Target product profiles for tuberculosis screening tests

World Health Organization

Target product profiles for tuberculosis screening tests

World Health Organization

Target product profiles for tuberculosis screening tests

ISBN 978-92-4-011357-2 (electronic version)
ISBN 978-92-4-011358-9 (print version)

Suggested citation. Target product profiles for tuberculosis screening tests. Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Design by Inis Communication

Contents

Acknowledgements

This document on target product profiles (TPPs) was prepared by staff of the World Health Organization (WHO) Global Programme on Tuberculosis & Lung Health (WHO/GTB) – namely, Cecily Miller, Dennis Falzon and Nazir Ismail – under the guidance of Matteo Zignol and the overall direction of Tereza Kasaeva, Director of WHO/GTB.

WHO thanks the members of the Scientific TPP Development Group for their contribution (in alphabetical order): Chukwuma Anyaike (National TB, Leprosy and Buruli Ulcer Control Programme, Nigeria), Helen Ayles (London School of Hygiene & Tropical Medicine [LSHTM], United Kingdom of Great Britain and Northern Ireland [United Kingdom]), Ramon Basilio (National TB Reference Laboratory, Research Institute for Tropical Medicine, Philippines), David Branigan (Treatment Action Group, United States of America [USA]), Adithya Cattamanchi (University of California, Irvine, USA), Daniela Maria Cirillo (WHO Collaborating Centre and TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Italy), Frank Cobelens (University of Amsterdam, Netherlands), Jacob Creswell (Stop TB Partnership), Claudia M. Denkinger (University of Heidelberg, Germany), David Dowdy (Johns Hopkins Bloomberg School of Public Health, USA), Petra de Haas (KNCV Tuberculosis Foundation, Netherlands), Rumina Hasan (Aga Khan University, Pakistan and LSHTM, United Kingdom), Cathy Hewison (Médecins Sans Frontières, France), Jamilya Ismailova (Abt Associates, Civil Society Representative, Tajikistan), Davaalkham Jagdagsuren (Mongolia National Centre for Communicable Diseases, Mongolia), Rajendra Panduranga Joshi (Ministry of Health and Family Welfare, India), Gulmira Kalmambetova (National TB Programme [NTP], Kyrgyzstan), Jacqueline Kisia (NTP, Kenya), Katharina Kranzer (LSHTM, United Kingdom), Rhea Lobo (independent health journalist, Denmark), Peter MacPherson (University of Glasgow, United Kingdom), Sandeep Meharwal (FHI 360 Asia Pacific Regional Office, Thailand), Paolo Miotto (WHO Collaborating Centre and TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Italy), Troy Murrell (Clinton Health Access Initiative, USA), Ruvandhi Nathavitharana (Harvard Medical School, USA), Norbert Ndjeka (Department of Health of South Africa, South Africa), Van Hung Nguyen (National TB Reference Laboratory, National Lung Hospital, Viet Nam), Mark Nicol (University of Western Australia, Australia), Rustam Nurov (NTP, Tajikistan), Shaheed Vally Omar (National Institute for Communicable Diseases, WHO Supranational TB Reference Laboratory, South Africa), Madhukar Pai (McGill University, Canada), Tiffany Tiara Pakasi (NTP, Indonesia), Zhi Zhen Qin (Stop TB Partnership, Switzerland), Paulo Redner (National TB Reference Laboratory, Oswaldo Cruz Foundation, Brazil), Andriansjah Rukmana (University of Indonesia, Indonesia), Anastasia Samoilova (National Medical Research Centre on Phthisiopulmonology and Infectious Diseases, Russian Federation), Mahafuzer Rahman Sarker (TB–Leprosy and AIDS/STD programme, Bangladesh), Siva Kumar Shanmugam (National Institute for Research in TB, India), Thomas Shinnick (independent laboratory consultant, USA), Nicole de Souza (NTP, Brazil), Willy Ssengooba (Department of Medical Microbiology, Makerere University, Uganda), Sabira Tahseen (National TB Reference Laboratory, Pakistan), Diana Vakhrusheva (National Medical Research Centre of Phthisiopulmonology and Infectious Diseases, Russian Federation), Dinh Van Luong (National Lung Hospital, Viet Nam) and Zhao Yanlin (National Center for Tuberculosis Control and Prevention, China).

Special thanks to Alexandra de Nooy and Tom Ockhuisen (University of Amsterdam, Netherlands) for carrying out the modelling work used to inform this current update, and to Mikashmi Kohli, Brooke Nichols, Morten Ruhwald, Nick Banks and Olukunle Akinwusi (Foundation for Innovative New Diagnostics, Switzerland) for their input during the process of updating this TPP. WHO acknowledges the participation of observers from technical, development and regulatory agencies, including Grania Brigden (Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland), Puneet Dewan (Bill & Melinda

Gates Foundation, USA), Anisa Ghadrshenas (Unitaid, Switzerland), Brian Kaiser (Global Drug Facility, Switzerland), Helen Rees (South African Health Products Regulatory Authority, South Africa), Sella Senthil (Central Drugs Standard Control Organisation [CDSCO], India), Venugopal Girdharilal Somani (CDSCO, India), Wayne Van Gemert (Stop TB Partnership, Switzerland) and Aihua Zhao (National Institutes for Food and Drug Control, China).

WHO also acknowledges the participation of additional members of the WHO Secretariat: Saskia den Boon, Patricia Hall-Eidson, Alexei Korobitsyn, Carl-Michael Nathanson and Samuel Schumacher (WHO/GTB), Corinne Merle (Special Programme for Research and Training in Tropical Diseases), Mark Lanigan, Anne-Laure Page, Irene Prat and Uta Ströher (Regulation and Prequalification), Jean de Dieu Iragena (WHO Regional Office for Africa), Ernesto Montoro (WHO Regional Office for the Americas), Kenza Benani and Martin van den Boom (WHO Regional Office for the Eastern Mediterranean), Soudeh Ehsani (WHO Regional Office for Europe), Vineet Bhatia (WHO Regional Office for South-East Asia), and Kyung Hyun Oh and Kalpeshsinh Rahevar (WHO Regional Office for the Western Pacific).

The contributions of all individuals who provided input through the online public call for comments to support the development of this TPP are also gratefully acknowledged.

Abbreviations and acronyms

CAD	computer-aided detection of TB on digital chest radiography
CDR	case detection rate
CRP	C-reactive protein
CXR	chest X-ray or radiography
GTB	WHO Global Programme on Tuberculosis & Lung Health
HIV	human immunodeficiency virus
IGRA	interferon gamma release assay
NTP	national TB programme
TB	tuberculosis
TPP	target product profile
TPT	TB preventive treatment
WHO	World Health Organization
Xpert	Xpert® MTB/RIF Ultra

Executive summary

In 2023, over 8.2 million cases of tuberculosis (TB) were detected and notified to the World Health Organization (WHO); nevertheless, an estimated 2.6 million people who developed TB in that year were not detected *(1)*. In light of this persistent gap in case detection and sustained high TB incidence, systematic TB screening is an essential intervention to find and treat people with TB who are missed by the health system, and thus reduce transmission and prevalence of TB. However, if TB screening is to be implemented at the levels needed to significantly reduce the global TB burden, there is an urgent need for new tools for TB screening that can be readily and rapidly deployed and brought to scale.

WHO first published target product profiles (TPPs) for a test to improve the early detection of TB in 2014. The goal was to spur the development of novel tools that could detect a significant proportion of prevalent TB cases while also reducing the volume of individuals going on for diagnostic evaluation with rapid molecular testing *(2)*. In the decade since the first TPPs were released, there have been significant and rapid advancements in screening technology, including mobile and even portable digital radiographic equipment, alongside innovations driven by artificial intelligence (AI) in computer-aided detection software, which can provide automated interpretation of chest X-ray for TB screening, anywhere and at any time. These advancements, matched with the wider availability of molecular diagnostic tests, have enabled impressive scaling up of screening in many high TB burden settings.

Despite the advances, important challenges remain in bringing screening to the scale needed to close the case detection gap and reduce the TB burden globally. Foremost among these challenges are the availability of screening tools with the low cost and high accuracy required to conduct screening in lower prevalence populations, such as those encountered in community-based screening activities. There has been a growing recognition that the burden of undiagnosed prevalent TB is larger than previously realized, and that a substantial portion of TB is likely to be asymptomatic *(3)*, underscoring the need for community-based screening activities using symptom-agnostic tools to substantially reduce the burden of TB. In addition, better tools for differentiating TB from other pulmonary conditions to enable rapid diagnosis and treatment are still needed for screening in health facilities and similar higher prevalence settings.

The process of updating these TPPs for screening tools was undertaken to bring the document in line with the needs of end users and with the strategic priorities of WHO, including the End TB Strategy, which promotes systematic screening as part of the first pillar of patient-centred care and prevention *(4)*. This updated TB screening TPP document was developed with input from a multidisciplinary expert advisory group. The process included a Delphi-like consultation to achieve consensus, and guidance from many stakeholders from various fields who provided feedback through an open public call for input. For the updating, modelling was conducted to inform the expert discussions about the impact of test accuracy on the performance of screening algorithms, and the resulting requirements for diagnostic testing and associated programme costs.

A core update in this document is the inclusion of three distinct types of screening tools that may be effective in implementing TB screening in different settings, prevalences and situations:

- a high-sensitivity, high-specificity screening test that can be implemented as a single screening step before referral for diagnostic testing or effective ruling out of TB;
- a high-sensitivity screening test to be implemented as part of a two-step screening approach (i.e. in combination with another screening test) before referral for diagnostic testing; and
- a screening test with moderate sensitivity but high specificity, which can be deployed in settings and situations that have limited access to health systems and cannot be reached by existing screening tools, to improve case detection and access to care in underserved areas and populations.

The TPPs described in this document are intended to provide product- and technology-agnostic guidance, and to encompass all possible approaches used for screening. Any newly developed technology that can meet most or all of the product profile characteristics could be considered for use in screening, if proven effective. It is hoped that these updated TPPs for novel TB screening tests can inform key stakeholders in research and development, and spur further innovation in this key area for global TB care.

References for the Executive summary

1. Global tuberculosis report 2024. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/379339). Licence: CC BY-NC-SA 3.0 IGO.
2. Meeting report: high-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting (WHO/HTM/TB/2014.18). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf).
3. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I et al. Subclinical tuberculosis disease – a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. Clin Infect Dis. 2021;73:e830–e41 (https://doi.org/10.1093/cid/ciaa1402).
4. The End TB Strategy [website]. Geneva: World Health Organization; 2014 (https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/the-end-tb-strategy).

1. Introduction

Despite being a preventable and curable infectious disease, tuberculosis (TB) has continued to elude global control efforts. In 2023, 8.2 million people with TB were diagnosed and notified to the World Health Organization (WHO), the highest number ever reported since WHO began tracking; yet these cases still represent only three quarters of the estimated 10.8 million incident TB cases for that year *(1)*. Given the persistence of the global TB epidemic, and to achieve the targets of the End TB Strategy *(2)*, there is an urgent need to deploy strategies to improve case detection for people with TB globally, especially among communities and populations with prevalent undetected TB, and groups or areas lacking adequate access to care. One key strategy is systematic screening for TB disease. TB screening is a central component of the first pillar of the End TB Strategy, aimed at ensuring early diagnosis for all people with TB *(3, 4)*.

There are two primary objectives of screening for TB disease:

- to ensure that TB disease is detected early and treatment is initiated promptly among those at high risk for TB, to improve health outcomes and reduce the risk of morbidity, mortality, and the adverse social and economic consequences of TB; and
- to reduce population prevalence of TB disease, thus reducing transmission of *Mycobacterium tuberculosis* and averting future incident TB disease.

Additionally, TB screening can help to bolster TB case detection in areas where it is suboptimal, and identify individuals eligible for TB preventive treatment (TPT) once TB disease is ruled out, thus further minimizing incident TB.

Tests for TB screening are essential to implement screening interventions effectively and at scale. The development of target product profiles (TPPs) for novel TB screening tests helps to ensure that developers align with the needs of the global TB community when developing new products for the next generation of TB screening tests and tools.

1.1 Objectives and target audience

WHO TPPs are strategic reference documents that are intended to facilitate and accelerate the development of medical products and devices addressing the greatest and most urgent public health needs. In terms of tests for TB screening, the overall objective of TPPs is to align developers' performance and operational characteristics with the needs of users.

The objective of this document is to inform test manufacturers, researchers and research funders about the nature and significance of new tools for screening for TB disease and the relevant implications for the development of new diagnostic technologies. This document defines key TPP specifications, such as the target population, performance, operational characteristics and pricing. Any newly developed technology that can meet most or all of the product profiles could be considered for screening use, if proven accurate and advantageous. The TPPs described in this document are intended to be product- and technology-agnostic, and to encompass all possible approaches used for screening. WHO will not

publish separate TPPs for specific screening technologies or products such as computer-aided detection (CAD) software for chest X-ray (CXR) reading or C-reactive protein (CRP) assays.

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

1.2 Background

Systematic screening for TB disease is defined as the systematic identification and evaluation of people at risk for TB disease, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Screening can be conducted in a single step or in multiple steps. A positive or abnormal result on a screening test indicates that the individual should undergo evaluation with a WHO-recommended rapid diagnostic test (WRD) to confirm a diagnosis of TB, or to rule out the disease and investigate alternate causes for the abnormal test result. A negative or normal result on a screening test indicates that TB disease can effectively be ruled out and the individual can be referred for TPT if eligible.

To achieve the primary objectives of screening, including protecting individuals at high risk and reducing community burden of disease, a screening test must be able to:

- distinguish individuals who have a higher likelihood of having TB (and who should thus go on to further diagnostic testing) from those who are unlikely to have TB; and
- ensure an adequate pretest probability of TB among people being referred for confirmatory testing.[1]

Confirmatory tests typically cost more than screening tests; hence, a screening step is needed to identify who should undergo further diagnostic testing, to ensure prudent use of resources.

TB screening has fallen into and out of favour globally over the past century. For much of the early 20th century, in many high-resource countries where TB was still a leading cause of death, mass community-wide screening using CXR was routinely conducted *(5, 6)*. Many of these mass screening campaigns were successful at detecting a large number of people with prevalent TB, and some found a substantial reduction of community TB prevalence in follow-up activities *(7)*. Later in that century, once TB was no longer a major cause of death in western countries, interest in screening waned and mass TB screening campaigns were discontinued in much of the world; however, some countries in Eastern Europe continued population-wide TB screening *(8)*.

Since the early 2000s, interest in screening has been renewed, with a particular emphasis on protection and care for the most vulnerable groups. Screening for TB in groups at highest risk was first emphasized in 2011, with WHO recommendations for screening people living with HIV; this was followed in 2012 by recommendations for screening of close contacts of people with TB, and in 2013 by consolidated guidance for screening of high-risk groups *(9–11)*. Around that time, more sensitive and decentralizable diagnostic tools became available, with the advent of automated nucleic acid tests for TB *(12)*.

One factor that has driven interest in more broad-scale screening is the revelation of the magnitude of prevalent, undetected TB; in particular, the fact that a substantial portion of such TB is asymptomatic *(13)*. National TB prevalence surveys over recent years have consistently found that about half of prevalent TB detected in the community is bacteriologically confirmed among people who do not report symptoms of TB disease *(14)*. Asymptomatic TB is a substantial challenge to a system of care based on passive case detection, and it requires a more active case-finding approach *(15)*. Recognition of the contribution of

[1] Diagnostic tests are typically performed among a population of individuals who are ill and seeking care, and their performance and the interpretation of the results are designed for a population with a higher pretest probability of TB than the overall screening population.

asymptomatic TB to the overall TB burden also highlights the urgent need for better tools for screening for TB disease that are not based on symptom status *(16)*.

The rapid advancement of technology in recent years has brought about great innovations in TB screening, including digital radiography with mobile and portable options, and CAD software programmes for automated interpretation of CXR imaging for TB screening *(17)*. Artificial intelligence (AI) holds enormous promise for continuing and accelerating the development of new tools and technologies for TB screening. Alongside this, developments in TB diagnostics have greatly expanded the available options to test people who screen positive.

This document is designed to help ensure efficient and effective progress in developing the next generation of TB screening tools.

1.3 WHO guidance on systematic TB screening and its implementation

The current WHO guidance recommends screening for TB among high-risk groups and in targeted geographies or communities with higher risk of TB, in both facility-based and community-based screening interventions. Screening is strongly recommended for four risk groups who are at highest risk of TB and of poor outcomes from the disease: household and close contacts of TB patients, people living with HIV, prisoners and those who reside or work in penitentiary institutions, and miners with silica exposure. Screening is also strongly recommended for children who are contacts of TB patients or living with HIV. For these risk groups, screening is recommended across all global settings *(18)*.

Screening is conditionally recommended in facilities and health care settings among people seeking care who have risk factors for TB, in areas with a TB prevalence of 0.1% or higher, and among people with fibrotic lesions identified on CXR. Community-based screening is recommended in the general population in areas with a very high TB prevalence (≥0.5%) or among specific populations with a high risk of TB and limited access to health care; examples of such populations are urban poor communities, homeless populations, remote or isolated communities, indigenous populations, migrants, refugees and internally displaced populations *(18)*.

Currently, WHO recommends various tools for screening. Symptoms can be used for screening in any population; however, there are limitations in accuracy, and the ability to detect asymptomatic TB is lacking. CXR can be used to screen most populations and has the best demonstrated sensitivity of available screening tools. CAD software for automated interpretation of CXR imaging can be used alongside CXR for screening all adults aged 15 years and older; such software greatly increases the ability to implement screening at scale globally, given the limited availability of radiologists or even physicians in many settings. Molecular WHO-recommended rapid diagnostic tests for TB are also recommended for screening all adults, and CRP can be used to screen adults living with HIV *(18)*.

The different populations targeted for screening require very different modalities for screening tools. Facility-based screening can use stationary laboratory and imaging equipment, such as stationary CXR or quantitative CRP assays; in contrast, community-based or household-based screening requires mobile or portable devices that can be implemented in various conditions *(19)*. Portable radiology equipment combined with CAD software has enabled the implementation of screening to a broader extent than has previously been achieved; however, the ability to scale up community-based screening to the most hard-to-reach areas and to adequate coverage levels is still limited by a lack of tools that can be easily transported and implemented across all possible settings and environments.

In addition, some populations that require screening to improve case detection are particularly challenging to diagnose (e.g. people living with HIV or children at high risk of TB). The detection of childhood TB is an important global health need; hence, a test that improves the quality of diagnosis and overall case detection in children will have significant benefits for TB programmes. Therefore, manufacturers should try to expand their initial validation studies and include children, wherever possible.

2. Methodology

In line with WHO methodology for development of TPPs, the update of the WHO TPPs for novel screening tests followed a consultative process that included a multidisciplinary group of experts and input from a wide range of stakeholders. 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 the feedback gathered throughout the process.

2.1 Previous WHO TPP values for TB screening

Previous TPP values applied for TB screening were based on the desired accuracy of a point of care triage test, as published by WHO in 2014 *(3)*. Since then, there has been a significant expansion of interest in broader TB screening interventions, targeting larger populations with lower TB prevalences. The release in 2021 of the updated WHO guidelines on systematic TB screening expanded the recommendation for community-wide screening from 1% prevalence settings to 0.5% prevalence settings, based on evidence of reduction of prevalence and transmission *(18, 20)*. Beyond research, several countries are undertaking much larger scale community-based screening initiatives as part of efforts to reach the End TB Strategy targets of reducing TB incidence by 90% by 2030, and the United Nations high-level meeting targets of detecting and treating 90% of people with TB by 2027 *(21)*. Examples of such initiatives include the Community Awareness, Screening, Testing, Prevention and Treatment for TB (CAST-TB) campaign of community-wide education and screening activities in high TB burden communities in Uganda, and the Double X screening campaign that combines CXR screening and Xpert® MTB/RIF Ultra testing of people with TB risk factors in Viet Nam *(2, 16)*.

Therefore, the focus of the current document has expanded to include more emphasis on effective community-based screening at larger scale in lower TB prevalence settings and populations. This necessitates the development of new screening tools and technologies that can enable such community-based screening interventions in a cost-effective and scalable way, while maintaining high accuracy to minimize the risk of overdiagnosis. This expansion of scope does not lessen the importance of developing new tools that can effectively be used to screen populations in poorer health and with a relatively higher TB prevalence, often within health facilities or among people seeking care. The screening of populations and risk groups in health facilities is an essential component of the WHO screening recommendations. For this updated document, the term “triage” has been replaced with “screening”, given that both represent a screening intervention targeted to a specific risk group. The distinction lies only in the population being screened, whether it be a community-based population of largely healthy individuals with low TB prevalence, or a facility-based group of people either in hospital or seeking care, in settings with a higher prevalence of TB.

2.2 Establishment of the Scientific TPP Development Group

A Scientific TPP Development Group was established for this update of the TPP for screening tests, alongside a process of updating the TPPs for diagnostic tests for TB *(22)*. 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. The group also had balanced geographical and gender representation, and 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 the 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 a real or perceived 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 Guiding principles for the development of TPPs for TB screening

An ideal screening test is one that is easy to conduct; does not require invasive sampling, extensive training or resources; and has a short turnaround time to enable rapid clinical decision-making. Tools for TB screening have traditionally had an emphasis on high sensitivity for detecting TB, the goal being to maximize TB case detection. There has been less focus on specificity, given that a positive screening test is usually followed by a diagnostic evaluation and further testing to either confirm or rule out a diagnosis. However, the challenges of implementing screening with a high-sensitivity, low-specificity test include the testing burden and associated expenses of conducting confirmatory tests for all who screen positive. These challenges compound as screening is expanded and implemented in lower prevalence settings. Therefore, for the purposes of this updated TPP, tests with a wide range of performance characteristics were explored for their potential utility in screening.

Accuracy for TB screening tools has typically been evaluated against a microbiological reference standard, to determine the tools' performance in detecting bacteriologically confirmed TB. However, a composite reference standard incorporating unconfirmed diagnosis may sometimes be appropriate, for example, when considering:

- screening of populations in which obtaining a bacteriological confirmation is difficult and a diagnosis is often established by clinical evaluation (e.g. children or people living with HIV); or
- the accuracy of screening tests being conducted in a population that often cannot produce a sputum sample required for laboratory testing, such as screening in a healthy population with a very low burden of TB and other lung conditions.

Above all, a screening test must be affordable and scalable, to enable implementation of screening interventions at the scale required to reduce the population level prevalence and transmission of TB in high-burden areas. Such characteristics could be achieved by screening activities using tests that have a small per-test cost and little to no equipment or capital investments. Tests that require more centralized equipment for processing would need to achieve low per-test costs and implementation requirements overall, taking into account expenses for transportation of samples and transmission of results.

2.4 Screening algorithms

Screening tests are not performed in isolation; they are conducted in algorithmic combination, sometimes with other screening tests and always concluding with diagnostic testing. The ideal would be to have a single screening step before referral for diagnosis, but sometimes multiple screening steps are required to achieve the defined objectives of screening in very low prevalence settings. Multiple screening tests conducted in parallel result in a screening step with higher sensitivity and lower specificity than any single test on its own. Multiple screening tests conducted serially, with a positive or abnormal result on a first screening test leading to a subsequent screening step before diagnostic confirmation, can greatly reduce the overall volume of people referred for diagnostic evaluation, though with some loss to sensitivity. Screening based on symptoms or signs of TB should NOT be an initial step in such an algorithm, because individuals with signs or symptoms of TB should always go directly to diagnostic evaluation without further screening *(23)*. Additional screening algorithm options are described in the "WHO operational handbook on tuberculosis: module 2: screening: systematic screening for tuberculosis disease" *(19)*.

In this TPP document, the performance of novel screening tests was considered within a screening algorithm, and the performance of the algorithm as a whole was modelled. Both a single screening test algorithm and a two-step positive sequential algorithm were modelled. Although there was no explicit modelling of parallel or negative sequential screening algorithms, the performance of either of these algorithms can be represented by a single screening step algorithm, with the combined accuracy of two tests performed in parallel or negative sequential succession.

2.5 Modelling of required accuracy of screening tests

For the performance aspect of this screening TPP document, modelling was conducted to determine what levels of accuracy (i.e. sensitivity and specificity) are required from a screening test to achieve the objectives of screening. The parameters required of a screening test and algorithm were set as follows:

- The screening algorithm as a whole – comprising one or more screening tests and a diagnostic evaluation – should detect at least 60% of the prevalent TB cases in the population being screened (for one option, an exception was made and a 50% minimal case detection was considered).
- The screening test or tests should result in a post-screen prevalence of TB of 5% among the population that has screened positive and is being referred for diagnostic testing. This is representative of the pretest probability of TB for which diagnostic tests for TB have been evaluated; thus, it ensures that the results of the diagnostic tests can be interpreted as intended.
- The initial prevalence of TB in the population being screened should be representative of the populations in which TB screening is currently recommended and in which screening needs to be scaled up globally. Given the current WHO recommendations for screening and the need for tools that can enable broader scale screening in lower prevalence settings, the minimum requirements were set for tools that can achieve the above parameters in populations with a TB prevalence down to 1%, and the optimal requirements were set to a prevalence of 0.25%.

Modelling was conducted to assess the required accuracy for novel TB screening tools by fixing one parameter of accuracy and estimating the requirements in the other parameter (i.e. fixing sensitivity and estimating specificity, or vice versa) to achieve the above targets for case detection and post-screen prevalence. Novel screening tests were modelled as part of a single step or sequential algorithm, implemented in various TB prevalence settings ranging from 1% down to 0.1%.

2.6 Profiles of screening tests

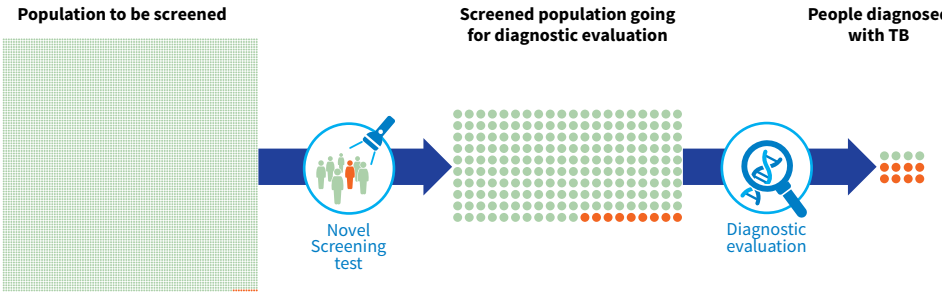
The results of the modelling performed to inform this updated TPP document illustrated the challenges inherent in screening very low prevalence settings; they also highlighted a range of different screening approaches that could achieve the required parameters of the model in most settings. No hypothetical test in the model could achieve the required parameters for screening in a single or two-step serial algorithm in settings with a 0.1% prevalence. In settings with a prevalence of TB of 0.25% or higher, three possible approaches to screening emerged that achieved the requisite screening parameters. These approaches correspond to three different profiles of possible novel screening tests (see **Fig. 2.1**):

- **A high-sensitivity, high-specificity screening test as a single screening test**: Such a test could be implemented as a single screening test algorithm and would result in the highest case detection from all scenarios presented here; however, it has the highest requirements for accuracy.
- **A high-sensitivity screening test in a two-step screening algorithm**: Such a test would lessen the requirement for specificity by employing a second screening test; however, the accompanying complexity and costs would need to be taken into account.
- **A high-specificity screening test (with moderate sensitivity) as a single screening test**: Such a test can achieve most of the required parameters for screening in a single screening step but would have lower case detection than the high-sensitivity screening approaches. However, such a novel screening test would only have value over currently available screening tools if it were low cost, easily implementable in a wide variety of environmental conditions and contexts, and able to be brought to scale to improve case detection in areas that are not currently well served. This would improve the standard of care for these populations.

Fig. 2.1. Performance of three screening test types, conducted among a hypothetical population of 1000 people with a TB prevalence of 1%, within an algorithm that raises the prevalence of TB in the population being screened to at least 5% among individuals being referred for diagnostic evaluation, and detects at least 50–60% of prevalent TB in the population. In the figure, each person is represented by a dot; green dots represent individuals without TB and red dots represent individuals with TB

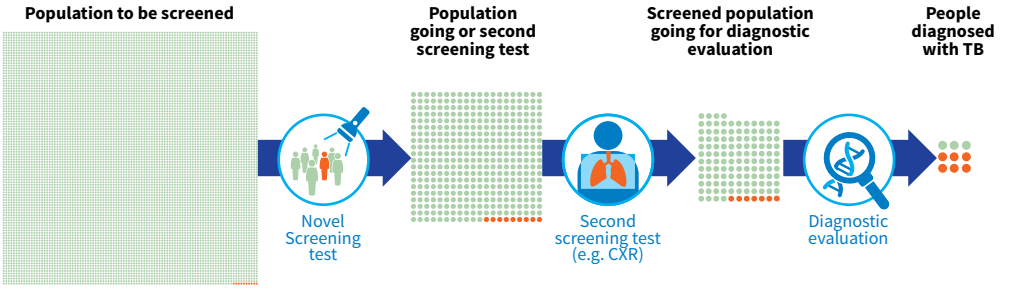
Test type 1: High-sensitivity, high-specificity screening test

% of overall population	100%	20%	1.2%
% of individuals with TB	100%	90%	80%



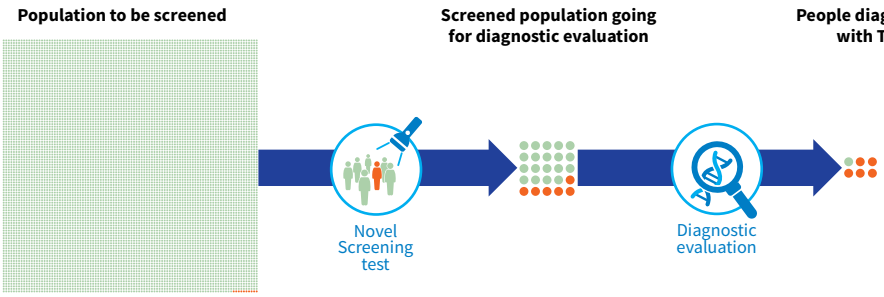
Test type 2: High sensitivity screening test followed by a second screening test

% of overall population	100%	40%	12.5%	0.9%
% of individuals with TB	100%	90%	72%	60%



Test type 3: Moderate-sensitivity, high-specificity screening test

% of overall population	100%	2.5%	0.6%
% of individuals with TB	100%	60%	50%



CXR: chest X-ray; TB: tuberculosis.

2.7 Delphi-like process

After initial discussions, an early draft TPP document with modelling results was prepared and discussed among the Scientific TPP Development Group on 2 September 2023. From October to November 2023, a Delphi-like survey was conducted within the Scientific TPP Development Group. For this process, one round of survey was conducted and 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-like 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). For characteristics where the consensus was less than 80%, qualitative comments from the group were collated and analysed to further refine the document.

Overall, the outcomes of the Delphi-like process showed a high level of agreement for most of the attributes described in this TPP, with some areas being resolved through discussion leading to consensus.

2.8 Public consultation and comment process

A draft TPP document including the results of the Delphi-like survey and resulting updates was shared online for public commentary through the WHO Dataform system from 31 January 2024 to 29 February 2024. The intended audience for the document included TB programme managers, laboratory specialists, clinical practitioners, implementers, researchers, representatives of civil society organizations and industry, and patient advocates. Comments were analysed and incorporated into the final draft TPP document. Results of the public comment process are provided in Annex 1.

2.9 Scientific TPP Development Group final consultation

A final consultation of the Scientific TPP Development Group was held on 4–6 March 2024. Feedback received through the online public comment process and the outcomes of the Delphi-like consultation were presented during the consultation for each characteristic of the 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; overall, it ensured 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.

3. Target product profiles

Table 3.1 shows the minimal and optimal characteristics of novel tests for screening for TB. It is expected that potential screening products would meet all of the required minimum criteria of the "TPP for TB screening tools", and as many of the optimal requirements as possible. However, potential trade-offs on performance, cost, impact and operational characteristics would need to be considered for WHO policy; thus, the criteria are indicative rather than absolute.

Table 3.1. Minimal and optimal characteristics of novel tests for screening for TB

Characteristic	Minimal	Optimal	Explanatory notes
Scope			
Intended use	To provide characteristics for a test that can help identify people: • presumed to have TB who require further active TB diagnostic evaluation; and • unlikely to have TB and in whom the test can effectively rule out TB disease.		Systematic TB screening is intended to be conducted among populations at risk of TB, irrespective of symptom status or clinical presentation, to identify individuals with presumptive TB. The goal of screening as described here is primarily to detect pulmonary TB. It is important to note that individuals presenting with signs or symptoms of TB should proceed directly to diagnostic evaluation using a WRD.
Target population	Populations and groups at risk of TB, down to 1% TB prevalence.	Populations and groups at risk of TB, down to 0.25% TB prevalence.	Values shown here reflect the results of modelling that informed the development of this TPP. The target populations here for minimal and optimal use cases reflect different scenarios in which screening may be conducted. The minimal test described here would be better suited for screening populations at higher risk (e.g. contacts) or facility-based screening, where TB prevalence tends to be higher; in contrast, the optimal test would be better suited for broad screening in communities and populations with lower risk. Screening is increasingly being implemented in lower TB prevalence settings, but the implementation is hindered by the performance of current tools. Manufacturers should endeavour to make tools that can perform more effectively in lower TB prevalence settings, described in the optimal use case here. Manufacturers should also aim to develop new screening tests that can be effective for screening among populations in whom existing screening tests do not perform as effectively, including among people living with HIV, pregnant women and paediatric populations of different age ranges.

<table>
<tr><th>Characteristic</th><th>Minimal</th><th>Optimal</th><th>Explanatory notes</th></tr>
<tr><td>Intended user of test</td><td>Health care worker or technician with some training in conducting TB screening tests.</td><td>Laypeople or caregivers with minimal to no training or instruction required (can include self-testing).</td><td>Community health workers are an important target user group for future screening tests, given the importance of community-based screening.</td></tr>
<tr><td>Setting</td><td colspan="2">Tests that can be performed in community settings, at health facilities with basic infrastructure (including electricity and water) and in household settings.</td><td>Tests that can be conducted in community settings may also include self-tests that can easily be done in a household setting. For self-testing, it is critical that the test manufacturers also think about linkage to care, so that people can easily follow the care cascade.

Where the screening test involves multiple steps (e.g. sample collection, processing and testing at a centralized facility), it is imperative that the first step in the workflow be simple and easy enough that it can be done in community settings as described.</td></tr>
<tr><td colspan="4">Performance</td></tr>
<tr><td>Test accuracy</td><td colspan="2">Test accuracy characteristics are described for three distinct types of screening tests, corresponding to three possible approaches to screening, which achieve the required parameters of 5% post-screen TB prevalence and 60% detection[a] of all prevalent TB:
• a high-sensitivity, high-specificity screening test as a single screening test;
• a high-sensitivity screening test in a two-step screening algorithm; and
• a high-specificity screening test as a single screening test.

<table>
<tr><th>Test type</th><th>Minimal accuracy[b]</th><th>Optimal accuracy[c]</th></tr>
<tr><td>High-sensitivity, high-specificity screening test</td><td>90% sensitivity
80% specificity</td><td>95% sensitivity
95% specificity</td></tr>
<tr><td>High-sensitivity screening test</td><td>90% sensitivity
60% specificity</td><td>95% sensitivity
85% specificity</td></tr>
<tr><td>High-specificity screening test</td><td>60% sensitivity
98% specificity</td><td>70% sensitivity
98% specificity</td></tr>
</table>
[a] One screening approach does not meet this level of CDR, as explained below.

[b] Achieves the defined parameters in settings down to 1% prevalence, except for the high-specificity approach, which achieves 50% CDR rather than 60% CDR for minimal values.

[c] Achieves the defined parameters in settings down to 0.25% prevalence.</td><td>Each of these screening approaches, with its associated screening test type, emerged from the modelling as an acceptable approach to achieve the required parameters of screening.

A one-step screening approach using a high-sensitivity and high-specificity screening test would result in the highest case detection from all of the scenarios presented here – it would be the most straightforward algorithm to implement but has the highest requirements for accuracy.

A high-sensitivity, two-step screening approach lessens the requirement for specificity by employing a second (different) screening test. A novel test that is decentralized and scalable, even if not highly specific, would provide added value in such a screening scenario. The accuracy estimates provided for this approach are for one test in the algorithm. To model the performance of this approach, an exemplary additional screening test was used based on the estimated accuracy of CXR as a screening tool performed as a second screening test on a population pre-screened for symptoms (85% sensitivity and 70% specificity) (24–27). The order of the two tests in the screening algorithm does not impact the accuracy of the algorithm as a whole, but does impact costs. It is important that screening based on symptoms or signs of TB should NOT be an initial step in such an algorithm, because individuals with signs or symptoms of TB should always go directly to diagnostic evaluation without further screening (23).

A high-specificity screening test with lower sensitivity will have a lower case detection capacity overall and a high false negative rate. However, such a test can still have programmatic utility if it is affordable and easy to implement, with a possibility of achieving high population coverage, especially among hard-to-reach groups and areas that are not easily reached with current technology and health programmes. This approach did not achieve all the parameters desired, because in the minimal requirement space, the high-specificity test achieves only 50% CDR.</td></tr>
</table>

Characteristic	Minimal	Optimal	Explanatory notes
			Screening tests should be evaluated against the best possible objective reference standard of TB status available; currently, in most cases this is a microbiological reference standard. Where a microbiological reference standard is not available or not optimal (e.g. in paediatric populations or people who cannot produce the necessary clinical specimen), an appropriate composite reference standard could be used, combining bacteriological testing with clinical and histological findings. In screening populations, many people will not be able to produce a sputum sample, which limits the ability to confirm the disease status.
Pricing			
Pricing of individual test (reagent costs only, at scale and ex-works)			
Cost per test			The costs described here include the total cost per test, including ancillary costs (e.g. capital, consumables, equipment and maintenance costs of an instrument-based test) and excluding any shipping and import. Ideally, a new test should be priced according to the cost of goods and estimated volumes, and should include a reasonable profit margin. Ensuring access to tests while maintaining business interests can be achieved through fair pricing, which requires transparency about the cost of goods and estimated volumes, and a reasonable profit margin. The price of a test affects access and requires due consideration. It may be acceptable to have a more expensive screening test or a combination of tests if this improves overall accuracy, especially specificity, and thus reduces the volume of subsequent diagnostic testing required. However, a test may be considered unaffordable for some health programmes, even if studies have shown it to be cost effective.
High-accuracy test (1 step)	≤US$ 3	≤US$ 1	
High-sensitivity test (2 step)	≤US$ 2		
High-specificity test	≤US$ 2		
Operational characteristics			
Sample or specimen type	Requires easy-to-obtain samples, including non-physical samples such as imaging and sound.	Does not require a physical sample, or requires an easy-to-obtain sample that is self-collectible.	Easy-to-obtain samples include urine, tongue or oral swabs, saliva, exhaled breath and capillary blood. Non-physical samples such as CXR images and sounds are also included in this category.
Manual preparation of samples	Minimal manual preparation at the site of collection, without strict timing or measurements.	No manual preparation, strict timing or measurements.	–
Instrument	Portable or mobile device that has an option of using battery or solar power for POC settings or a centralized instrument with highly efficient batch testing of samples.	No instrumentation required.	Ideally, if an instrument is needed, a single device is preferred but modular solutions would be acceptable (e.g. for separate sample processing and detection). For centralized testing, samples should be easy to collect onsite from remote settings and then easy to transport to a centralized facility with efficient batch testing.

Characteristic	Minimal	Optimal	Explanatory notes
Time to result	<30 minutes	<5 minutes	Time to result refers to the time from conducting the test, including sample processing, to receiving the final results. Time to result is closely linked to throughput; ideally, a novel screening test would have very low time to result, whereas a longer time to result would need to engage batching to maintain high throughput capacity. If the test is instrument-based, it should allow for multiple samples to be tested at the same time. If the test is not instrument-based, the testing time should be short enough to accommodate the screening of a large number of people.
Power requirements	Standard operating currents with built-in UPS for use in locations with variable power.	Can run on battery or solar power, or requires no power supply (if no instrument is involved).	–
Maintenance and calibration	Preventive maintenance and calibration after 1 year or >20 000 tests (whichever comes first); include maintenance alert.	Maintenance not needed. Self or remote calibration.	The frequency of preventive maintenance and calibration will be determined based on a combination of usage patterns, throughput, environmental factors and risk assessment findings. Units used more frequently may require more frequent maintenance and calibration to ensure consistent performance. Manufacturers should develop robust instruments or devices, considering that screening tests are intended to be conducted in large volumes, and that frequent preventive maintenance for the instrument might make uptake and implementation more onerous.
Training and education	1 day for staff with the skills to perform other health-related procedures.	Minimal training or education.	If a test involves specialized equipment or machinery, additional training time will be required to gain proficiency. For self-screening or where a user has no previous training on conducting any health-related procedures, a short, self-explanatory quick reference guide on performing the test should be sufficient.
Documentation and display of results data	Digital readouts to display test details, including results. Ability to save results should be included, and results should be exportable in a standard format (e.g. XML or CSV) to a third-party instrument (e.g. via USB) or connectivity software.	An instrument-free test with visual readouts (e.g. for barcodes) on a test device to digitally record and report data. Transmission of result data to the staff conducting screening should be digitized to enhance efficiency and linkage to care.	–
Data storage	The administrative institution (MoH or NTP) managing sites where tests are deployed should be able to specify or agree with the storage location of the test data without affecting the support and optimal use of the test.		Data governance policies (e.g. that ensure privacy protection, de-identification and anonymization) of test manufacturers and administrative institutions should align.
Data ownership	Test data, their management and ownership must comply with local regulations.		–

Characteristic	Minimal	Optimal	Explanatory notes
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 test should provide configurable features so that personal data can be: • gathered with transparency for users and people who are taking the tests, including 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.		Tests should adhere to internationally recognized standards for security of sensitive information. The bullet points are adapted from Article 5, Section 1 of the European Union General Data Protection Regulation *(28)*.
Regulatory requirements	Design, development and manufacturing of the assay and system should comply with ISO 13485 and ISO 14971 or higher standards or regulations, and comply with ISO 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). If applicable, the test must be registered for in vitro diagnostic use. For non in vitro diagnostic tests, appropriate regulatory requirements should be followed.		See the following ISO publications: *IEC 62304:2006 Medical device software – software life cycle processes (29)* *ISO 13485:2016 Medical devices – quality management systems (30)* *ISO 14971:2019 Medical devices – application of risk management to medical devices (31)*
Language support	For each country in which the test is deployed, instructions should be provided in one popular language; for example, the official language or de facto national language, and any language mandated by local regulatory or trade compliance requirements.	Same as minimal plus additional languages that enable use by additional residents of the location of deployment.	The instructions for use and screen instructions (if applicable) should also adhere to these language requirements. Including more languages will make a test more usable and acceptable. In designing tests, manufacturers should cater to the varying populations and different regional languages for the locations where the test is intended to be used.

Characteristic	Minimal	Optimal	Explanatory notes
Operating temperature, humidity level and storage	Between 5 °C and 40 °C with up to 70% humidity.	Between 5 °C and 50 °C with up to 90% humidity.	Countries where TB is endemic often have high environmental temperatures, dust, high humidity and flooding. Manufacturers should take this into consideration and carefully design the tests, keeping in mind the operating temperatures, environmental conditions and humidity levels that may be found in the intended settings. These considerations also apply to reagent storage and shelf life.
Environmental impact	Tests and any associated instruments should minimize adverse impact on the environment; for example, by: • having the potential to be produced locally; • minimizing waste; • maximizing the reusability and recycling of by-products; • creating multi-use platforms; • providing for recycling of instruments at the end of their life; and • having low power consumption and radiation emissions.		Manufacturers should provide clear and environmentally friendly guidance on disposal of used products and there should be no disposal of toxic waste.

CDR: case detection rate; CSV: comma-separated values; CXR: chest X-ray; HIV: human immunodeficiency virus; MoH: ministry of health; NTP: national TB programme; POC: point of care; TB: tuberculosis; TPP: target product profile; UPS: uninterruptible power supply; USB: universal serial bus; WHO: World Health Organization; WRD: WHO-recommended rapid diagnostic test; XML: extensible markup language.

4. Other considerations

The TPPs presented here include the attributes that are considered essential for future tests for screening; that is, target population, target user of the test, setting, cost, accuracy and operational characteristics. It may be difficult for a single test to satisfy all of these characteristics. Thus, manufacturers may have to consider trade-offs, whereby a novel test has some clear advantages that may offset other downsides. For example, the benefits of a portable technology with a shorter time to result that can reach a larger population may come at the expense of lower specificity. Likewise, a more expensive test may be justified if it brings substantial added value in terms of improved performance and better suitability for decentralization, and if it reduces the need for confirmatory tests or other operational costs.

For an infectious condition such as TB, with a large global burden of disease and death and a persistent shortfall in case detection, the potential impact of a new screening technology will depend heavily on operational factors that also influence a screening test's ability to fulfil its role (i.e. to identify more people who require further diagnostic work-up accurately and decrease their time to starting treatment). Although the TPPs indicate the attributes to be considered at the developmental stage of the test, these should not be dissociated from the factors to be considered at the implementation stage in the framework of overall TB-oriented activities within a programme, such as the optimal positioning of the test when scaling it up, the need to back it up with appropriate capacity to confirm or exclude a TB diagnosis, the provision of appropriate treatment for TB and comorbidities, and sustained infection control activities.

5. Conclusion

Current WHO recommendations on tools to use for TB screening are an important step for countries as they move towards the global targets for case-finding. However, by themselves, these recommendations will be insufficient to fully achieve the targets and bridge the gap in TB treatment coverage. Technologies that are intended for use at the level of the community or primary health care, and for which it is easy to collect biological samples, are likely to be critical going forward. WHO is issuing these TPPs to guide and encourage product development for new screening tools in these settings.

The pursuit of improved approaches to TB screening fits into the global commitment to reduce the TB burden of disease and death. Providing access to effective screening to larger numbers of people at risk of TB requires clear communication of programmatic needs among stakeholders, particularly researchers, developers of technology and funders. Rapid identification of affected individuals needs to be matched with the timely provision of appropriate treatment. Although recent years have seen advances in the pipeline of tests for screening, 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 low- and middle-income countries, and can provide accurate, rapid and comprehensive solutions for detecting TB.

Addressing current challenges effectively and sustainably requires a multifaceted strategy that integrates technological innovation with considerations of scalability, affordability and adaptability to populations at risk. Ideally, future screening tests would satisfy all the optimal requirements set out in this document for the different test attributes. However, achieving such alignment across the different characteristics is unrealistic and trade-offs will be necessary; for example, prioritizing the characteristics that are likely to help in reaching universal health coverage, and delivering technologies that are reliable and practical to use. Collaboration among stakeholders, ongoing research and sustained innovation will be vital to overcome challenges on the path towards the realization of the ambitious targets set for TB.

References

1. Global tuberculosis report 2024. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/379339). Licence: CC BY-NC-SA 3.0 IGO.
2. The End TB Strategy [website]. Geneva: World Health Organization; 2014 (https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/the-end-tb-strategy).
3. Meeting report: high-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting (WHO/HTM/TB/2014.18). Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf).
4. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM et al. WHO's new End TB Strategy. Lancet. 2015;385:1799–801 (https://doi.org/10.1016/s0140-6736(15)60570-0).
5. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Respir Dis. 1967;95:935–43 (https://pubmed.ncbi.nlm.nih.gov/6026165/).
6. Comstock GW, Philip RN. Decline of the tuberculosis epidemic in Alaska. Public Health Rep. 1961;76:19–24 (https://pmc.ncbi.nlm.nih.gov/articles/PMC1929584/).
7. Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis. 2005;9:1183–203 (https://pubmed.ncbi.nlm.nih.gov/16333924/).
8. Bogdanova E, Mariandyshev O, Hinderaker SG, Nikishova E, Kulizhskaya A, Sveshnikova O et al. Mass screening for active case finding of pulmonary tuberculosis in the Russian Federation: how to save costs. Int J Tuberc Lung Dis. 2019;23:830–7 (https://doi.org/10.5588/ijtld.18.0449).
9. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf).
10. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/bitstream/handle/10665/77741/9789241504492_eng.pdf).
11. Systematic screening for active tuberculosis: principles and recommendations (WHO/HTM/TB/2013.04). Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/84971/1/9789241548601_eng.pdf).
12. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system: policy statement. Geneva: World Health Organization; 2011 (https://iris.who.int/handle/10665/44586).
13. Law I, Floyd K. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Trop Med Int Health. 2020;25:1308–27 (https://doi.org/10.1111/tmi.13485).
14. Frascella B, Richards AS, Sossen B, Emery JC, Odone A, Law I et al. Subclinical tuberculosis disease – a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. Clin Infect Dis. 2021;73:e830–e41 (https://doi.org/10.1093/cid/ciaa1402).

15. Report of the WHO consultation on asymptomatic tuberculosis, Geneva, Switzerland, 14–15 October 2024. Geneva: World Health Organization; 2025 (https://iris.who.int/handle/10665/380616).

16. Report of the WHO consultation on systematic screening for tuberculosis, Geneva, Switzerland, 16–18 October 2024. Geneva: World Health Organization; 2025 (in press).

17. Portable digital radiography system: technical specifications. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/344514).

18. WHO consolidated guidelines on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/340255).

19. WHO operational handbook on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/340256).

20. Marks GB, Nguyen NV, Nguyen PTB, Nguyen TA, Nguyen HB, Tran KH et al. Community-wide screening for tuberculosis in a high-prevalence setting. N Engl J Med. 2019;381:1347–57 (https://doi.org/10.1056/NEJMoa1902129).

21. Resolution 78/5: Political declaration of the second high-level meeting of the General Assembly on the fight against tuberculosis. New York: United Nations General Assembly; 2023 (https://digitallibrary.un.org/record/4025280).

22. Target product profiles for tuberculosis diagnosis and detection of drug resistance. Geneva: World Health Organization; 2024 (https://iris.who.int/handle/10665/378358).

23. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/342331).

24. National tuberculosis prevalence surveys 2007–2016. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/341072).

25. Aung ST, Nyunt WW, Moe MM, Aung HL, Lwin T. The fourth national tuberculosis prevalence survey in Myanmar. PLoS Glob Public Health. 2022;2:e0000588 (https://doi.org/10.1371/journal.pgph.0000588).

26. Moyo S, Ismail F, Van der Walt M, Ismail N, Mkhondo N, Dlamini S et al. Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–19: a multistage, cluster-based, cross-sectional survey. Lancet Infect Dis. 2022;22:1172–80 (https://doi.org/10.1016/s1473-3099(22)00149-9).

27. Matji R, Maama L, Roscigno G, Lerotholi M, Agonafir M, Sekibira R et al. Policy and programmatic directions for the Lesotho tuberculosis programme: findings of the national tuberculosis prevalence survey, 2019. PLoS One. 2023;18:e0273245 (https://doi.org/10.1371/journal.pone.0273245).

28. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Luxemborg: Official Journal of the European Union; 2016 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32016R0679).

29. IEC 62304:2006: Medical device software – software life cycle processes (edition 1). Geneva: International Organization for Standardization/International Electrotechnical Commission; 2006 (https://www.iso.org/standard/38421.html).

30. ISO 13485:2016: Medical devices – quality management systems – requirements for regulatory purposes. Geneva: International Organization for Standardization; 2016 (https://www.iso.org/obp/ui/en/#iso:std:iso:13485:ed-3:v1:en).

31. ISO 14971:2019: Medical devices – application of risk management to medical devices (edition 3). Geneva: International Organization for Standardization; 2019 (https://www.iso.org/standard/72704.html).

Annex 1. Overview of the results of the Delphi-like consultation and WHO public comment process for the TPP for TB screening tests

To develop the updated World Health Organization (WHO) target product profiles (TPPs) for novel screening tests for tuberculosis (TB), a Delphi-like consultation was conducted with the Scientific TPP Development Group, to facilitate consensus-building around the core components of the updated TPP. Following the consultation, a public commentary process was held to seek input from a broad range of constituents; a total of 276 individuals expressed interest in this process, and 163 (59%) individuals consented to participate and provided input.

During the Delphi-like consultation with the Scientific TPP Development Group, overall, there was a high level of consensus on many key aspects of the TPP. Through subsequent discussions and incorporating feedback from the public commentary, consensus was achieved on all parameters. This annex summarizes the survey results, key discussions and inputs from public commentary on all aspects of the TPP.

Scope

Overall, there was a high level of agreement for the parameters included in the "Scope" section. There was complete agreement on the goal of a screening test; a public comment suggested separating out symptomatic and asymptomatic populations for minimal and optimal tests but the expert group agreed this was not ideal, given the desire for the next generation of screening tests to be able to detect asymptomatic TB across all settings.

There was 98% and 91% agreement from the expert group on the target populations for novel screening tests in the minimal and optimal cases, respectively. Some members of the group felt that targeting populations down to 0.25% TB prevalence for screening was unrealistic given the high costs involved, but ultimately the group felt that it was important to keep this level of ambition in the updated TPP document. There were suggestions to include mention of pregnant women and paediatric populations of different age ranges wherever possible.

There was 93% and 86% agreement on the target user of novel screening tests in the minimal and optimal cases, respectively, with the expert group encouraging the inclusion of a self-testing modality in the TPP.

There was 93% agreement on the target setting of the test, with the expert group agreeing that, ideally, novel screening tests should be able to be conducted in a variety of settings and not limited to health care facilities, even in a minimal case.

Performance

Although there was a diversity of thinking with regard to test performance, overall, there was high agreement (>80%) on all the specific accuracy values (sensitivity and specificity) for all types of screening tests included in the document, with two exceptions. The first exception was the minimum specificity of a high-sensitivity test in a two-step algorithm; originally, this was set at 50%, and this value had 72% agreement. However, the expert group felt that the value of 50% was too low and would result in extraneous costs for screening implementation; thus, it was amended to 60%. The second exception was the minimum sensitivity of a high-specificity test; originally, this was set at 50%, and this value had 68% agreement. However, the expert group again felt that the value of 50% was too low and would result in unacceptable case detection for screening programmes; thus, it was amended to 60%.

Throughout the discussions, it was noted that the target accuracy values need to be combined with other characteristics (e.g. the setting of the test, time to result and ease of use), to ensure that such a novel test would be useful in programmatic screening implementation.

Pricing

Initially, there was less agreement in the area of pricing, with agreement levels of 56% and 66%, respectively, for proposed minimal and optimal per-test costs. Many group members felt the proposed unit costs were too high, given the volume of testing required in large-scale screening. There was extensive discussion during the expert consultation, which resulted in updated unit costs for all three types of screening tests described in the document. Although the group acknowledged the importance of market value in screening tests, it also felt strongly that it is necessary to advocate for cheaper screening tests, especially for a benchmark of a US$ 1 per test in the optimal case.

The group also felt that having a separate price point for capital costs for a screening test was unnecessary; rather, members preferred to include all aspects of pricing under a unit cost.

Operational characteristics

There was generally high agreement across operational characteristic parameters. On the specimen type, agreement was 88% and 84%, respectively, for the minimal and optimal cases, with some discussion to ensure that the document included a broad array of potential sample types that would be easy to obtain.

There was 70% and 86% agreement for the minimal and optimal time to result, respectively, with the group largely agreeing on the optimal time frame for a screening test. Subsequent discussion focused on the acceptable time to result for the minimal case. There was 86%agreement on the minimal requirements for the instrument type for novel screening tests, but a slightly lower agreement level of 79% for the optimal case, as members of the Scientific Expert Group discussed how to capture a wide range of possible new test technologies within the document.

The following characteristics all had over 80% agreement from the expert group in the Delphi-like consultation: preparation of samples, instrument type, power requirements, maintenance and calibration, training and education, documentation and display of results, regulatory requirements, language support, operating temperature and storage, environmental impact, data storage, data ownership, and security and privacy.

For further information, please contact:

Global Programme on Tuberculosis & Lung Health
World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Web site: www.who.int/tb