during the clinical encounter or on the same day in peripheral settings.	A diagnostic test to detect pulmonary TB and extrapulmonary TB with drug-resistance detection at the peripheral level, to support initiation of TB therapy during the clinical encounter in peripheral settings.	For drug resistance, manufacturers should refer to the DST TPP and should prioritize drugs (individually or in combination) based on the priority ranking and sequence of them appearing in the DST TPP.	*(6)*
Target population	Adults and adolescents presumed to have pulmonary TB, irrespective of HIV status.	Adults, adolescents and children presumed to have pulmonary TB or extrapulmonary TB disease, irrespective of HIV status.	Children have a limited ability to provide large volumes of respiratory specimens, which is a usual requirement for initial validation studies. Diagnosis of childhood TB is an important global health need; hence, a test that improves the diagnosis of TB in children will have significant benefits for individual patients. Therefore, where possible, manufacturers should try to expand their initial validation studies in children.	–
Target user of test	Health workers with basic technical skills (e.g. non-precision pipetting and minimal sample processing).	Community health workers or lay caregivers with minimal training.	Self-testing would be beneficial if a TB detection test is easy to perform, produces a rapid result and does not require laboratory infrastructure. Such testing involves people testing themselves in their own homes or in a separate room in the health care facility, and thus can reduce stigma.	–
Setting (level of the health care system)	Peripheral microscopy centres and primary health clinics.	Primary health clinics without laboratories at community level.	To reach people affected with TB and to decrease the diagnostic gap in the care cascade for TB, it is important to decentralize testing and have real POC tests that can be performed without specialized laboratory settings or technical skills. Additionally, to have an efficient linkage to care, these test results should be available in the same clinical encounter.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Pricing				
Price of individual tests (reagent costs only; at scale; ex-works)				
Low-complexity assay	≤US$ 8	≤US$ 5	The cost mentioned here refers to the cost per test, including the costs of reagents and consumables, but excluding the price of shipping and import, and any ceiling price (i.e. a price control imposed by a government). These price points were established based on modelling, then further rounded (see **Methodology** section); hence, they are indicative and not absolute. Ideally, the price of tests should be based on evidence of the actual cost of goods and estimated volumes, and a reasonable profit margin. Currently, an Xpert Ultra cartridge is priced at US$ 7.97, and the Molbio Truenat® MTB at US$ 7.90. A price that is higher than available technologies would be justified only if the cost is evidence based and the new test brings substantial added value in terms of improved performance, greater suitability for decentralization, clinical utility (i.e. improves decision-making) and the number of anti-TB agents for which the test can detect resistance. Ultimately, cost–effectiveness analysis considers whether a product demonstrates value for money; thus, it is more meaningful than a simple price point. However, a cost-effective product may be unaffordable, especially in high-burden, low- and middle-income settings, so providing an indicative price is helpful. The price of tests should be based on evidence of the actual cost of goods and estimated volumes, and a reasonable profit margin. Fair pricing can help to ensure access to tests while maintaining business interests. Such pricing requires transparency about the cost of goods and estimated volumes, and a reasonable profit margin.	*(28)*
Near-POC	≤US$ 6	≤US$ 4		
POC	≤US$ 4	≤US$ 2		

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Capital cost for the instrument	<US$ 2000	None (optimally, a POC test).	The lower the capital costs of the instrument, the lower the initial cost would be, and thus the lower the barrier to implementation, particularly given the sizeable number of instruments that would be distributed to peripheral centres. The cost of the instrument should be evidence based and should include warranties, service contracts and technical support. Cost–effectiveness should be evaluated during implementation, according to the simplicity of the technology, the maintenance and support required, and the multidisease options offered. Test developers and manufacturers could also consider offering different acquisition models, such as a reagent rental agreement or a cost-per-result model. The reagent rental agreement would allow for countries or end users to purchase the test at a set cost per test, including the machine, service, maintenance and technical support. Price would depend on volume of tests, including tests for different indications on multiplexing instruments, whereas the cost-per-result model includes the above plus any tests that do not provide an actionable result (e.g. invalid tests).	–
Performance				
Diagnostic sensitivity for TB detection				
Sputum, low-complexity assay	90%	≥95%	Accuracy estimates for TB diagnostic tests were evaluated using a modelling approach that assessed the trade-offs between test accuracy and increased access to testing; the evaluation provided evidence to inform this TPP document. Access to testing was modelled using specimen type (sputum or non-sputum) and level of health care setting (POC, near-POC and low-complexity assay). For example, providing tests that are non-sputum-based will increase access to testing for people who cannot produce sputum (e.g. children and people living with HIV).	*(28)*
Sputum, near-POC	85%			
Sputum, POC	75%			
Non-sputum, low-complexity assay	80%			
Non-sputum, near-POC	75%			
Non-sputum, POC	65%			
Diagnostic specificity for TB detection	>98% for a single test when compared with liquid culture.		–	–
Non-actionable (indeterminate + invalid) results	<5%	<3%	Non-actionable results include any test results that cannot be used to make a clinical decision. Results that have errors due to factors such as machine failure or sample processing would be considered non-actionable.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Treatment monitoring capability	Not required.	Preferrable.	An affordable test that can replace smear microscopy or culture conversion for treatment monitoring (e.g. can distinguish viable bacteria) is more likely to be adopted and to completely replace smear microscopy, and thus would have a larger market. The complexities of what a test should consider for treatment monitoring capability are captured in a separate TPP *(27)*.	–
Multidisease platform	No.	Yes.	Any technology entering this market should be able to diagnose diseases other than TB. The diseases to be targeted should be those included in the WHO list of poverty-related diseases; for example, communicable diseases (e.g. SARS-CoV2, HIV, malaria and HCV infection) and antimicrobial resistance activities (i.e. priority pathogens). Proper implementation strategies should be in place to select which additional diseases should be targeted along with TB in any given setting. Quality-assurance procedures need to be performed for each disease included in the platform; thus, multiplex testing on the same sample or the possibility of using the same platform for different tests is likely to increase the acceptability of the new assay.	–
Operational characteristics				
Sample and equipment requirements				
Sample type	Sputum or non-sputum samples that are not more complex to obtain than sputum.	Self-collectable clinical specimens.	Additional clinically relevant specimens for TB could be alternative sample types that can easily be collected (especially for different categories of people in whom sputum is difficult to obtain), and specimens for extrapulmonary TB. If specimen processing is required, it should be minimal. Optimally, self-collectable specimens in this category are those that do not require any isolation and are easy to collect in a non-laboratory-based health clinic.	–
Manual preparation of samples (steps needed after obtaining sample)	Up to 3 steps for pre-processing and running the test. No requirement for precise measuring and sampling.	Integrated sample preparation and detection in a closed system with minimal technical input.	There should be no need for precise volume control and timing. Only basic laboratory skills should be required to perform the tests, no specific analytical procedures based on additional instruments (e.g. DNA quantification, gel electrophoresis and serial dilutions). Ideally, the procedure should be fully automated.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Time-to-result	<60 minutes.	<15 minutes.	The need for rapid turnaround is affected by throughput capacity, sample preparation and analytical time. Rapid turnaround time is critical to reducing pretreatment loss to follow-up. A similar outcome can be achieved in different ways; for example, through batching of multiple samples for the same tests or of multiple samples for different tests, or the use of random access for testing. The ideal time-to-result (including sample preparation and processing time) has not been studied and might vary significantly between countries and between settings where patients are tested; however, a rapid test is more likely to be integrated into the workflow and result in a decision being made during the same visit. This parameter refers only to the time required from sample collection, processing and obtaining results from the test. Further downstream steps (e.g. passing on the results to the patient or the health care provider) are implementation steps and will vary depending on the health care setting and the country.	–
Daily throughput	≥8 tests.		The daily throughput needed in most peripheral centres is <10 tests per day. Daily throughput requirements must be considered with time-to-result and sample capacity in mind, because these characteristics are strongly interrelated. In the case of POC tests, which have a rapid time-to-result, this number might be higher or not applicable.	–
Sample capacity and throughput	It should be possible to test multiple samples at the same time and provide random access to testing.		Ideally, a single sample occupying the instrument should not stop the instrument being able to process other samples (i.e. random access or parallel analyses should be possible). If the platform is multiplexed, then it should be possible to run different assays at the same time.	–
Walk-away operation	No more than 2 steps of operator intervention should be needed once the sample has been placed into or on the test or system.	No instrument required.	Once the sample has been loaded into an instrument, further operator intervention should not be required until detection has occurred. This is related to the characteristics of sample preparation and assay processing (i.e. the steps needing to be completed after a sample has been obtained).	–
Biosafety	Requirements are similar to those for smear microscopy (low-risk TB laboratories).	Minimal infectious aerosol risk.	To be feasible to implement at the peripheral level, the infrastructure required for biosafety should be minimal. The technology must pose a low safety risk (comparable to that of microscopy) to health workers and others within the facility. Minimum biosafety requirements are described in WHO's Tuberculosis laboratory biosafety manual.	*(30, 31)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Waste disposal – solid	Should require no more than current WHO-endorsed TB assays at the peripheral level.	Should require less than current rapid molecular tests for TB, with reusable, recyclable or non-plastic alternatives to disposable materials.	Further information is provided in WHO's Tuberculosis laboratory biosafety manual. Ideally, increasing the amount of waste generated in comparison to that produced by smear microscopy should be avoided. Environmentally friendly, sustainable packaging that minimizes the environmental impact of packaging should be considered for the product's entire lifecycle.	*(30, 31)*
Waste disposal – infectious	Similar to those for smear microscopy (low-risk TB laboratories).	Less than smear microscopy (low-risk TB laboratories).	Low-risk TB laboratories are described in WHO's Tuberculosis laboratory biosafety manual. The baseline biosafety risk for managing infectious waste at the peripheral level should not be increased.	*(30, 31)*
Instrument	For instrument-based tests, build on a modular concept that allows tailoring to meet needs and to upgrade or add functionalities at any time.	No instrument required.	As a minimum, the tests should be using instruments that can be placed in a peripheral setting with basic laboratory infrastructure (e.g. low-complexity tests or near-POC tests, such as a test with a battery-operated reader). Optimally, the tests should be instrument-free POC tests.	–
Power requirements	Standard operating currents with built-in UPS for use in locations with variable power. Using battery-powered platforms or other forms of renewable energy (e.g. solar power) is preferrable.	Not applicable.	Continuous power is not always available, and in settings where power supply can be intermittent it can be difficult to find appropriate UPS solutions for a given instrument. UPS should be supplied with the instrument, and manufacturers must provide UPS that can meet the goal of ensuring enough power for a cycle to be completed. Also, optimally, it should be possible to switch the system to a battery-operated device that can be recharged, possibly using solar power (or another renewable source of energy where applicable).	–
Maintenance and calibration	Preventive maintenance after 1 year or >1000 samples, or after a maintenance alert. Need for calibration onsite annually by a technician with minimal training, or the instrument should calibrate itself.	No maintenance; instead, swap out or replace ancillary devices when needed. Can be calibrated remotely or no calibration is needed.	Maintenance and calibration represent two challenging points for any device that is placed at the peripheral level. A maintenance alert is necessary to ensure proper functioning in settings where different people may handle the device and where there may be difficulties in keeping records about the duration of use.	–
Regulatory requirements	Manufacturing of the assay and system should comply with ISO 13485 and with ISO 14971 or higher standards or regulations, and comply with IEC 62304; the manufacturing facility should be assessed at a high-risk classification and certified for use by one of the regulatory authorities of the founding members of the International Medical Device Regulators Forum (formerly known as the Global Harmonization Task Force); and the assay must be registered for in vitro diagnostic use.		See the following ISO publications: IEC 62304:2006 Medical device software – software life cycle processes ISO 13485:2016 Quality management systems ISO 14971:2019 Application of risk management to medical devices	*(32–35)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Operating environment, temperature and humidity level	Between +5 °C and +40 °C with up to 70% humidity. It is important to adequately protect optics from dust in these settings.	Between +5 °C and +50 °C with up to 90% humidity.	High environmental temperatures and high humidity are often present in countries where TB is endemic. In designing the tests, manufacturers should keep in mind the operating temperatures and humidity levels for intended settings. Diagnostic instruments or devices should be available for implementation in such settings.	–
Reagent kit – transport	No cold chain should be required, and samples should be able to tolerate stress during transport for at least 72 hours at –15 °C to +40 °C.	No cold chain required, and samples should be able to tolerate stress during transport for at least 96 hours at –25 °C to +50 °C.	Refrigerated transport is costly and often cannot be guaranteed for the entire transportation process. Delays in transport are commonplace.	–
Reagent kit – storage and stability	12 months at +5 °C to +35 °C with up to 70% humidity; samples should be able to tolerate stress during transport for at least 72 hours at +40 °C; no cold chain should be required.	2 years at +5 °C to +40 °C with up to 90% humidity; samples should be able to tolerate stress during transport for at least 72 hours at +50 °C; no cold chain should be required.	High environmental temperatures and high humidity are often present in countries where TB is endemic; they are especially problematic during the transport of reagents and systems. For new products, 12 months is acceptable, because evidence to support a longer shelf life will be unavailable initially.	–
Training and education	1 day for staff with the ability to perform low-complexity assays.	No training and education, or <1 day for caregivers or community health workers with minimal training.	–	–
Environmental impact	Minimize adverse impact on the environment.	Tests and any associated instruments should minimize adverse impacts on the environment; for example, by producing tests locally, minimizing waste and maximizing reusability and recycling of by-products, employing multiuse platforms, recycling instruments at the end of their life, and ensuring low power consumption and radiation emissions.	–	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Data requirements				
Built-in analytics (for instrument-based tests)	Analytics for instrument and test data should be built into the instrument; a PC should not be required.		Raw data (e.g. on trends, error codes, reasons for failures and internal controls) should be built into the instrument, to help in identifying any issues with the instrument or the test runs. Ideally, for a POC test with an ancillary instrument such as a mobile phone or small reader, it is preferable to also have built-in features for data analysis.	–
Result documentation, data display	Digital readouts to display assay details (including a results screen) and the ability to save and export results should be included.	Access to assay details (e.g. quick response code on a test device or POC tests to digitally record and report data) should be included.	Results should be simple to interpret (ideally automatically interpreted), document and display. Ideally, no instrument should be required; however, if POC tests have any ancillary readers or instruments, these should be able to give simple digital readouts for documentation and reporting of results.	–
Connectivity	All test and device data can be securely transmitted via a standard cable connection interface (USB, ethernet) or wireless connection, including at least one of the following: Bluetooth, Wi-Fi or mobile broadband modem (embedded or external). Data from the instruments should be compatible with different information systems at health facility level using industry standard formats or protocols.	For device-based tests, offline data storage should be available for data up to 3 months; it should be interoperable over WLAN and with information management systems. Non-device-based tests may have ancillary readers and other data capture apps.	A combination of connectivity interface and channel is recommended, given that the test settings and facility infrastructure at peripheral facilities and centres will vary. The full functionality of the test device should not depend on the availability of connectivity ports or solutions. Connectivity of diagnostic devices should allow for the visibility of data for reporting at both local and national levels, which can be used to further improve national programmes. Connectivity solutions associated with instruments should allow external solutions to be incorporated without affecting the functionality of the instrument.	–
Interoperability standards and format	Data (e.g. device usage data, error rates and number of invalid tests) can be exported in standard formats such as XML, CSV or a third-party instrument (e.g. USB).	As for the minimal requirements; in addition, transmitted data (including results) from devices should be encoded using HIE standards, including HL7 FHIR.	Interoperability standards are a set of rules and specifications for exchanging electronic health care data and include the HL7 and FHIR standards, to allow data to be shared across different health care information systems. WHO has incorporated HL7 FHIR into the foundation of WHO SMART guidelines, as a dynamic way of repackaging existing evidence-based guidance to inform countries' investment in digital systems.	*(36)*
Software and OS maintenance	As applicable, a POC device should allow for routine software or OS maintenance (automatically or manually).		Connected devices should be able to update automatically or manually at a time that is suitable for the user but with minimal downtime so that it does not affect testing throughput.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	Reference
Data storage	The institution (ministry of health or TB programme) administering the sites where tests are deployed should be able to specify or agree on the storage location of the device data, without affecting the support and optimal use of the device.		Data governance policies (e.g. those that ensure privacy protection, deidentification and anonymization) of test manufacturers and administrative institutions should align.	–
Data ownership	Test data and their management and ownership must be in compliance with local regulations.		–	–
Security and privacy	To facilitate use by health programmes in accordance with the laws, regulations and policies in their settings and with best practices, the device should provide configurable features so that personal data can be: • gathered transparently to users and people who are taking the tests, ensuring consent; • collected and processed only for purposes compatible with the health programme's purposes; • limited to what is relevant and necessary; • collected accurately; • stored in an identifiable form no longer than necessary; and • secured for integrity and confidentiality, with encryption at rest and in transmission.		The bullet points are adapted from article 5, section 1 of the European Union General Data Protection Regulation 2016/679 (GDPR).	*(37)*
Language support	For each country in which the test is deployed, one main language (e.g. the official or de facto national language) should be used, plus any language mandated by local regulatory or trade compliance requirements.	As for the minimal requirements; in addition, other languages that enable use by further residents of the location of deployment.	–	–

app: application; CSV: comma-separated values; DNA: deoxyribonucleic acid; DST: drug-susceptibility testing; HCV: hepatitis C virus; HIE: health information exchange; HIV: human immunodeficiency virus; HL7 FHIR: Health Level Seven International Fast Healthcare Interoperability Resources; IEC: International Electrotechnical Commission; ISO: International Organization for Standardization; OS: operating system; PC: personal computer; POC: point of care; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; SMART [in reference to WHO SMART guidelines]: standards-based, machine-readable, adaptive, requirements-based and testable; TB: tuberculosis; TPP: target product profile; UPS: uninterruptible power supply; USB: universal serial bus; WHO: World Health Organization; WLAN: wireless local-area network; XML: extensible markup language.

3.2 TPP on next-generation DST for *M. tuberculosis* at the peripheral level

In envisioning new diagnostics, new approaches could consider one solution for TB detection and DST. This TPP has taken the developers' perspective by assuming that new TB medicines and regimens will be implemented and available in parallel with current standard-of-care regimens, at least initially. This TPP also aims to provide support for timely and effective TB treatment in the context of the roll-out of new TB medicines and regimens, and to provide the characteristics and qualities of a test that would have a sufficiently rapid turnaround time for TB detection while also providing data about DST that can be used to inform treatment decisions.

Table 3.2. TPP on next-generation DST for *M. tuberculosis* at the peripheral level

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Scope				
Intended purpose	Diagnosis of TB disease and detection of drug resistance to provide rapid triage of patients and identification of adequate treatment regimen (first-line treatment versus second-line treatment).	Diagnosis of TB disease and detection of drug resistance to inform decision-making about the optimal (individualized) regimen.	The market for a test that includes TB detection and DST is all people with presumptive TB, which is about 10 times the number of detected cases, or about 60–70 million patients. If DST were performed in a second step, the market would be all individuals in whom bacteriologically confirmed TB had been detected (about 7 million people). The market for a test to detect BDQ resistance is different because the current achievable performance characteristics of a molecular test for BDQ resistance are still uncertain. Furthermore, BDQ is currently recommended for use in MDR/RR-TB patients only; therefore, a test for BDQ resistance could be used as a follow-on test only if RIF resistance has been confirmed (because a higher prevalence of resistance leads to a higher PPV for the detection of resistance to a particular anti-TB agent). Thus, the market for testing for BDQ resistance is as large as the number of patients confirmed to have MDR/RR-TB, which was about 206 000 in 2019, although the estimated number was much larger, at about 465 000 MDR/RR-TB incident cases.	–
Target population	People of all ages in need of evaluation for TB and those requiring drug-resistance assessment.		Children aged <11 years have limited ability to produce sputum for testing; therefore, initial validation studies should focus on adults and adolescents.	–
Target user of test[a]	Health workers with minimal or moderate training.	Health care workers with minimal training necessary.	Minimal training: users are health care workers with limited or no competency in general laboratory practice (beginner users). Moderate training: users are health care workers with minimal or moderate competency in general laboratory practice (competent or proficient users). The publication Competency guidelines for public health laboratory professionals was used to provide a term of reference.	*(38)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Setting (level of the health care system)	Peripheral level of the health care system.	Point of care.	Implementation at the peripheral level should be feasible using the specifications outlined. This would embed the test in an infrastructure that is based around smear microscopy. However, the test could also be implemented at higher levels of care. Testing for resistance to the anti-TB agents included in second-line treatment could be incorporated into separate reactions, but ideally it would be feasible to run this test on the same specimen. For optimal requirements, it is suggested that the test be at POC, with immediate accessibility for patients (e.g. bedside availability for any patient).	*(39–42)*
Priority of anti-TB agents for testing[a]	RIF + INH + FQs + BDQ (see information on BDQ in the explanatory notes). (FQs always include LFX and MFX.)	In order of decreasing importance: Minimal + 1. PZA+ LZD + Pa/DLM + CFZ 2. AMK + DCS 3. Any additional drug listed in the WHO treatment guidelines.	Drug prioritization considers the need for universal access to DST (as per the End TB Strategy) and that effective administration of TB treatment can be achieved only by knowing susceptibility testing results. This is a general principle that is becoming crucial, especially for the treatment of DR-TB. The proposed prioritization for minimal requirements considered the following: Impacts of undetected RIF and INH resistance on patient outcomes. FQs are relevant for both first-line and second-line treatment regimens, and resistance to these drugs is central to the updated definitions of pre-XDR-TB and XDR-TB. BDQ is now one of the medicines that define XDR-TB; it is a Group A medicine that is included in all DR-TB regimens (including the current shorter MDR/RR-TB regimens). New tests should inform decision-making for shorter and novel MDR/RR-TB treatment regimens. The differentiation of resistance among FQs is more a function of interpreting mutations (i.e. evaluating the hierarchical structure of mutations) than of detecting different mutations. **BDQ** is a high-priority drug, but relevant mutations associated with resistance are currently not fully elucidated. This is expected to change in the coming years. Furthermore, conducting DST for this medicine at the peripheral level may require alternative technological approaches compared with those used for other drugs (e.g. RIF). The optimal requirements are aimed to be aligned with the new WHO guidelines and to consider cross-resistance of certain drugs (e.g. BDQ and CFZ).	*(15, 20, 43)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
			Sequence of TB detection and drug-resistance testing: The proportion of patients diagnosed with TB who experienced pretreatment loss to follow-up is in the range of 4% to 38%. This scenario might vary substantially among countries. Initially, testing for TB and DST might come at the expense of the sensitivity for TB detection, depending on the platform used and cost of the test. However, a delay in DST might result in patients receiving inappropriate treatment until they return. In the interim, disease transmission may have occurred. The acceptability of a longer wait time might vary among countries, and informing the patient of results on the same day if the result is not available during the first visit might be associated with substantial costs.	
Assay design	The assay should be designed in such a manner that the addition or removal of analytes does not require extensive analytical and clinical reverification and revalidation of the assay.		The assay should be designed to be capable of being modified or upgraded as needed, with minimal redevelopment required. For sequencing-based assays, this should include the possibility to adjust sequence interpretation for new drugs. This is not a regulatory requirement; rather, it refers to the adaptability of the assay for updating and adding ntewer analytes.	–
Pricing				
Price of individual test, applicable to all public programmes, NGOs, international organizations in LMIC (includes the cost of reagents and consumables only, after scale-up, ex-works; excludes shipping and price subsidies. Ceiling price)[a]	RIF + INH + FQs: US$ 10–15. Adding BDQ (price not defined – see the explanatory notes).	RIF + INH + FQs: maximum US$ 5. PZA + LZD + Pa/DLM + CFZ (price not defined – see the explanatory notes). AMK + DCS (price not defined – see the explanatory notes).	The right to health contains entitlements that embrace access to basic health services; this includes early access to TB diagnostic tools and detection of drug resistance. The price of a test affects access and requires due consideration. Ideally, cost–effectiveness analysis should be performed because the results provide a framework for comparing the costs and benefits of a product against relevant comparators, including current practice. Ultimately, cost–effectiveness analysis considers whether a product demonstrates value for money; thus, it is more meaningful than a price point alone. Even a cost-effective product may be unaffordable, especially in high-burden, low- and middle-income settings, so providing an indicative price is helpful. A price range is provided for the minimal requirement with DST for RIF, INH and FQs, but these ranges are indicative not absolute. Ideally, the price of tests should be based on evidence of the actual cost of goods and estimated volumes, and a reasonable profit margin. Currently, the price of a single Xpert XDR-TB assay (for INH, FQs, second-line injectables and ethionamide) is about US$ 20. This test was originally aimed at MDR/RR-TB patients, but expanding this to all TB patients or all presumptive TB cases would substantially increase the market. A price that is higher than available technologies would be justified only if it is evidence based and the new test brings substantial added value in terms of greatly improved performance, greater suitability for decentralization, clinical utility (i.e. affects decision-making) and the number of anti-TB agents for which resistance can be detected.	*(44–49)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
			The **addition of BDQ-resistance detection** to the test would require special consideration because new types of technologies may be needed and the molecular basis of resistance has not been fully elucidated; thus, an indicative price could not be determined at this time. Furthermore, a price range for tests covering the "optimal" list of prioritized drugs could also not be provided because: • the price might vary depending on the number of drugs considered; and • there are no data for predicting the cost of assays testing for new drugs such as DLM, LZD and CFZ. The cost of phenotypic DST for first-line and second-line drugs is estimated to be in the range of US$ 50–100 (±30%). A new test should ideally be priced lower, based on evidence of the cost of goods and estimated volumes, and a reasonable profit. A price within the same range or higher would need to be evidence based and could be justified through a cost–effectiveness analysis. Ensuring access to tests while maintaining business interests can be achieved through fair pricing, which requires transparency of the cost of goods and estimated volumes, with a reasonable profit margin.	
Capital costs for the instrument (ceiling prices)	Less than US$ 20 000 (including warranties, service contracts and technical support – at least for 3 years).	Less than US$ 5000 (including warranties, service contracts and technical support – at least for 3 years).	The lower the capital costs of the instrument are, the lower the initial cost would be, and thus the barrier to implementation would also be lower, particularly since the volume of instruments that would be distributed to peripheral centres is sizeable. The cost of the instrument should be evidence based and should also include warranties, service contracts and technical support. Cost–effectiveness should be then evaluated during implementation according to the number of drugs and targets that a given technology can cover, the assay multiplexing and the multipurpose options offered. Additionally, test developers and manufacturers could consider offering different acquisition models, such as a reagent rental or a cost-per-result model. The reagent rental agreement would allow for countries or end users to purchase the test at a set cost per test, including the machine, service, maintenance and technical support (with price depending on volume of tests, including tests for different indications on multiplexing instruments), whereas the cost-per-result model includes the above plus any tests that do not provide an actionable result (e.g. invalid tests).	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Performance				
Diagnostic sensitivity for TB detection[a]	Sensitivity should be >80% for a single test when compared with 2 liquid cultures; for smear-negative TB it should be >60% and for smear-positive TB it should be 99%.	Sensitivity for detecting TB should be >95% for a single test when compared with 2 liquid cultures; for smear-negative TB it should be >68% and for smear-positive TB it should be 99%.	The sensitivity specified considers the currently available technologies as baseline.	*(50)*
Diagnostic specificity for TB detection[a]	Specificity should be >98% for a single test when compared with culture.	Specificity should be >98% for a single test when compared with culture.	–	*(51–53)*
Limit of detection – for DST	≤10^4 CFU/mL of sputum (or clinically relevant specimens).	≤10^2 CFU/mL of sputum (or clinically relevant specimens).	As a point of reference for CFU/mL, the corresponding smear status for the minimal requirement is a 1+ smear-positive specimen and for the optimal requirement is a smear-negative but TB-positive specimen (paucibacillary specimens). Limit of detection testing should be performed, as outlined in the US FDA's guidance document. For RIF, INH and FQs, smear-negative samples should also be detected as a minimum because current tests already achieve this.	*(54, 55)*
Analytical sensitivity for DST compared with genetic sequencing as the reference standard[a]	Sensitivity should be >98% for detecting targeted SNPs for resistance when compared with genetic sequencing.		For diagnostic assays based on NGS technology, currently there are no clear guidelines on the reference standard for such assays. In general, validating NGS results using different platforms plus different analysis pipelines is considered appropriate.	*(51–53)*
Diagnostic sensitivity for DST compared with phenotypic DST as a reference standard[a]	RIF: >95% sensitivity for detection of phenotypic resistance; INH, FQs: >90% sensitivity for detection of phenotypic resistance; BDQ, LZD, CFZ, DLM, Pa, AMK, PZA: ≥80% sensitivity for detection of phenotypic resistance.	RIF, INH, FQs, BDQ, LZD, CFZ, DLM, Pa, AMK, PZA: >95% sensitivity for detection of phenotypic resistance.	Modelling data suggest that for rapid DST to be more cost-effective than culture on a currently available platform it must attain an aggregated sensitivity of 88% for all clinically relevant mutations. A lower sensitivity could be tolerated for a test with high specificity, particularly if the prevalence, and thus the pretest probability, is high. The sensitivity achieved against a phenotypic internationally recognized reference standard (e.g. WHO, Clinical Laboratory Improvement Amendments) will only be as good as the mutations that are targeted (i.e. even if all known mutations conferring INH resistance are detected with 100% sensitivity when compared with a sequencing reference standard, 100% sensitivity cannot be achieved against a phenotypic reference standard because the knowledge of all molecular targets that confer resistance is incomplete). Frequency of mutations at different drug-resistant loci may vary depending on various factors (e.g. geographical region, local epidemiology and outbreaks); thus, implementation of molecular assays should carefully consider the local epidemiology to achieve the required sensitivity.	*(51–53)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Analytical specificity for DST compared with genetic sequencing as the reference standard[a]	Specificity should be ≥98% for any anti-TB agent for which the test can identify resistance when compared with genetic sequencing as the reference standard.		If alternative regimens are available, effective, safe and not too cumbersome, then a lower PPV might be tolerated. Because the pretest probability is low when individuals presenting without any additional risk factors are tested in settings with a low prevalence of resistance, the specificity must be very high. For example, if the prevalence of resistance is about 3% according to surveillance data, then a specificity of 99% results in a PPV of only 74%. A very high specificity (e.g. ≥99.7%) is thus necessary to reach a PPV of >90%. If the prevalence of resistance is ≥20% (e.g. when resistance to RIF is used as an indicator or when testing is only done in high-risk patients), a specificity of >97% is sufficient to achieve a PPV of 90%. Some mutations conferring resistance are systematically missed by current phenotypic reference standard methods, and some mutations are not associated with phenotypic resistance *(56)*.	*(57, 58)*
Diagnostic specificity for DST compared with phenotypic DST as a reference standard[a]	Specificity for mutations included for any anti-TB agent for which the test can identify resistance should be ≥98% when compared with the phenotypic reference standard recommended for each anti-TB agent.		The estimates of specificity for molecular tests in comparison with phenotypic testing as a reference standard might be falsely low because the reference standard has limited sensitivity. Therefore, it is important to use the optimized quality-assured phenotypic reference standard for a drug in comparison. Some mutations conferring resistance are systematically missed by current phenotypic reference standard methods, and some mutations are not associated with phenotypic resistance *(56)*.	*(51–53)*
Limit of detection of minor variants	≤20% (i.e. 20 resistant bacteria out of 100).	≤3% (i.e. fewer than 3 resistant bacteria out of 100).	This parameter is highly dependent on the bacillary load. Clinical relevance of minor variants is not fully understood.	–
Analytical specificity for TB detection	No cross-reactivity with other organisms including nontuberculous mycobacteria.		–	–
Indeterminate results during DST[a]	<10%	<3%	Indeterminate: inconclusive results that are valid; that is, where an adequate test result has been obtained, but the result is not clearly positive or negative. Invalid: inconclusive results that are invalid; that is, the key diagnostic feature cannot be interpreted or the actual result is missing.	–
Reproducibility for DST	The interassay coefficient of variance should be ≤10% at the high and low extremes of the assay for DST.		This applies if the quantitative outcomes of a test are measurable (e.g. limit of detection and cycle threshold values).	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Interfering substances	No interference should be caused by those substances known to occur in the human respiratory and pulmonary tracts, including blood that could potentially inhibit an assay (e.g. a PCR reaction), and substances used to treat or alleviate respiratory disease or symptoms.	No interference should be caused by different material for collecting swab-based and alternative paediatric specimens (e.g. stool).	–	–
Treatment monitoring capability	Not required.	Preferable.	A test that can replace smear microscopy for treatment monitoring (e.g. by detecting viable bacteria) is more likely to be adopted and to completely replace smear microscopy; thus, it would also have a larger market.	–
Multiuse platform	Yes (achievable).	Yes (demonstrated).	Any technology entering this market should be able to diagnose relevant diseases other than TB. The diseases to be targeted should be those among the WHO list of poverty-related diseases; for example, communicable diseases such as SARS-CoV2, HIV, malaria, HCV infection and antimicrobial resistance activities (i.e. priority pathogens). Proper implementation strategies should be in place to select which additional diseases should be targeted along with TB in any given setting. Quality-assurance procedures would need to be performed for each disease included in the platform; multiplex testing or the ability to use a platform to perform different tests will probably increase the acceptability of the new assay.	–
Operational characteristics				
Sample type	Sputum and other clinically relevant specimens for TB, including (but not limited to) gastric aspirate, induced sputum, nasopharyngeal aspirate and stool.	Unprocessed sputum and additional clinically relevant specimens for TB or other targeted diseases (see "Multiuse platform").	Additional clinically relevant specimens for TB could be alternative sample types that can easily be collected (especially for categories of patients where sputum is difficult to obtain), and specimens for extrapulmonary TB. There should be minimal specimen processing involved, if required.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Sample volume processed by the test	0.5–2 mL	0.1–10 mL	The lowest volume possible for all types of samples ideally would be 0.1 mL, especially since HIV-positive patients and paediatric populations may have difficulty providing a sample. Similarly, if a higher volume is available, the test should be able to use that higher volume if doing so would increase sensitivity. This is especially relevant for extrapulmonary samples, which may need an additional concentration step before testing. **However, in both high and low volume specimens, performance should not come at the expense of decreased sensitivity.** At a minimum, the test should be able to meet performance requirements with clinically relevant specimens with volumes of 0.5–2 mL, as used by current tests. The test should need only 1 sample. Any follow-on steps or reactions should not require additional samples.	–
Manual preparation of samples (steps needed after obtaining sample)[a]	≤5 steps.	≤1 step.	There should be no need for precise volume control or precise timing. Only tests that require basic and simple laboratory skills are suited to peripheral level centres; no specific analytical procedures based on additional instruments should be required (e.g. DNA quantification, gel electrophoresis and serial dilutions). The procedure should take advantage of automation as much as possible.	*(41, 42)*
Reagent integration	No specific indications, but refer to reagent kit storage and stability for restrictions.	All reagents should be contained in a single device.	–	–
Time to result[a]	<6 hours for detection and DST; achieve next-day treatment decisions.	<30 minutes for detection and DST (<2 hours acceptable); achieve same-day treatment decisions.	The need for rapid turnaround is affected by throughput capacity and duration of testing. Rapid turnaround time is critical to reducing pretreatment loss to follow-up. A similar outcome can be achieved in different ways; for example, through matching of multiple samples for the same tests or multiple samples for different tests, or by using random access for testing. The time-to-result (defined as time for sample processing through test completion, excluding storing time for batching) is probably the most important parameter because extending the wait time for too long may result in patient loss to follow-up. The minimal criterion has been increased, considering newer technologies such as NGS that are currently unable to meet the previous criterion of <2 hours but would provide DST to multiple drugs simultaneously. In coming years, all technologies should be able to produce test results in <6 hours; this is critical because peripheral settings usually keep 6–8-hour work-days. Finally, because patients are unlikely to wait longer than 30 minutes for a test result, any wait longer than that will typically lead to results being delivered the following day.	*(59, 60)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Daily throughput	≥ 10 tests.	≥25 tests.	The daily throughput needed in most peripheral centres is <10 tests per day. Daily throughput requirements must be considered with time-to-result and sample capacity in mind, because these characteristics are all highly interrelated.	–
Sample capacity and throughput	Batching should be possible.	Multiple samples should be able to be tested at the same time; random access should be possible.	Ideally, a single sample should not occupy the instrument without that instrument still being able to process other samples (i.e. random access or parallel analyses should be possible). If the platform is multiplexed, then running different assays at the same time should be feasible.	–
Walk-away operation	No more than 1 step of operator intervention should be needed once the sample has been placed into or on the system.	These features are required; there should not be a need for operator intervention once the sample has been placed into or on the instrument.	Once the sample has been loaded into an instrument, then further operator intervention should not be required until detection has occurred. This characteristic is related to the characteristics for sample preparation and assay processing (i.e. the steps needing to be completed after a sample has been obtained).	–
Biosafety	Requirements are similar to those for smear microscopy (low-risk TB laboratories).		To be feasible to implement at the peripheral level, minimal infrastructure for biosafety should be required. It is unlikely that biosafety cabinets will be available. The technology must pose a low safety risk (comparable to that of microscopy) to health workers and others within the facility. Consult the minimum biosafety requirements as described in WHO's *Tuberculosis laboratory biosafety manual (30)*.	*(30, 61)*
Waste disposal – solid	Should require no more than current WHO-endorsed TB assays at the peripheral level.	Should require no more than current rapid molecular tests for TB, with reusable, recyclable or non-plastic alternatives to disposable materials.	Further information is provided in WHO's *Tuberculosis laboratory biosafety manual (30)*. Increasing the amount of waste generated in comparison to that produced by smear microscopy should ideally be avoided. Environmentally friendly, sustainable packaging minimizing the environmental impact of packaging should be considered for the product's entire lifecycle.	*(30)*
Waste disposal – infectious	Similar to those for smear microscopy (low-risk TB laboratories).		Low-risk TB laboratories are described in WHO's *Tuberculosis laboratory biosafety manual (30)*. The baseline biosafety risk for managing infectious waste at the peripheral level should not be increased.	*(30)*
Instrument	For instrument-based tests, build on a modular concept that can be tailored to meet needs and upgraded with additional functionalities at any time.	For instrument-based tests, this ideally would be a single integrated system that is modular, to allow throughput to be increased if necessary.	This characteristic only applies to instrument-based tests. It is not a recommendation that a test be instrument based. Ideally, a single device is preferred but modular solutions would be acceptable (e.g. for separate sample processing and detection).	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Power requirements[a]	Capable of running on standard electricity plus an ad hoc certified UPS unit delivered with the system, to enable a cycle to be completed in case of a power outage; a circuit protector must be integrated within the system; the UPS should be integrated within the system where possible; and the system should be compatible for switching to a battery-operated device with the ability to run for at least 1 day on the battery and to be recharged.	Capable of running on standard electricity plus an ad hoc certified UPS unit delivered with the system to enable a cycle to be completed in case of a power outage; the UPS and circuit protector must be integrated within the system; and the system should be compatible for switching to a battery-operated device with the ability to run for 1 day on the battery and to be recharged (e.g. solar-powered).	Continuous power is not always available at the level of a peripheral centre, and the use of electrical devices in settings where power supply can be intermittent has been challenging in terms of finding appropriate UPS solutions suitable for a given instrument. UPS should be included with the instrument, and manufacturers must provide UPS capable of meeting the goal of ensuring enough power for a cycle to be completed. Also, in the optimal situation, it should be possible to switch the system into a battery-operated device that can be recharged, possibly using solar power (or another renewable source of energy where applicable).	*(41, 42)*
Maintenance and calibration[a]	Preventive maintenance should not be needed more than once a year. Users should be able to monitor the machine status independently from manufacturers' intervention by using appropriate internal or external controls; results for such controls can be shared with manufacturers or appropriate control bodies to schedule appropriate on-demand intervention (maintenance or calibration); an alert should be included to indicate when maintenance is needed according to manufacturers' indications; software updates should be provided remotely.	Preventive maintenance should not be needed more than once every 2 years. Users should be able to monitor the machine status independently from manufacturers' intervention by using appropriate internal or external controls; results for such controls can be shared with manufacturers or appropriate control bodies to schedule appropriate on-demand intervention (maintenance or calibration); an alert should be included to indicate when maintenance is needed according to manufacturers' indications; software updates should be provided remotely.	Maintenance and calibration represent two challenging points for any device to be placed at the peripheral level. A maintenance alert is necessary to ensure proper functioning in settings where it is unlikely that the same person will always handle the device and that records will be kept about the duration of use. It is essential that only simple tools and minimal expertise are necessary to perform maintenance, given the number of devices that are likely to be used; additionally, service visits are unlikely to be feasible outside of urban settings. The cost of maintenance should be low and service agreements should be included in the cost.	–

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Data analysis	Exported data should be analysable on a separate or networked PC.	Data analysis should be integrated into the device; a PC should not be required; exported data should be capable of being analysed on a separate or networked PC.	–	–
Result documentation, data display	An integrated results screen and the ability to save results should be included; the device should have a commonly used interface port (e.g. USB or USB-c port).	An integrated results screen and the ability to save and print results should be included; the device should have a commonly used port (e.g. USB or USB-c port).	Results should be simple to interpret (e.g. positive versus negative for TB detection, or present versus absent for drug resistance). Information that would allow a more detailed interpretation of results should be available (e.g. information on the mutations detected) for surveillance purposes or more differentiated clinical decision-making; however, it should be possible to hide this information if necessary.	–
Regulatory requirements	Manufacturing of the assay and system should comply with ISO 13485 and with ISO 14971 or higher standards or regulations, and comply with IEC 62304 (Medical Device Data Systems); the manufacturing facility should be assessed at a high-risk classification and certified for use by one of the regulatory authorities of the founding members of the International Medical Device Regulators Forum (formerly known as the Global Harmonization Task Force); and the assay must be registered for in vitro diagnostic use.		–	*(35, 62, 63)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Data export (connectivity and interoperability)	There should be an integrated capability for all data to be securely exported from the device in a user-friendly format (including data on the use of the device, error rates or rates of invalid tests, and non-personalized results) over a USB port; Bluetooth connectivity should also be available, and it should be possible to import data (e.g. software for updating interpretation rules or databases).	All data should be able to be securely exported (including data on the use of the device, error rates and rates of invalid tests, and personalized, protected results) over a USB port and network; network connectivity should be available through an ethernet, Wi-Fi or GSM/UMTS mobile broadband modem, or a combination of these; results should be encoded using a documented standard (e.g. HL7) and be formatted as JSON text; JSON data should be transmitted through HTTP or S-HTTP to a local or remote server as results are generated; results should be stored locally and queued during network interruptions to be sent as a batch when connectivity is restored; Bluetooth connectivity should also be available; and it should be possible to import data (e.g. software for updating interpretation rules or databases).	Mobile phone capacity is frequently available even at the level of peripheral centres. This could be leveraged for data export, quality control, supply-chain management and surveillance. Because the systems will be implemented in peripheral centres, data connectivity should be adapted to the actual situation (data transfer cannot rely on high-speed internet connectivity, and the format of the data should be adapted accordingly). Data export must include raw data and interpreted results, allowing further re-analysis in case of updated interpretation guidelines. Connectivity solutions associated with instruments should be nonproprietary, so that external solutions can be incorporated. Where cloud-based storage solutions (or third-party hosting) are included, they should be compliant with country regulations and must be able to be turned off without affecting instrument functionality.	*(61, 64, 65)*
Electronics and software	These should be integrated into the instrument.		If an external device (e.g. a separate PC, tablet or mobile) is needed, it will probably limit the ability to update software, because not all peripheral centres have staff with the skills needed to operate a PC. Furthermore, theft or misplacement can be an issue, and separate PCs should have a mechanism for secure placement.	–
Operating environment, temperature and humidity level	Between +5 °C and +40 °C with up to 70% humidity. It is important to adequately protect optics from dust in these settings.	Between +5 °C and +50 °C with up to 90% humidity.	High environmental temperatures and high humidity are often present in countries where TB is endemic. Instruments or devices fit for use in tropical conditions should be available for implementation in such settings.	*(61, 66)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Reagent kit – transport	No cold chain required; should be able to tolerate stress during transport for at least 72 hours at –15 °C to +40 °C.	No cold chain should be required; should be able to tolerate stress during transport for at least 72 hours at –15 °C to +50 °C.	Refrigerated transport is costly and often cannot be guaranteed for the entire transportation process. Frequent delays in transport are commonplace.	*(41, 42, 67)*
Reagent kit – storage and stability	12 months at +5 °C to +35 °C with up to 70% humidity; should be able to tolerate stress during transport for at least 72 hours at +40 °C; no cold chain should be required.	2 years at +5 °C to +40 °C with up to 90% humidity; should be able to tolerate stress during transport for at least 72 hours at +50 °C; no cold chain should be required.	High environmental temperatures and high humidity are often present in countries where TB is endemic; they are especially problematic during the transport of reagents and systems. For new products, 12 months is acceptable, because evidence to support a longer shelf life will be unavailable initially.	*(61, 66)*
Additional supplies (not included in kit)	None.	None.	–	–
Internal quality control	Full controls for sample processing, amplification and detection of TB and any target for detection of resistance should be included; internal controls for analysis and reporting (e.g. software version) should be included; a monitor (remote) system for checking results on the controls should be also considered.		The system should be compliant with external controls.	*(66, 68)*
Training and education	3 days (or 24 work-hours) for staff at the level of a laboratory technician.	6 work-hours for staff at the level of a microscopy technician.	Training should be developed according to continuing education and training models and individualized training programmes, to ensure that only properly trained, accredited people can perform the assay. Online and remote support systems should be available for retraining, monitoring or evaluating, and updating ("refresher") training. All the phases of the training should be properly documented. All training and instructions for use must be fully available in English, and ideally in multiple other languages as well.	–

AMK: amikacin; BDQ: bedaquiline; CFU: colony forming unit; CFZ: clofazimine; DCS: D-cycloserine; DLM: delamanid; DNA: deoxyribonucleic acid; DR-TB: drug-resistant TB; DST: drug-susceptibility testing; FDA: Food and Drug Administration; FQ: fluoroquinolone; GSM: Global System for Mobile Communications; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HTTP: hypertext transfer protocol; IEC: International Electrotechnical Commission; INH: isoniazid; ISO: International Organization for Standardization; JSON: JavaScript Object Notation; LFX: levofloxacin; LMIC: low- and middle-income countries; LZD: linezolid; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; MDR/RR-TB: multidrug- or rifampicin-resistant TB; MFX: moxifloxacin; NGO: nongovernmental organization; NGS: next-generation sequencing; Pa: pretomanid; PC: personal computer; PCR: polymerase chain reaction; PPV: positive predictive value; pre-XDR-TB: pre-extensively drug-resistant TB; PZA: pyrazinamide; RIF: rifampicin; S-HTTP: secure hypertext transfer protocol; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; SNP: single nucleotide polymorphism; TB: tuberculosis; TPP: target product profile; UMTS: Universal Mobile Telecommunication System; UPS: uninterrupted power supply; US: United States; USB: universal serial bus; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

[a] These characteristics were considered to be the most important.

4. Conclusion

It is crucial to adopt current WRDs; however, on its own this will be insufficient to fully achieve the WHO standard for universal access to rapid TB diagnostics *(12)*. Technologies that are fit for purpose at the PHC level, along with the use of alternative sample types, are likely to be critical going forward. To support new product development for the detection of TB and drug resistance at the peripheral level of the health care system, WHO updated these TPPs to guide R&D targets and priorities for funders and developers.

The pursuit of innovative TB diagnostic tools is underscored by a shared commitment to address the longstanding impact of TB, marked by high preventable mortality. Providing TB patients with new, effective tools requires ongoing collaboration, research and innovation as we collectively endeavour to enhance diagnostics and care. Rapid identification of affected individuals, detection of drug resistance and timely provision of appropriate treatment are, therefore, pivotal to advancing the broader global health agenda. Although recent years have seen advances in the TB diagnostic pipeline for detecting *M. tuberculosis* and drug resistance, important gaps remain. Hence, there is a need for improvements to existing technologies or the development of new technologies that can be used closer to the level of patient care, are priced affordably for LMIC and can provide an accurate, rapid and comprehensive solutions for diagnosing TB and for DST.

Additionally, addressing current challenges effectively and sustainably requires a multifaceted strategy that integrates technological innovation with considerations of scalability, affordability and adaptability to diverse clinical presentations of TB disease, with attention to specific populations. In an optimal scenario, diagnostic tests for TB and drug resistance would satisfy all defined needs and requirements as set out in these TPPs; however, achieving such a level of alignment across multiple stakeholders and end users would be unrealistic. By aligning with basic principles of universal health coverage and considering potential trade-offs, the updated TPPs strive to guide the development of TB diagnostic tools that are not only technically sound and practical but also accessible, equitable and aligned with the broader global health goals.

In summary, it is crucial to recognize that the criteria outlined in these TPPs are indicative rather than absolute. As we navigate the path forward, collaboration among stakeholders, ongoing research and sustained innovation will be vital for overcoming challenges and realizing the ambitious targets set for TB diagnostics and care. This acknowledgement underscores the dynamic nature of health care development, where responsiveness to evolving needs and contexts is integral and where the criteria serve as guideposts rather than rigid constraints.

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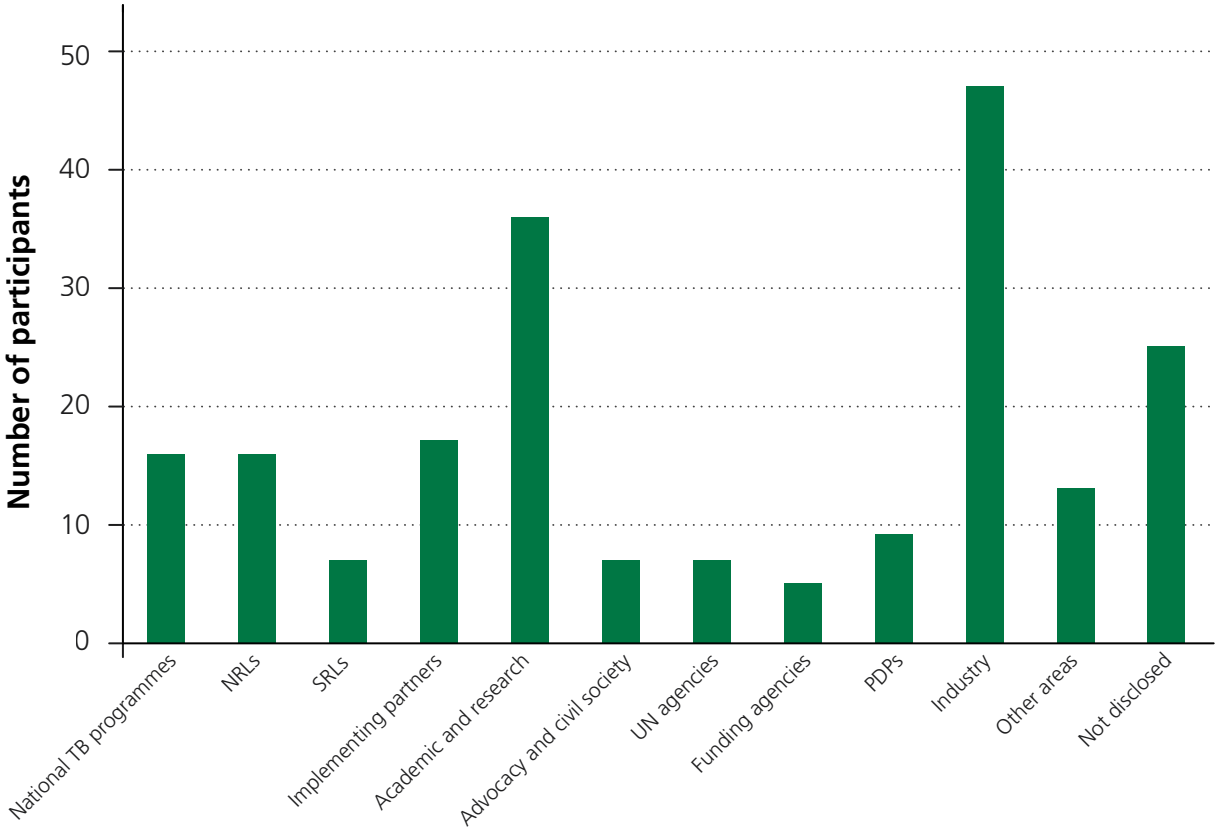
Annexes

Annex 1. Overview of the results of the Delphi-like consultation and WHO public comment process for the TPP on a rapid test for detecting *Mycobacterium tuberculosis* at peripheral level

The initial draft target product profile (TPP) for a rapid test for detecting *Mycobacterium tuberculosis* at peripheral level was subjected to a Delphi-like consultation and WHO public comment process, to facilitate consensus building. Forty-nine experts took part in the Delphi-like consultation, and 362 individuals expressed interest in participating in the public comment process and accessed the TPP. Of those accessing the public comment platform, 57% (205 individuals) granted consent to participate and provided input (**Fig. A1.1**).

A meticulous consolidation process distilled key themes from individual comments collected via the Delphi-like consultation and online public comment process. Overall, participants demonstrated a high level of consensus throughout the process. A summary of the key areas of discussion and subsequent modifications to the draft TPP is provided below.

Fig. A1.1. Overview of participation and distribution of responses by sector (*n*=205)



NRL: national reference laboratory; PDP: product development partnership; SRL: supranational reference laboratory; TB: tuberculosis; UN: United Nations.

Summary of comments

In general, the feedback gathered through these processes aligned closely with most of the proposed characteristics in this TPP, with slight variations. There were a few exceptions for some characteristics, where some respondents expressed differing views on specific areas of the TPP; these are expanded on below.

Scope

The feedback showed 85% agreement on minimal characteristics and 91% agreement on optimal characteristics for the key assumptions in this TPP, and 100% agreement for specifications under the rationale and goal of the TPP. However, those responding on the public comment platform sought clarification on the inclusion of detection of extrapulmonary TB, and on batching of samples[4] and considerations for drug resistance.[5] In response, the Scientific TPP Development Group further revised this section, and consolidated key assumptions, rationale and goals into "intended purpose".

[4] As batching of samples at peripheral settings is considered suboptimal, members of the Scientific TPP Development Group opted to remove the term "batching".

[5] As for the considerations for drug resistance (as presented under the rationale considerations), this should exclusively be seen under an aspirational (optimal) scenario; also, there is a separate TPP on next-generation drug-susceptibility testing.

Target population

The proposed target population initially included adults with presumed pulmonary TB, regardless of HIV status, as a minimal requirement, whereas children and individuals with extrapulmonary TB were considered under optimal requirements. Delphi results showed 83–92% agreement on these requirements. However, clarification was needed regarding the definition of presumed TB. The group suggested adding adolescents to the minimal requirement (owing to similarities in TB manifestation with adults) and giving attention to children (emphasizing validation studies and tailored regulatory indications).

Performance characteristics

The initial modelling informed the accuracy of estimates specified in the TPP, with minimal criteria ranging from 70% for non-sputum samples taken at the point of care (POC) to 90% for sputum samples to be tested through low-complexity assays. An aspirational threshold of 95% or higher was set as an optimal target (**Table A1.1**). One concerning area was that of referencing high minimal standards, which could pose challenges for diagnostic manufacturers attempting to meet these targets. The group discussed what would be the minimally acceptable sensitivity value that would not compromise the primary objective of accurately identifying and confirming TB patients. Revised sensitivity estimates are provided in **Table A1.1**.

Table A1.1. Main changes proposed to the domains under the performance section

Diagnostic sensitivity for TB detection	Initially proposed estimates		Revised estimates	
	Minimal	Optimal	Minimal	Optimal
Sputum, low-complexity assay	90%	≥95%	90%	≥95%
Sputum, near-POC	85%		85%	
Sputum, POC	80%		75%	
Non-sputum, low-complexity assay	80%		80%	
Non-sputum, near-POC	75%		75%	
Non-sputum, POC	70%		65%	

POC: point of care; TB: tuberculosis.

Multidisease testing capacity was discussed further under test performance. The Delphi-like consultation achieved 81% and 87% agreement for minimal and optimal targets, respectively. Although such testing is highly desirable, the group had reservations, owing to lack of evidence on use of platforms and tests. The group confirmed that multidisease testing is not required for the minimal profile.

Operational characteristics

The discussion on operational characteristics emphasized the need for tests that are rapid, simple and easy to use, and that require easy-to-collect samples that are clinically relevant. During this process, consensus emerged on sample types, with 87% agreement for both sputum and non-sputum samples as minimal requirements, and a robust 94% for non-invasive, preferably self-collectable clinical specimens under optimal conditions. However, questions arose regarding blood as a specimen and challenges related to specimen collection for extrapulmonary TB. The group made further revisions to the proposed text for the purposes of clarification and simplification. Additional comments or considerations on the use of non-sputum samples are provided in the explanatory notes of the TPP.

In relation to the manual preparation of samples, only a 77% agreement was reached on the minimal requirements, with feedback highlighting the need for streamlining post-sample collection steps,

with two to three steps favoured for optimal efficiency; the group favoured a reduction to only two to three steps.

Extensive discussions focused on the acceptable time-to-result under both scenarios. There was significant agreement (85%) on the optimal time-to-result of less than 30 minutes. However, there was only 56% agreement on the proposed minimal time frame of 3–4 hours. The group encouraged further reduction in the minimal requirement, specifically endorsing a time frame of less than 60 minutes. Additionally, within the optimal scenario, the recommendation was extended to achieving results in less than 15 minutes. The draft TPP text initially posited that both minimal and optimal requirements for daily testing capacity (daily throughput) should be equal to or greater than 10 tests per day. Initially proposing a daily testing capacity of 10 tests, the Scientific TPP Development Group reconsidered because of concerns about achieving this within an 8-hour workday, aligning it with the minimal turnaround time of less than 60 minutes. Consequently, the daily throughput was amended to eight tests per day, to ensure consistency. Concerning "maintenance and calibration", the results of the Delphi-like consultation revealed an 85% agreement on the proposed minimal requirements and a 77% agreement on the optimal requirements. Maintenance and calibration parameters, with 85% agreement on minimal requirements and 77% on optimal scenarios, were further clarified to specify maintenance frequency and annual onsite calibration requirements as part of the minimal requirements; also, a maintenance-free approach was introduced for optimal scenarios.

Pricing

The initially proposed pricing for individual tests varied based on specimen type and setting, starting at a baseline of US$ 8 for low-complexity assays with sputum, and decreasing for non-sputum POC tests (**Table A1.2**). The results of the Delphi-like consultation showed about 50–60% agreement on proposed prices, with feedback suggesting a need to round off the proposed figures and advocating for lower pricing, particularly for POC tests. The online public comment process echoed these sentiments, emphasizing that prices were perceived as being too high, with suggestions to reduce them to as low as US$ 5, especially for sputum-based tests. However, contrasting views suggested that non-sputum tests should be priced the same as sputum tests or higher. The group aimed to balance these perspectives, while ensuring fair pricing to incentivize innovation. They guided this discussion using a cost-neutralization approach described in the **Methodology** section. The pricing requirements were further modified, as shown in **Table A1.2**. Additionally, the group highlighted that the price should be related to the production costs or cost of goods, and that only a high cost of production could justify higher prices.

Table A1.2. Main changes proposed for the section on pricing

Initially proposed text, informed by the cost-neutral approach (as presented in the Delphi-like consultation)		
Pricing	**Minimal**	**Optimal**
Sputum, low-complexity assay	$8.00	$4.00
Sputum, near-POC	$7.70	$3.80
Sputum, POC	$7.00	$3.60
Non-sputum, low-complexity assay	$6.80	$3.50
Non-sputum, near-POC	$6.30	$3.30
Non-sputum, POC	$5.70	$2.80
Note: The pricing figures presented above resulted from the cost-neutral approach; they were later revised, as shown below, to incorporate the suggestions and comments made by experts.		
Revised text, after the Delphi-like consultation		
Diagnostic sensitivity for TB detection	**Minimal**	**Optimal**
Sputum, low-complexity assay	$8.00	$4.00 ($4.92)
Sputum, near-POC	$7.50	$3.50 ($4.65)
Sputum, POC	$7.00	$3.00 ($4.38)
Non-sputum, low-complexity assay	$6.00	$3.00 ($4.92)
Non-sputum, near-POC	$5.00	$2.50 ($4.10)
Non-sputum, POC	$4.00	$2.00 ($3.83)
Note: The pricing figures given above were adjusted subsequent to the Delphi-like consultation and public comment process. Figures within parentheses, corresponding to the optimal scenario, reflect a secondary cost-neutralizing exercise, in which a 30% increase in case detection was assumed, consequently elevating the overall price of the test.		
Final pricing figures included in the TPP for TB detection		
Diagnostic sensitivity for TB detection	**Minimal**	**Optimal**
Low-complexity assay	$8.00	$5.00
Near-POC	$6.00	$4.00
POC	$4.00	$2.00

POC: point of care; TB: tuberculosis; TPP: target product profile.

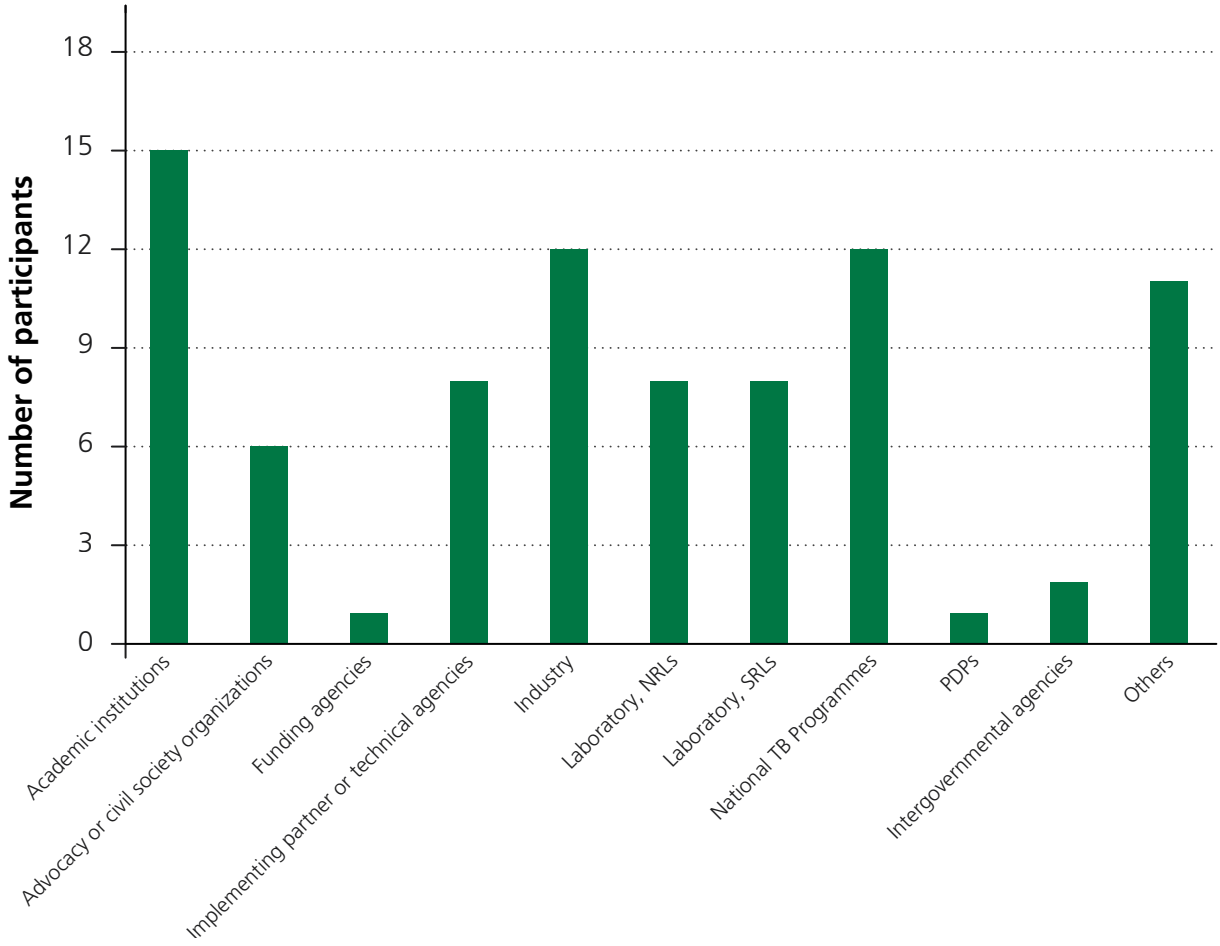
Regarding instrument costs, in the context of minimal requirements it was specified that the capital cost could be up to US$ 1000. Conversely, in an optimal scenario, it was articulated that there would be no costs associated with the instrument, aligning with the aspiration for an instrument-free POC test. The results of the Delphi-like consultation showed that there was only 52% agreement on the specified cost. Public comments also suggested that the initial range of US$ 1000 for minimal requirements was unrealistic, with recommendations proposing a wider range, from US$ 3000 to US$ 7000. The group recognized the challenge of establishing a suitable cost range for the instrument, highlighting its dependence on factors such as volume, consumables and operational considerations. These factors were duly acknowledged and reflected in the revised capital cost for the instrument under minimal requirements.

Annex 2. Overview of the results of the WHO public comment process for the TPP on next-generation drug-susceptibility testing (DST) for *Mycobacterium tuberculosis* at peripheral level

To finalize the revised TPP document, in January 2021, WHO launched an online public comment process to obtain feedback from a wide range of stakeholders. The process aimed to ensure that proposed changes were objective and balanced in terms of the needs and values of patients and other end users, and of industry.

Through this process, stakeholders were invited to comment and share their views on the scope, target users or use setting, pricing, test performance and operational characteristics. Stakeholders were also invited to provide additional comments and questions on the proposed updated TPP. A total of 128 individuals accessed the call for public comment, of whom 82 agreed to participate. **Fig. A2.1** provides an overview of the sectors represented by participants.

Fig. A2.1. Distribution of responses by sector (*n*=82)



NRL: national reference laboratory; PDP: product development partnership; SRL: supranational reference laboratory; TB: tuberculosis.

Summary of comments

Overall, the survey comments did not differ widely from the proposed TPP, and most were relatively minor. For a few specific areas in the TPP, divergent views were expressed by multiple respondents; these areas were as follows:

- giving higher priority to new drugs, particularly pyrazinamide (PZA), because the TPP is intended to provide guidance for the next 5 years;
- expanding the target population to include children, using paediatric-friendly samples such as stool if needed; and
- lowering pricing criteria to levels that are more realistic for low-income countries.

Finally, there were some specific comments on diagnostic performance that also require attention.

Scope

Five respondents stated that PZA must be assigned higher importance, given its role in many regimens, including for people living with HIV. One respondent stated that the "optimal requirements" (optimal) first level should also include bedaquiline (BDQ), linezolid (LZD), clofazimine (CFZ) and PZA. Two respondents stated that pretomanid (Pa) should replace CFZ in the optimal second level, whereas three respondents said it should simply be added to the regimen. One respondent suggested including delamanid (DLM) with BDQ, LZD and CFZ in the optimal second level, given its role in shortened paediatric regimens; another suggested adding D-cycloserine to the optimal third level. For the "minimal requirements" (minimal), one respondent stated that first level should include fluoroquinolones (FQ), four respondents stated that BDQ ± LZD should replace amikacin (AMK) in the third level, and one stated that BDQ and CFZ, with or without LZD, must be included.

Target population

Four respondents stated that the target population must be expanded to include children, noting that stool works well as a sample. Five respondents suggested that stool and other WHO-recommended extrapulmonary samples be included and mentioned in explanatory notes.

Performance characteristics

Three respondents suggested changing the optimal limit of detection to 10 colony forming units (CFU)/mL to align with Xpert® MTB/RIF Ultra (Xpert Ultra), and one noted that a limit of detection of 10^4 is too high for many people living with HIV.

Regarding TB detection sensitivity, stated criteria were generally seen as too low. Separately, respondents stated that sensitivity must be equal to Xpert Ultra and higher than existing tests (and much higher in smear-negative cases). However, one respondent suggested that the criteria for minimal smear-positive should be at least 95%. Drug-susceptibility testing (DST) sensitivity compared with a sequencing reference standard will differ for each drug, so a uniform requirement may be unrealistic. Compared with a phenotypic reference standard, DST sensitivity of more than 95% for all drugs is probably not feasible; instead, it would be acceptable to update targets as genetic information is elucidated (two respondents). Exceptionally, rifampicin (RIF) sensitivity should be more than 98% and PZA minimal sensitivity should be more than 90%.

Regarding DST specificity, performance criteria are needed for the case of composite reference standards (phenotypic and sequencing combined). For analytical specificity, respondents were both appreciative and ambivalent that non-tuberculous mycobacteria were mentioned.

The optimal limit of detection for minor variants should decrease to 1%, aligning with the mycobacterial growth indicator tube (MGIT™), and decrease to less than 5% for the minimal requirement, because this is critical for understanding treatment success (three respondents).

Concerning indeterminant DST results, one respondent stated that the optimal value must decrease to less than 1%, while another believed that these stringent values would stifle test development. One respondent suggested including distinct values for smear-positive and smear-negative cases. Three respondents stated that reproducibility criteria should decrease to less than 5%.

Operational characteristics

Five respondents (from academia, implementing partners and professional medical societies) raised concerns about the possibility of high costs if daily throughput is low, and suggested that distinct options for low and high incidence settings should be specified. The definition of optimal should decrease to 10 tests or fewer, and for minimal it should be changed to 11–25 tests. Three implementing partner respondents did not want batching considered, citing concerns about waiting to test.

Pricing

Individual test pricing was thought to be too high for low- and middle-income countries (LMIC) by six respondents from India, Japan, the Netherlands (Kingdom of the) and the United States of America (USA), representing academia, advocacy, implementing partners and industry. Pricing should be based on cost of goods sold and volume, not on the ability to pay or value (two respondents from academia and advocacy). Suggested minimal prices for RIF and isoniazid (INH) were US$ 10–15 (one respondent, advocacy) and US$ 18–25 (one respondent, industry). Suggested optimal prices for RIF/INH were less than US$ 5 (two respondents, advocacy and industry) and less than US$ 5 (one respondent, industry). Optimal pricing suggestions for RIF/INH/FQ/AMK were less than US$ 10 (two respondents, advocacy and industry) and US$ 15–20 (one respondent, industry).

One industry respondent disagreed with the approach of setting minimum prices, because this may stifle innovation. One advocacy respondent stated that basing non-culture DST pricing on culture is unreasonable; instead, pricing should be based on the cost of existing molecular tests.

Considering the limited ability of low-income countries to pay, four respondents (from academia, government, industry and implementing partners) stated that instrument costs must decrease, and three stressed the need to prioritize generic or universal instruments that will only require limited updating. New service and delivery models could be considered; for example, reagent rental models that include instrument and maintenance spread over a large volume of tests. One industry respondent noted that costs are unrealistically low for individual tests, and unrealistically high for equipment, maintenance and warranties.

Additional comments

Two respondents highlighted ambiguity regarding the minimal target user, noting that the required level of qualification would vary depending on whether the individual is conducting the test (e.g. a health worker) or interpreting the results (e.g. laboratory personnel or other health worker); this was further clarified through the consensus process. Two respondents stated that treatment monitoring capability was unnecessary. Separately, respondents asked for distinct performance specifications for asymptomatic and symptomatic patients, and for the list of interfering substances to be expanded to include other respiratory pathogens and flora, transport media and stool. One respondent suggested adding guidelines regarding product longevity. Another suggested that the instrument should run

in non-air-conditioned temperatures, while another stated that it must be able to withstand high levels of ambient dust. One respondent stipulated that minimal battery power should be 24 hours.

Turnaround time should be decreased, and the goal should be a rapid test format that could be performed at the POC or bedside. Five respondents considered the minimal time to results as being too long, suggesting times of 4–6 hours (one respondent) and less than 2 hours (three respondents); also, optimal timing should decrease to less than 30 minutes.

Respondents separately noted that maintenance should be inexpensive, achievable by local staff and included in the cost of equipment; also, that equipment manufacturers should have at least one support person available in each WHO region. Another respondent thought that these criteria were not feasible. Regarding training, three respondents suggested reducing the minimal time to 2 days or less, and one mentioned the need for training for maintenance and software updates.

Four respondents mentioned a desire for reusable, recyclable or non-plastic alternatives to disposables. One respondent suggested changing biosafety and all waste disposal requirements to those of rapid molecular tests rather than microscopy. Another suggested referencing basic laboratory supplies (e.g. pipettes and a timer), which may be unavailable at peripheral settings. One respondent suggested adding a data export criterion for reporting results to clients, while two respondents suggested adding requirements for virus or malware protection and data security.

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