WHO standard

Universal access to rapid tuberculosis diagnostics

World Health Organization

WHO standard

Universal access to rapid tuberculosis diagnostics

World Health Organization

WHO standard: universal access to rapid tuberculosis diagnostics

ISBN 978-92-4-007131-5 (electronic version)
ISBN 978-92-4-007132-2 (print version)

Suggested citation. WHO standard: universal access to rapid tuberculosis diagnostics. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

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

Design and layout by Inis Communication

CONTENTS

ACKNOWLEDGEMENTS

Development of the WHO standard: universal access to rapid tuberculosis diagnostics was led by Nazir Ahmed Ismail and Carl-Michael Nathanson, with support from Alexei Korobitsyn, Cecily Miller, Dennis Falzon and Matteo Zignol and under the overall direction of Tereza Kasaeva, Director of the World Health Organization (WHO) Global TB Programme (WHO/GTB).

The following individuals at WHO headquarters and regional and country offices who contributed to review and development of the document are gratefully acknowledged:

Kleydson Alves (WHO Country office for Brazil, Brasilia, Brazil), Sridhar Anand (WHO Country office for India, New Delhi, India), Miguel Aragón López (WHO Country office for Brazil, Brasilia, Brazil), Pedro Avedillo (WHO Regional Office for the Americas, Washington DC, United States of America), Annabel Baddeley (Global TB Programme), Kenza Bennani (WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt), Vineet Bhatia (WHO Regional Office for South-East Asia, New Delhi, India), Martin van den Boom (WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt), Saskia den Boon (Global TB Programme), Regina Christian (WHO Country office for Indonesia, Jakarta, Indonesia), Soudeh Ehsani (WHO Regional Office for Europe, Copenhagen, Denmark), Ines Garcia-Baena (Global TB Programme), Princess Esguerra (WHO Country office for Philippines, Manila, Philippines), Philippe Glaziou (Global TB Programme), Michel Gasana (WHO Regional Office for Africa, Brazzaville, Congo), Christian Gunneberg (Global TB Programme), Karina Halle (Global TB Programme), Aleksandr Goliusov (WHO Country office for the Russian Federation, Moscow, Russian Federation), Clarissa Halum (WHO Country office for Philippines, Manila, Philippines), Anupama Hazarika (WHO Country office for Bangladesh, Dhaka, Bangladesh), Jean de Dieu Iragena (WHO Regional Office for Africa, Brazzaville, Congo), Ernesto Jaramillo (Global TB Programme), Tauhidul Islam (WHO Regional Office for the Western Pacific, Manila, Philippines), Laeeq Khawaja (WHO Country office for Pakistan, Islamabad, Pakistan), Giorgi Kuchukhidze (WHO Regional Office for Europe, Copenhagen, Denmark), Hughes Lago (WHO Regional Office for Africa, Brazzaville, Congo), Setiawan Laksono (WHO Country office for Indonesia, Jakarta, Indonesia), Rafael Lopez (WHO Regional Office for the Americas, Washington DC, United States of America), Partha Mandal (WHO Regional Office for South-East Asia, New Delhi, India), Fuad Mirzayev (Global TB Programme), Jonathan Marbun (WHO Country office for Indonesia, Jakarta, Indonesia), Ernesto Montoro (WHO Regional Office for the Americas, Washington DC, United States of America), Nobuyuki Nishikiori (Global TB Programme), André Ndongosieme (WHO Regional Office for Africa, Brazzaville, Congo), Kyung Oh (WHO Regional Office for the Western Pacific, Manila, Philippines), Eunice Omesa (WHO Country office for Kenya, Nairobi, Kenya), Amos Omoniyi (WHO Country office for Nigeria, Abudja, Nigeria), Raghavan Parthasarathy (WHO Country office for India, New Delhi, India), Philip Patrobas (WHO Country office for Nigeria, Abudja, Nigeria), Anuzaya Purevdagva (WHO Country office for Mongolia, Ulan Bator, Mongolia), Kalpeshsinh Rahevar (WHO Regional Office for the Western Pacific, Manila, Philippines), Lakshmi Rajagopalan (WHO Country office for India, New Delhi, India), Ranjani Ramachandran (WHO Country office for India, New Delhi, India), Kamar Rezwan (WHO Regional Office for South-East Asia, New Delhi, India), Nazis Saki (WHO Country office for Bangladesh, Dhaka, Bangladesh), Mukta Sharma (WHO Regional Office for South-East Asia, New Delhi, India), Nympha Sia (WHO Country office for Philippines, Manila, Philippines), Charalampos Sismanidis (Global TB Programme), Ireneaus Sindani (WHO Country office for Somalia, Hargeisa, Somalia), Hazim Timimi (Global TB Programme), Evelyne Tibananuka (WHO Country office for Uganda, Kampala, Uganda), Rajendra Yadav (WHO Regional Office for the Western Pacific, Manila, Philippines), Askar Yedilbayev (WHO Regional

Office for Europe, Copenhagen, Denmark), Saltanat Yegeubayeva (WHO Country office for the Russian Federation, Moscow, Russian Federation).

The WHO is also grateful to the WHO technical advisory group for diagnostics and laboratory strengthening for their valuable contribution to the development of the WHO standard:

Heidi Albert (FIND, South Africa), Khalide Azam (East Central and Southern Africa Health Community, United Republic of Tanzania), Daniela Cirillo (San Raffaele Supranational TB Reference Laboratory, Italy), Christopher Coulter (Queensland Health, Australia), Valeriu Crudu (National TB Reference Laboratory, Moldova), Claudia Maria Denkinger (Heidelberg University Hospital, Germany), Patricia Eidson-Hall (Centers for Disease Control and Prevention, United States of America), Nguyen Van Hung (National Tuberculosis Reference Laboratory, Viet Nam), Farzana Ismail (National Institute for Communicable Diseases, South Africa), Irina Lyadova (Laboratory of Cellular and Molecular Basis of Histogenesis, Russian Federation), Sandeep Meharwal (FHI360, Thailand), Vithal Prasad Myneedu (SAARC TB and HIV/AIDS Centre, Nepal), Mark Nicol (University of Western Australia, Australia), Madhukar Pai (McGill University, Canada), Paulo Redner (National Reference Laboratory for Tuberculosis, Brazil), Sadia Shakoor (Aga Khan University Hospital, Pakistan), Siva Kumar Shanmugan (Indian Council of Medical Research, India), Thomas Shinnick (Independent Consultant, United States of America), Sabira Tahseen (National TB Reference Laboratory, Pakistan), Alaine Umubyeyi Nyaruhirira (Management Sciences for Health, South Africa), Xin Shen (Shanghai Municipal Center for Disease Control and Prevention, China), Zhao Yanlin (Chinese Centers for Disease Control and Prevention, China).

WHO is also grateful to the experts responsible for the systematic review, stakeholder consultations and development of the investment case:

Omolayo Anjorin (London School of Tropical Medicine, United Kingdom), Naveed Delorooz (Tulane University, United States of America), Matthew Edwards (Oxford University, United Kingdom), Nora Engel (Maastricht University, Netherlands [Kingdom of]), Andrew McDowell (Tulane University, United States of America), Troy Murrell (Clinton Health Access Initiative, United States of America), Ruvandhi Nathavitharana (Harvard Medical School and TB Proof, United States of America and South Africa), Matthew O'Bryan (Harvard Medical School , United States of America), Abarna Pearl (Harvard Medical School , United States of America), Karen Steingart (Cochrane Infectious Diseases Group, United Kingdom), Advaith Subramanian (Tulane University, United States of America), Helene-Mari van der Westhuizen (TB Proof and Oxford University, South Africa and United Kingdom) and Bruna Voldman (Technion's American Medical School, Israel).

The WHO standard was reviewed by representatives of national TB programmes and national TB reference laboratories, who provided important feedback on the overall standard, the individual benchmarks and implementation in countries. WHO is grateful for the insights, country experiences and suggestions made by the following people, who participated in many meetings to discuss the standard:

Rita Akamkpa (Nigeria), Elom Amaka (Nigeria), Chukwuma Anyaike (Nigeria), Sivavallinathan Arunachalam (India), Billy Banda (Malawi), Knox Banda (Malawi), Leonard Barreto (Brazil), Sayadul Bashar (Bangladesh), Ramon Basilio (Philippines), Daria Chaadaeva (Russian Federation), Roni Chandra (Indonesia), Obioma Chijioke-Akaniro (Nigeria), Samson Chitsulo (Malawi), Valeriu Crudu (Republic of Moldova), Daria Demina (Russian Federation), Fernanda Dockhorn (Brazil), Oyunchimeg Erdenee (Mongolia), Ailene Espiritu (Philippines), Allan Fabella (Philippines), Abdul Ghafoor (Pakistan), Azadar Gillani (Pakistan), Karen Gomes (Brazil), Ahmadul Hasan Khan (Bangladesh), Ratnameyda Kania (Indonesia), Michel Kaswa Kayomo (Democratic

Republic of the Congo), Jacqueline Kisia (Kenya), Nishan Kumar (India), Usman Lodji (Pakistan), Christina Lourenço (Brazil), Umme Tasnim Maliha (Bangladesh), Sandeep Meharwal (Thailand), Nicole Menezes de Souza (Brazil), Israel Nengi (Nigeria), Jeremiha Ogoro (Kenya), Mercy Oluya (Uzbekistan), Raghavan Parthasarathy (India), Pronab Kumar Modak (Bangladesh), Muharnis Putri (Indonesia), Ejaz Qadeer (Pakistan), Fatima Razia (Pakistan), Paulo Redner (Brazil), Dewi Retno (Indonesia), Anastasia Samoilova (Russian Federation), Charles Sandy (Zimbabwe), Cecilia Serrano (Philippines), Rupali Shishir Banu (Bangladesh), Titiek Sulistyowati (Indonesia), Fransisca Sunny (Indonesia), Eduardo de Souza Alves (Brazil), Adeel Tahir (Pakistan), Maiko Tonini (Brazil), Laziz Turaev (Uzbekistan), Emperor Ubochioma (Nigeria) and Diana Vakhrusheva (Russian Federation).

The WHO is grateful to the following representatives of partner organizations for their comments during development of the standard:

Puneet Dewan (Bill and Melinda Gates Foundation, United States of America), Celeste Gracia Edwards (Global Fund to Fight HIV, Malaria and Tuberculosis, Switzerland), Wayne van Gemert (Stop TB Partnership, Switzerland), Obert Kachuwire (Global Fund to Fight HIV, Malaria and Tuberculosis, Switzerland), Refiloe Matji (Global Fund to Fight HIV, Malaria and Tuberculosis, Uganda), YaDiul Mukadi (United States Agency for International Development, United States of America), Izabella Ogonezova (United States Agency for International Development, Uzbekistan), Amy Piatek (United States Agency for International Development, United States of America), Suvanand Sahu (Stop TB Partnership, Switzerland), Kaiser Shen (United States Agency for International Development, United States of America), Simon Walusimbi (Global Fund to Fight HIV, Malaria and Tuberculosis, Uganda), Eliud Wandawalo (Global Fund to Fight HIV, Malaria and Tuberculosis, Switzerland).

The WHO also thanks all the participants at the virtual End TB Summit hosted by WHO in 2022 for their contributions and feedback on the WHO standard during the session on diagnostics.

This product was developed with support from the Bill and Melinda Gates Foundation and the United States Agency for International Development.

ABBREVIATIONS AND ACRONYMS

CAD	computer-aided detection of TB-related abnormalities on chest radiography
CXR	chest X-ray
DST	drug susceptibility testing
FQ	fluoroquinolone
IQR	interquartile range
LF-LAM	lateral flow lipoarabinomannan
NTP	national tuberculosis programme
PLHIV	people living with HIV
RIF	rifampicin
RR	rifampicin-resistant
TAT	turn-around time
TB	tuberculosis
WHO	World Health Organization
WRD	WHO-recommended rapid diagnostic
XDR-TB	extensively drug-resistant TB

EXECUTIVE SUMMARY

The 2018 United Nations High-level Meeting set the target of treating at least 40 million people with tuberculosis (TB) between 2018 and 2022; however, only 66% of that target had been attained by 2021. Diagnostic tests are central to meeting the goal, but they are a weak link in the continuum of care. The World Health Organization (WHO)-recommended rapid diagnostics (WRDs) are highly accurate, reduce the time to treatment initiation, impact patient-important outcomes, and are cost-effective. Although the goal is for all notified patients to be tested initially with a WRD by 2025, in 2021, only 38% were tested with a WRD as an initial test, and access to diagnostics was identified as a critical issue. A major consequence of the insufficient use of WRDs is the large gap in the detection of drug resistance.

This *WHO standard: universal access to rapid tuberculosis diagnostics* is based on the WHO guidelines and the operational handbook. The objectives of the standard are to improve access to and use of WRDs as the initial test for individuals with presumptive TB identified through active and passive case finding, to increase detection of bacteriologically confirmed cases and drug resistance, and to reduce the time to diagnosis. The standard comprises 12 benchmarks to be computed by countries in the four steps of the diagnostic cascade: identifying presumptive TB, accessing testing, being tested, and receiving a diagnosis.

Mapping of enablers, approaches and solutions to scaling up use of WRDs is provided to assist countries in meeting the standard. In addition, two country case studies that provide real-world examples of implementation and specific considerations for investment in scaling up TB diagnostics are included. Universal access to TB diagnostics will result in better health for all and reduce the unacceptably high mortality rate due to this curable and preventable disease. This will require investment and concerted work by countries, partners, donors and civil society.

STEP 1

IDENTIFYING PRESUMPTIVE TB

Increase the number of people with presumptive TB in care

Benchmark 1

All household contacts, all PLHIV, and other locally relevant high-risk groups are screened for TB.

Benchmark 2

In all districts, chest X-ray is used regularly for TB screening.

STEP 2

ACCESSING TESTING

Increase access to WRDs

Benchmark 3

In all facilities in all districts, the TB diagnostic algorithm requires the use of a WRD as the initial diagnostic test for all individuals with presumed TB, including children and PLHIV (combined with lateral flow lipoarabinomannan [LF-LAM]) and extrapulmonary TB.

Benchmark 4

All primary health-care facilities have access to WRDs (on site or through sample referral).

Benchmark 5

All individuals with TB have access to a WRD as the initial diagnostic test.

Benchmark 6

WRD testing capacity meets expected needs, including surge capacity, according to the latest data.

STEP 3

BEING TESTED

Increase WRD and drug resistance testing

Benchmark 7

All functional instruments have an error rate ≤ 5%.

Benchmark 8

All individuals with presumptive TB are tested with a WRD.

Benchmark 9

All patients with bacteriologically confirmed TB undergo universal drug susceptibility testing.

STEP 4

RECEIVING A DIAGNOSIS

Increase WRD-based diagnosis

Benchmark 10

All patients with pulmonary TB receive an initial WRD result to inform their diagnosis.

Benchmark 11

All districts monitor the test positivity rate to optimize the impact of screening and testing strategies.

Benchmark 12

All TB testing laboratories achieve a turn-around time of ≤ 48 h for ≥ 80% of samples received for WRD testing.

PART 1

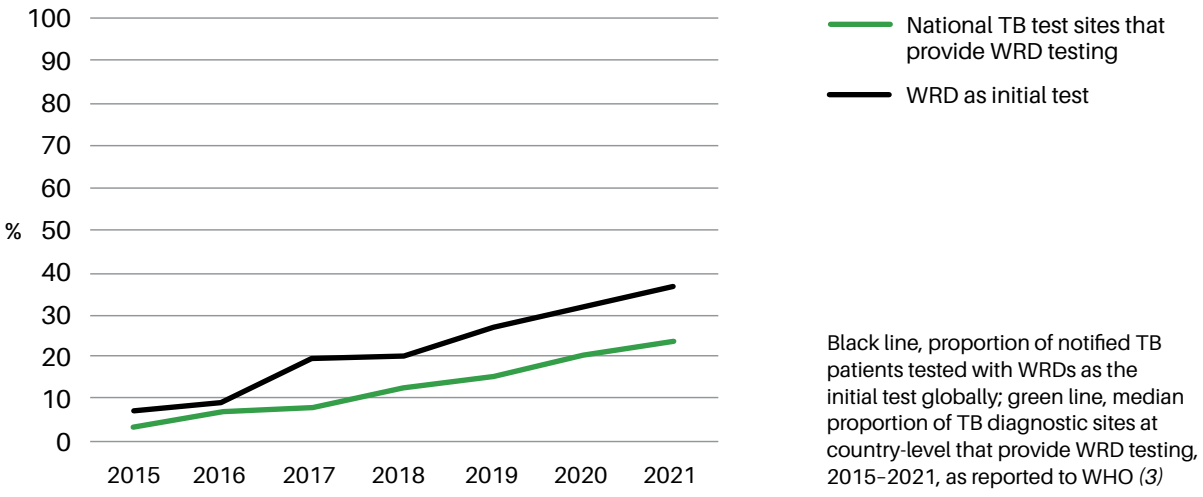
WHO STANDARD

UNIVERSAL ACCESS TO RAPID TUBERCULOSIS DIAGNOSTICS

INTRODUCTION

The End TB Strategy set milestones for significant reductions in the rates of mortality and incidence and catastrophic costs related to tuberculosis (TB) by 2025 *(1)*. The first action within pillar 1 is *integrated, patient-centred care and prevention*, early diagnosis of TB, including universal drug susceptibility testing (DST) and systematic screening of contacts and vulnerable groups. In 2021, a decade after the first WHO guidelines on use of WHO-recommended rapid diagnostics (WRDs), only 38% (Fig. 1, black line) of patients notified with new or relapse TB had been tested initially with a WRD *(2)*, whereas all people who require testing are expected to be tested with a WRD by 2025 *(1)*. Progress towards this target is lagging, due partly to limited access to WRDs; only 25% (Fig. 1, green line) of TB diagnostic sites in 2021 had WRDs.

Fig. 1. Improving access to WRDs



Black line, proportion of notified TB patients tested with WRDs as the initial test globally; green line, median proportion of TB diagnostic sites at country-level that provide WRD testing, 2015–2021, as reported to WHO *(3)*

WRDs are tests to be used as initial diagnostics for TB that detect *Mycobacterium tuberculosis* DNA or a biomarker. By definition, WRDs do not include sputum smear microscopy, although this test is still relevant for treatment monitoring. In this document, the term "WRD" refers to molecular WRDs unless otherwise specified and comprises products from seven manufacturers (Fig. 2). The list is likely to lengthen as a result of the WHO path for prequalification of additional molecular TB tests *(4,5)*. Currently, the only non-molecular biomarker-based WRD is the Alere Determine TB LAM Ag test. Its use currently is limited to specific indications among people living with HIV (PLHIV) and not for all patients with presumptive TB, irrespective of their current HIV status.

Fig. 2. WHO-recommended rapid diagnostic testing platforms to be used as initial tests for TB, 2022

Xpert MTB/RIF & Ultra

Truenat MTB, MTB Plus & -RIF Dx

Loopamp™ MTBC detection

Abbott *RealTime MTB & MTB RIF/INH*

BD MAX MDR-TB

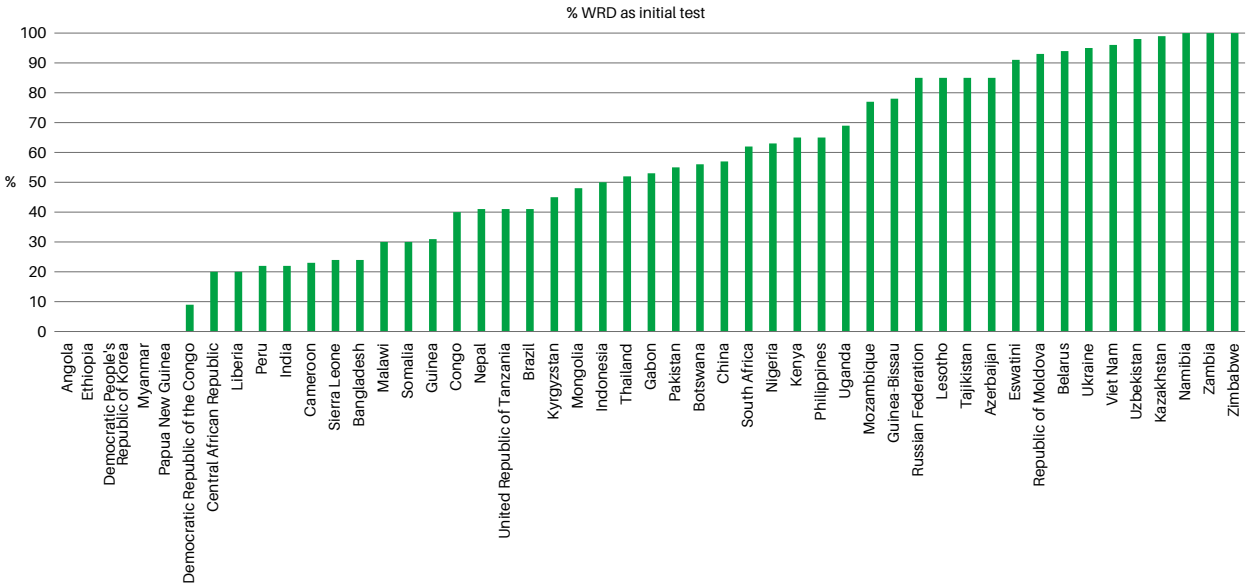
cobas® MTB & MTB-RIF/INH

FluoroType MTB & MTBDR

In 2021, the proportion of people notified with TB who had received a WRD as the initial diagnostic test varied significantly by country (Fig. 3). This proportion was low in many high-TB-burden countries, such as Bangladesh (24%), Democratic Republic of the Congo (9%), Ethiopia (< 1%) and India (22%), and moderate in others, such as China (57%), Indonesia (50%) and Pakistan (55%) *(2)*. These seven countries contributed almost 60% of all notified TB cases globally in 2021. There are nevertheless several low- and middle-income countries in which the rates were high, indicating the feasibility of scaling up use of WRDs as the initial test. These include Kazakhstan (99%), Viet Nam (96%) and Zambia (100%).

Low rates of testing for drug resistance are a further concern. Only 70% of all bacteriologically confirmed cases were tested for rifampicin (RIF) resistance; < 50% of all RIF-resistant (RR) TB patients were tested for fluoroquinolone (FQ) resistance; and testing for resistance to other group A drugs (e.g. bedaquiline and linezolid) remains very limited, despite its increasing importance *(2)*.

Fig. 3. Proportions of notified TB patients who received a WRD as an initial test, by high-burden country, 2021



Use of WRDs as the initial test for all patients with presumptive TB is essential for addressing diagnostic gaps. Other aspects of the diagnostic cascade that should also be addressed are:

- patient education and reducing stigmatization;
- diagnosis of early stages of TB disease, particularly in people who do not report symptoms;
- access to testing at peripheral level in the public and private sectors;
- quality assurance of diagnostic services;
- potential consequences of an incorrect diagnosis if not bacteriologically confirmed;
- turn-around time (TAT) for receiving results; and
- under-reporting due to either a poor data system or lack of reporting from the non-national TB programme (NTP) sector.

WHO has issued a consolidated guideline on TB diagnostics *(6)*, which provides recommendations for use of each test, and an operational handbook with concrete steps for implementing the tests and model algorithms *(7)*.

Part 1 of this document provides the *WHO standard for universal access to rapid TB diagnostics,* with 12 benchmarks mapped along the diagnostic cascade. Each benchmark is to be computed nationally to identify gaps and track progress in using and scaling up use of WRDs. The first draft of the standard and benchmarks were developed through iterative inputs from WHO headquarters, regional and country staff and a few individuals from countries and implementers. The technical advisory group for diagnostics (TAG) provided strategic input to the first draft. Thereafter, a series of consultations was held with several national TB programmes and partners in high-burden TB countries. Input was also received from the WHO Civil Society Task Force and the WHO Public–Private Mix working group. During the annual EndTB summit in 2022, additional input was received from national TB programmes, and the final draft was reviewed by the TAG. Participants providing input through the various consultations were not involved in the final decision making process and were not required to declare their interests.

Part 2 provides further guidance and describes enablers, approaches and solutions for scaling up the use of WRDs, with country case studies and considerations for investment. Researchers at Tulane University (United States of America) provided a report on stakeholders' perspective on barriers and enablers to use of WRDs; Harvard Medical School (United States of America) and TB Proof (South Africa) conducted a mixed methods systematic review of means to increase the uptake and impact of WRDs; and the Clinton Health Access Initiative (United States of America) summarized considerations for investing in universal access to WRDs.

WHO STANDARD

Objectives

The objectives of this *WHO standard* are to:

- improve access to and use of WRDs as initial tests for individuals with presumptive TB identified by active and passive case finding;
- increase detection of bacteriologically confirmed and drug-resistant TB; and
- reduce the time to diagnosis.

Core principles

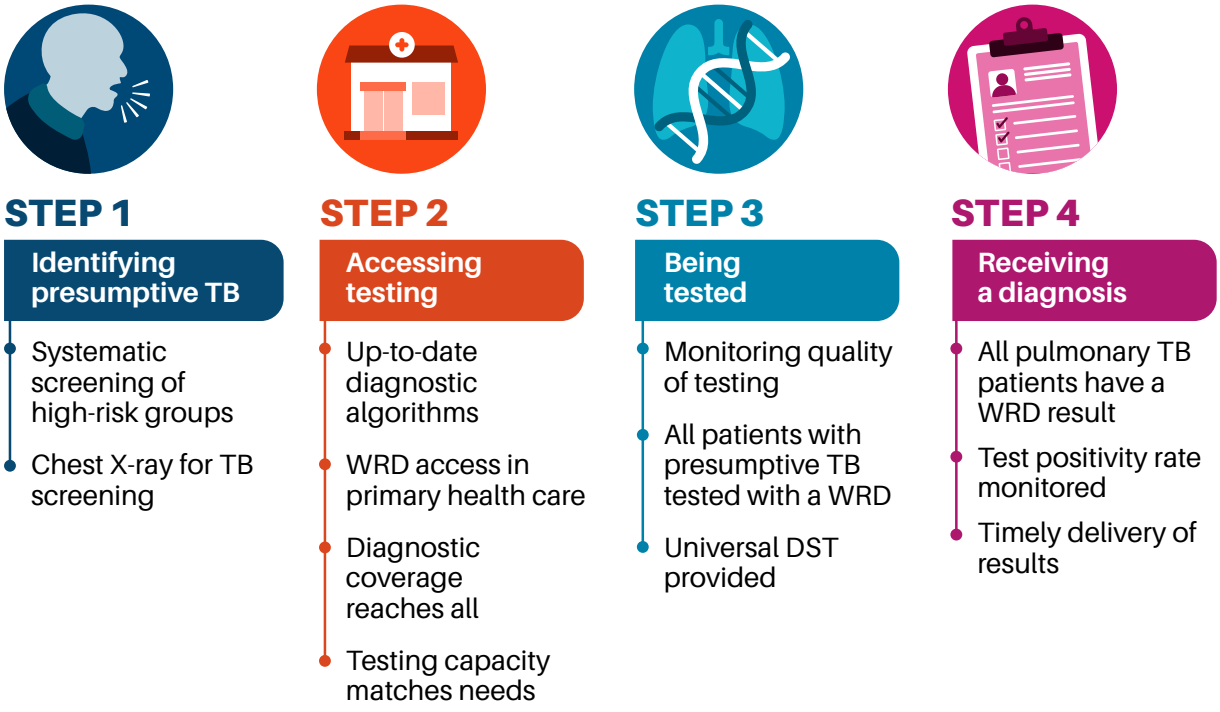
The following core principles underpin implementation of the *WHO standard: universal access to rapid tuberculosis diagnostics*.

Principle	Interpretation
1. Strong political and financial commitment is available to ensure access to TB diagnosis.	Financial, technical, and human resources should be specified in planning documents, with additional support from the ministry of finance and from partners, donors, and civil society.
2. Diagnostic testing is equitable.	All individuals with presumptive TB in all sectors (public, private, non-NTP) should be eligible for WRD testing.
3. The most accurate, rapid tests are used to diagnose TB.	Transition from smear microscopy to WRDs as the initial test for TB diagnosis should be accelerated.
4. The diagnostic approach is patient centred.	Barriers that result in a negative patient experience and related costs should be minimized.
5. Diagnostic coverage reaches all levels of the health system and covers patients in private and other non-NTP sectors.	In accordance with plans for universal health coverage, WRDs should reach all primary health care facilities systematically and progressively in public, private, and non-NTP sectors.
6. Diagnostic results are provided in a timely manner in order to be useful for patient management.	On-site WRD testing should be provided in high-workload settings or where timely results cannot be obtained by sample referral. Sample referral systems should be strengthened for all other health facilities. Digital systems are used to improve timely access to results and analysis.
7. Diagnostic capacity is optimally used according to the local context.	All individuals with presumptive TB identified through passive and active case finding should have access to TB diagnostic testing including multi-disease testing (for, e.g. COVID-19, early infant diagnosis, and viral load for HIV), according to the local context.

The diagnostic cascade

Patient care cascades are useful for identifying gaps and planning strategies to close them. These care cascades are used increasingly in TB control programmes *(8)*. The cascade adapted to attain universal access to TB diagnosis is shown in Fig. 4. The four-step cascade ensures that issues related to access and use of WRDs are addressed. The systematic review and case studies presented in Part 2 of this document demonstrate the critical importance of a multi-component approach.

Fig. 4. The four-step cascade of care used to structure the WHO standard: universal access to rapid tuberculosis diagnostics



This WHO standard for universal access to TB diagnostics is designed to increase the number of individuals who sequentially enter the four steps of the diagnostic cascade, each step having specific benchmarks. As screening is not the main focus of this standard, the first step is limited to two TB screening benchmarks. Similarly, as treatment and notification are done after the diagnostic cascade, no benchmarks are provided for those aspects of TB care.

There are 12 benchmarks in the four steps of the diagnostic cascade. Six of the benchmarks also have specific application in the non-NTP and private sector and should be included when those sectors contribute > 10% of the total notified burden. Such benchmarks are identified with an asterisk. The benchmarks are not meant to be all-comprehensive but focus on aspects that are important, can be monitored regularly and prompt further action. Numerators and denominators are proposed, which can be adapted to the country context after field testing. The measure should be computed at least annually.

STEP 1
IDENTIFYING PRESUMPTIVE TB

Increase the number of people with presumptive TB in care

The first step in the cascade of care, although not directly related to access and use of WRDs, addresses the population for which diagnostics are required. The objective of the benchmarks in this step is to increase the number of patients with presumptive TB who enter the pathway towards WRD testing and diagnosis. No benchmark is set for passive case finding, as this is performed routinely. Nevertheless, shortcomings in identifying individuals with presumptive TB and the overall patient flows in facilities can result in missed diagnostic opportunities *(9),* and quality improvement programmes should be included *(10).* The two benchmarks are based on strong recommendations by WHO for systematic TB screening. The first is to increase coverage of screening of specific populations, including household contacts, PLHIV, and other high-risk groups, according to the local context. The second benchmark is to increase access to highly sensitive tools for screening, beyond symptoms, by use of chest X-rays (CXR), with or without computer-aided detection (CAD).

STEP 1: Identifying presumptive TB

Benchmark

1 All household contacts, all people living with HIV, and other locally relevant high-risk groups are screened for TB*[1]

Gap to be addressed: PLHIV and household contacts of patients with bacteriologically confirmed TB, particularly children < 5 years, are among the groups at highest risk for developing TB. Systematic screening is strongly recommended to establish whether TB treatment or TB preventive treatment is required. The latest WHO consolidated screening guidelines *(11)* and operational handbook *(12)* list the high-risk groups that will benefit from systematic TB screening and describe the approaches and algorithms to be used. The uptake of TB screening has varied. Prioritization of high-risk groups for screening should be specified in country plans.

Application: Population-level screening of household contacts, PLHIV, and at least one other high-risk group should be conducted regularly. All household contacts of each patient with bacteriologically confirmed TB are screened with WHO-recommended methods and referred for testing if appropriate. The data on household contacts below are those currently reported to WHO. For PLHIV, the results of screening are documented at every encounter with the health-care system in high-burden settings, while screening of other risk groups is specified according to the local context. Risk groups should be selected on the basis of risk for TB disease or rapid progression to TB disease and mortality. (See the WHO guidelines for a list of high-risk groups, according to the available evidence *(11)*).

1A Screening of household contact

Numerator (household contact)

Number of household contacts of new and relapse cases of bacteriologically confirmed and notified pulmonary TB who were screened for TB

Denominator (household contact)

Number of household contacts of new and relapse cases of bacteriologically confirmed and notified pulmonary TB

1B Screening of other high-risk groups

Numerator (other risk group, e.g. PLHIV)

Number of individuals identified in additional high-risk group(s) screened for TB

Denominator (other risk group, e.g. PLHIV)

Number of individuals identified in the additional high-risk group(s)

* **Application in the non-NTP or private sector:** Groups at high risk in occupational and other settings should be screened. Examples include miners, prisoners and health-care workers. Data on individuals screened should be reported to the NTP annually. The numerator and denominator for "other high-risk group" can be used.

[1] The star against the title of this benchmark and against those of benchmarks 4, 5, 8, 9 and 10 signifies that the benchmark has specific application requirements in the non-NTP or private sector.

Benchmark

STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 1: Identifying presumptive TB

Benchmark

2 In all districts, chest X-ray is used regularly for TB screening

Gap to be addressed: Globally, approximately 10 million individuals are estimated to develop TB annually. The gap between the estimated and notified numbers of cases increased from 3 to 4 million per annum during the COVID-19 pandemic. Screening based only on symptoms misses approximately half of all cases of pulmonary TB in community settings *(2,13,14)*. The evidence presented in the 2021 screening guidelines indicates that the sensitivity of any cough or a cough of ≥ 2 weeks' duration for detection of TB disease is only 51% and 42%, respectively *(11)*. Screening by chest radiography (CXR) (and CAD when available) is a highly sensitive (≥ 85%) WHO-recommended approach for early identification of TB in high-risk or vulnerable groups with reasonable specificity (≥ 89%) *(11)*. This benchmark focuses on CXR in view of the sensitivity of this tool, longstanding familiarity of TB staff in its use and its relatively widespread availability in health services.

Numerator
Number of districts in which CXR is used regularly (with or without CAD) for TB screening

Denominator
Total number of districts in the country

Application: CXR for TB screening in a district is defined as its use as the primary tool for TB screening with or without CAD in high-risk groups. Regular screening in this context is defined as CXR screening every week of the year or at least in quarterly active case-finding campaigns. CXR equipment can be fixed (e.g. in a facility) or portable (e.g. in a mobile clinic). It should have sufficient capacity for the number of individuals to be screened by CXR. The proposed benchmark may have to be adapted to the local context. Exclusive use of CXR for other purposes, i.e. not for primary TB screening, should not be included in the numerator. Examples that would not qualify as primary TB screening are the use of CXR only for work-up of clinically unwell patients with chest findings (e.g. pneumonia) or for follow-on testing of people with TB symptoms. A district is an officially demarcated area known as a basic management unit or county in some settings. It is a level of the health system that is below that of a province or state. In districts with a large catchment population (e.g. more than one million) or with a vast territory, the benchmark should be modified to assess coverage at a lower level (e.g. sub-district).

Benchmark

STEP 1	Identifying presumptive TB	1	2			
STEP 2	Accessing testing	3	4	5	6	
STEP 3	Being tested	7	8	9		
STEP 4	Receiving a diagnosis	10	11	12		

Navigation

STEP 2
ACCESSING TESTING

Increase access to WRDs

The aim of the second step is to increase access to WRDs in health-care facilities. The benchmarks flow from the availability of the WRD-based diagnostic algorithm *(3)*, access to WRDs in all facilities *(4)* and for all patients *(5)*, and having the required testing capacity *(6)*. Access can be limited by outdated local policies and algorithms or restricting use of WRDs to certain populations. Benchmark 4 focuses on access in primary health care, as approximately 80% of individuals who seek health care do so at this level *(15)*. Access in primary health care is a proxy for early diagnosis and WRD availability, either on site or through efficient sample referral, is preferred, rather than patient referral for testing. Benchmark 5 addresses overall diagnostic coverage based on the number of notifications, as the burden is often geographically heterogeneous. Priority should be given to high-burden TB settings in order to reach the largest absolute number of patients with presumptive TB rapidly, if this has not already been done, and to increase access to facilities with a lower absolute burden progressively.

STEP 2: Accessing testing

Benchmark

3 In all facilities in all districts, the TB diagnostic algorithm requires use of a WRD as the initial diagnostic test for all patients with presumed TB, including children, PLHIV (combined with lateral flow lipoarabinomannan [LF-LAM]) and extrapulmonary TB

Gap to be addressed: In 2021, only 38% of all notified cases were initially tested with a WRD. According to the End TB strategy, all people with TB should undergo testing with a WRD by 2025. In order to achieve universal access to WRDs, all individuals with presumptive TB**,** and not only those in high-risk groups, should be tested with these accurate, rapid tools. Additionally, children and individuals with extrapulmonary TB represent a significant proportion of all notified patients. It is vital that these individuals benefit from rapid, accurate diagnostics, and WHO guidelines address these populations *(6,16)*. Specifically for PLHIV, as per WHO guidelines, the algorithm includes use of LF-LAM in the diagnosis of TB.

Application: A common TB diagnostic algorithm is applied at all health-care facilities in all districts. The algorithm specifies that WRDs are to be used as the initial diagnostic test for all patients with presumptive TB. In addition, clear processes for the work-up of TB in PLHIV, children and extrapulmonary sites TB are presented in the same or another algorithm or flow chart. Random audits of a sample of health-care facilities in a district could be used for confirmation.

Numerator

Number of districts in which all facilities have a TB diagnostic algorithm that requires a WRD to be used as the initial diagnostic test for all individuals with presumptive TB, including children and individuals with HIV (combined with LF-LAM) and extrapulmonary TB

Denominator

Total number of districts in the country

Benchmark

STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 2: Accessing testing

Benchmark

4 All primary health-care facilities have access to WRDs (on site or through sample referral)*

Gap to be addressed: More than 80% of individuals with symptoms of TB enter the health system at the level of primary health care *(15)*. In most settings, data are generally not available on access to WRDs in primary health-care facilities. An indirect measure is the number TB testing sites with access to WRDs in a country. In 2021, only 25% of all TB testing sites globally had access to WRDs, while smear microscopy was available in almost all settings. Lack of access at primary health-care level could therefore lead to an incorrect diagnosis, an economic burden for patients to access the next level of care, or delays in diagnosis, with associated morbidity or mortality. In many primary health-care facilities, access to WRD is feasible through sample referral; however, the timeliness of sample transport is important and is addressed in benchmark 12 of this WHO standard.

Application: Primary health care has been previously defined *(17)* and is the cornerstone of achievement of universal health coverage and the Sustainable Development Goals. The package of essential health services to be provided in primary health care should be defined at national level. Countries listed as having a high burden of TB, TB-HIV or MDR/RR-TB generally require access to TB services in primary health care. Access to WRD testing in primary health-care facilities is either on site or through a functioning sample referral system, the latter being a system in which samples are dispatched from a health facility within 24 h of collection. Facilities with a low workload should dispatch samples on demand. A primary health-care facility with access to WRD through sample referral can be included in this indicator if there is evidence of regular sample referral (e.g. every week of the year).

Numerator

Number of primary health-care facilities with access to WRDs (either on site or through a sample referral system)

Denominator

Total number of primary health-care facilities in the country

* **Application for non-NTP or private sector health facilities:** WRD testing should be provided to people with presumptive TB who present to private health facilities in high-burden countries. Access to WRD testing for these facilities can be provided by private intermediary agencies that can link privately managed patients to free testing services in the public sector or within private laboratory engagement models that ensure capping of WRD prices, access and reporting to the NTP. Numerator: Number of districts with a private sector access model for private health facilities. Denominator: Total number of districts in the country

Benchmark

STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 2: Accessing testing

Benchmark

5 All individuals with TB have access to a WRD as the initial diagnostic test*

Gap to be addressed: Access to WRDs is not only about ensuring availability in facilities but also ensuring individuals affected by TB are tested with a WRD. Only 38% of TB patients in 2021 who were in care received a WRD as the initial test *(2)*, with annual rates between 2017 and 2021 showing small increases: 21%, 22%, 28%, 33% and 38%, respectively. Significant changes are required to ensure that all individuals with presumptive TB receive a WRD, with prioritization of facilities with the highest burden of disease.

Numerator
Number of notified new and relapse TB cases tested initially with a WRD

Denominator
Total number of notified patients

Application: Diagnostic coverage can be measured in various ways. Benchmark 4 focuses on access in a health facility, while this benchmark addresses patient access. For practical reasons, the percentage of notified new and relapse TB cases tested with a WRD as the initial diagnostic test is used as a proxy for access. This measure has been monitored over time. Stratification by level of the health system (e.g. hospitals versus clinics), geographical area (e.g. urban versus rural) and sector (e.g. public versus private) is also useful for understanding and responding to gaps in coverage and broader issues of access to diagnostics. A limitation of using notification data as the denominator is that they do not include people who did not receive a diagnosis and those who were diagnosed but were not notified.

*Application for non-NTP or private sector health facilities: The numerator and denominator should be provided separately for the non-NTP or private sector.

Benchmark

STEP 1 Identifying presumptive TB — 1 2
STEP 2 Accessing testing — 3 4 5 6
STEP 3 Being tested — 7 8 9
STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 2: Accessing testing

Benchmark

6 WRD testing capacity meets expected needs, including surge capacity, according to the latest data

Gap to be addressed: To achieve universal access to WRDs, testing capacity must be available to ensure that all individuals with presumptive TB can be tested with a WRD. "Capacity" refers to the number of tests that can be performed within the recommended TAT on functioning instruments in relation to the expected number of individuals with presumptive TB. The diagnostic network might have to be improved, including a baseline diagnostic network assessment *(18,19)* and further diagnostic network optimization *(20)* for placement of instruments to maximize their impact.

Application: Testing capacity depends on the number, type and functionality of the instruments available. Testing capacity is the product of the number of tests that can be reasonably performed per day on a module/slot/run, the total number of modules/slots/instruments available, the number of shifts in a working day and the number of working days in a year. Only functional instruments, modules, or slots should be included in the assessment. Testing capacity should be assessed in relation to the total requirement for testing, which is the number of individuals with presumptive TB in a year. Ideally, the number of individuals with presumptive TB is recorded. If the number of patients with presumptive TB is not quantified from a registry, it can be estimated from data on testing volume in laboratory registers (for all types of TB tests), percentage increase applied for any expected change in demand (surge capacity) to account for seasonal variation (e.g. cough patterns), day-to-day variation, ad-hoc case-finding campaigns, and the number of invalid and repeated tests (e.g. two smears or one WRD test for initial diagnosis). A further adjustment to account for the estimated number of people not accessing any testing should be added. In settings in which WRDs are used widely as the initial test for TB, the test-positivity rate could also be used. As the capacity may be shared with other diseases, only the capacity allocated for TB testing should be included in the numerator.

Numerator

Number of WRD tests that can be performed with the existing instruments

Denominator

Number of tests required to test all patients with presumptive TB

Benchmark

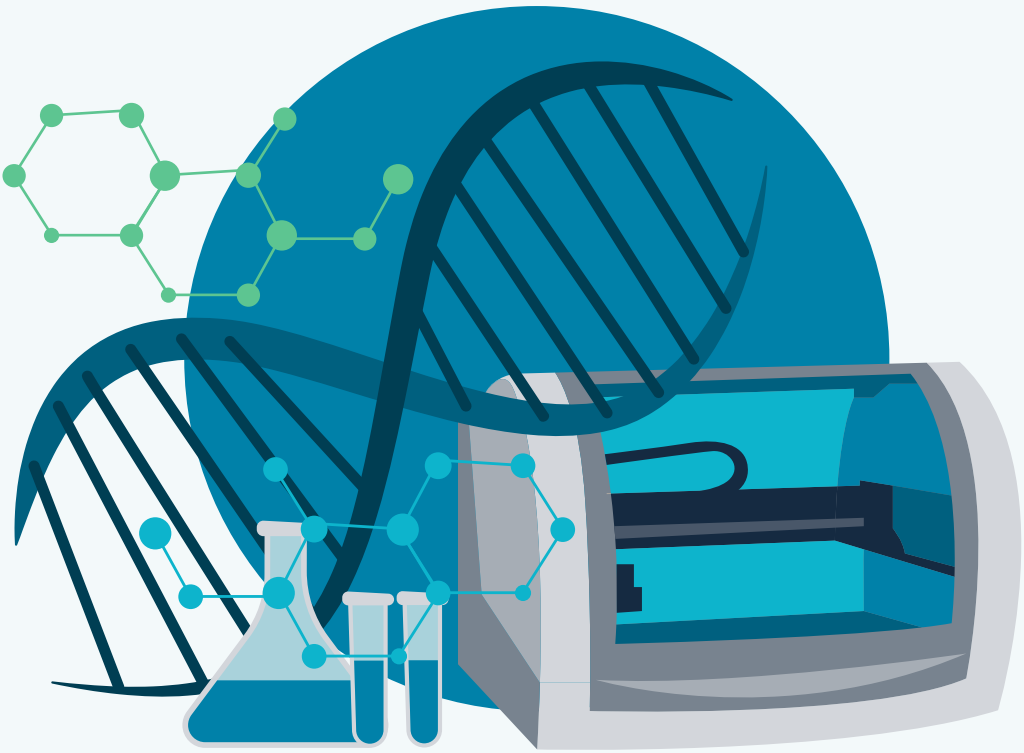
STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation



STEP 3
BEING TESTED

Increase WRD and drug resistance testing

The third step covers WRD use, with three benchmarks. Benchmark 7 addresses quality-assured testing, which is fundamental for the results generated. Various aspects influence quality. This benchmark is specific to WRDs and does not cover all the issues in diagnostic quality management systems. Benchmark 8 is the most direct measure of access: the percentage of patients with presumptive TB tested with a WRD as the initial diagnostic test. Benchmark 9 addresses universal DST at baseline and follow-on testing for susceptibility to additional drugs.

STEP 3: Being tested

Benchmark

7 All functional instruments have an error rate ≤ 5%

Gap to be addressed: WRDs are largely automated test methods that have internal controls to confirm the quality of the results. Quality can, however, be compromised by many factors at each stage: pre-testing (sample handling, labelling, processing), testing (operational issues and unsuccessful tests) and post-testing (reporting of results). Issues related to equipment servicing, maintenance and calibration and the dates of reagent expiration are documented. Such issues can result in error rates that are higher than expected and, ultimately, breakdown of instruments. Although the annual error rate should be < 3%, it is > 5% in many settings and may be significantly higher *(21–23)*. Monitoring indicators of test quality, such as the unsuccessful test rate, is an essential early indicator. Ideally, pre-testing, testing and post-testing steps in the diagnostic quality management system should be monitored. Monitoring of error rates is selected for its simplicity and is used as a proxy of quality.

Application: For this benchmark, only system-reported errors are considered. All WRD instruments should provide performance reports with an indication of system-generated error rates. Digital systems for real-time monitoring of instruments are useful; even where these are not available, error rates can be monitored directly from the instrument. Unsuccessful results, such as an indeterminate or no result, are not included. The 5% target for error rates is based on the average (4.6%; 3080/66925) in ten countries reporting routine data using a digital system between 1 January 2021 and 31 December 2022 *(24)*. The data represents real world experience in which only three of the ten countries achieved the Global Laboratory Initiative target of 3%. Nonetheless, the 3% target should be considered the preferred target for well-established sites that have the basic requirements (e.g. electricity, controlled temperatures, maintenance programmes) *(25)*. A TB testing site is defined as a place, laboratory or non-laboratory where instrumentation is available and used to test for TB. A testing site with several instruments should be counted only once. Sites with error rates above the 5% threshold should be investigated in supervisory visits, and specific root-cause analysis and corrective actions should be instituted. Details of diagnostic quality management systems are available elsewhere *(25)*.

Numerator
Number of WRD TB testing sites with annual error rates ≤ 5%

Denominator
Number of WRD TB testing sites in the country

Benchmark

STEP 1 Identifying presumptive TB — 1 2
STEP 2 Accessing testing — 3 4 5 6
STEP 3 Being tested — 7 8 9
STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 3: Being tested

Benchmark

8 All individuals with presumptive TB are tested with a WRD*

Gap to be addressed: In 2021, just over one third of all TB patients notified annually were tested with a WRD. A large proportion of individuals with bacteriologically confirmed TB are still diagnosed by smear microscopy, which has suboptimal sensitivity and does not detect drug resistance. Testing with WRDs is even more critical for cases identified through active case finding, as these individuals have lower bacillary loads than those found through passive case finding *(26)*. Similarly, cases of paediatric and extrapulmonary TB are paucibacillary, contribute a large proportion of the TB burden and are difficult to diagnose definitively. At a minimum, specimens from those populations should be tested for a diagnosis of TB and to detect drug resistance. The use of non-sputum sample types that are easy to collect and child friendly is now recommended *(16)*. Recommendations for testing extrapulmonary specimens with WRDs are also available *(6)*, although uptake of the recommendations is lagging. In most countries, data are not usually collected on the number of individuals with presumptive TB, and, when such registers exist, they are often fragmented and not used. This is unfortunate, as the data are essential in the diagnostic cascade and a direct measure of access to WRDs.

Application: Individuals with presumptive TB comprise all those who enter care after passive and active case finding, who should undergo a TB diagnostic test. Ideally, the actual number of individuals with presumptive TB and the number tested should be reported, i.e. quantified at the level of patients and not samples. However, such data may not be available, and laboratory registers can be used. The limitation is that these registers do not include all individuals with presumptive TB but only those from whom a sample was collected. Individuals who could not produce a sample or who were treated empirically without testing will not be counted. Nevertheless, in the absence of well-kept registers of presumptive TB, this value may be the best proxy. Possible approaches to estimating the total number of individuals with TB are described under Benchmark 6. The total number of WRD tests performed can be used as the numerator, even though some repeat testing may inadvertently be included.

Numerator
Total number of individuals with presumptive TB tested with a WRD

Denominator
Total number of individuals with presumptive TB

***Application for non-NTP or private sector health facilities:** In several high-burden countries, many patients first access care in the non-NTP or private sector. Testing of these patients with WRDs will reduce the time to diagnosis, the associated morbidity or mortality and catastrophic costs. The difficulties of estimating the number of individuals with presumptive TB in the public sector are applicable in the private sector, and the same pragmatic solutions can be applied. The same numerators and denominators should be used, with data derived only from private-sector laboratories and private facilities. Issues related to clinical diagnosis are addressed under Benchmark 11.

Benchmark

STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 3: Being tested

Benchmark

9 All patients with bacteriologically confirmed TB undergo universal drug susceptibility testing*

Gap to be addressed: Timely drug susceptibility testing (DST) is critical in the management of TB in order to ensure access to appropriate treatment and care and to minimize the risk of transmission. Only 70% of all bacteriologically confirmed TB cases reported globally in 2021 *(2)* were tested for resistance at least to RIF. Testing of resistance to other drugs is much more limited: only 50% of patients with RR-TB received testing for FQ resistance in 2021, and even fewer were tested for resistance to other Group A drugs (e.g. bedaquiline and linezolid). According to the target set in WHO's End TB Strategy for 2020, all bacteriologically confirmed TB cases should receive DST.

Application: Universal DST for this benchmark is defined as testing of all patients with bacteriologically confirmed TB for resistance to RIF, all patients with RR TB for resistance to FQ and all patients with pre-XDR-TB for resistance to bedaquiline and linezolid. These are minimum requirements, and testing for resistance to drugs according to the regimen used is preferred. Among patients with RIF-susceptible TB, testing for isoniazid and FQ resistance is increasingly important, especially in settings where the prevalence of resistance to these drugs is > 5%. Ideally, testing should also be performed at lower prevalence, accompanied by robust quality assurance monitoring. The numerators and denominators listed are based on the data currently reported by NTPs to WHO annually. The panel of drugs to be tested should be adapted according to the treatment regimens in use in the country, which may change over time as new regimens become available. Further disaggregation by test method may be useful for tracking transition to the use of rapid, accurate molecular tests for drug resistance as a proxy for early detection of resistance.

9A Rifampicin DST coverage

Numerator (RIF)

Number of patients notified with bacteriologically confirmed pulmonary TB with DST results for **RIF**.

Denominator (RIF)

Number of patients notified with bacteriologically confirmed pulmonary TB

9B Fluoroquinolone DST coverage

Numerator (FQ)

Number of patients notified with bacteriologically confirmed RR pulmonary TB and DST results for **FQ**

Denominator (FQ)

Number of patients notified with bacteriologically confirmed RR pulmonary TB

9C Bedaquiline DST coverage

Numerator (other group A)

Number of patients notified with bacteriologically confirmed RR and FQ-resistant pulmonary TB with DST results for **bedaquiline**

Denominator (other group A)

Number of notified patients with bacteriologically confirmed RR and FQ-resistant pulmonary TB

9D Linezolid DST coverage

Numerator (other group A)

Number of patients notified with bacteriologically confirmed RR and FQ-resistant pulmonary TB with DST results for **linezolid**

Denominator (other group A)

Number of notified patients with bacteriologically confirmed RR and FQ-resistant pulmonary TB

*Application for non-NTP or private-sector health facilities: The same numerator and denominator should be used but limited to data from private facilities. Test-level data could be used while systems are being established.

STEP 4

RECEIVING A DIAGNOSIS

Increase WRD-based diagnosis

The aim of the fourth step in the cascade is to increase the number of individuals with a diagnosis of TB based on a WRD result (Benchmark 10), use of that information to guide screening and testing to maximize detection *(11)* and timely reporting of results *(12)*. Benchmark 10 is designed to increase the proportion of patients with bacteriologically confirmed pulmonary TB diagnosed with a WRD. Clinical diagnosis of TB without diagnostic testing remains common in some parts of the world, despite the availability of highly accurate WRDs. The number of individuals diagnosed with TB depends directly on activities in steps 1, 2 and 3 of the cascade.

STEP 4: Receiving a diagnosis

Benchmark

10 An initial WRD result is available to inform a diagnosis of pulmonary TB*

Gap to be addressed: Only 63% of pulmonary TB cases notified globally in 2021 were bacteriologically confirmed, and, in several high-burden TB countries, this indicator is close to 40%. Low coverage with bacteriological confirmation of TB could lead to wrong diagnoses, unnecessary treatment and delays in making the correct diagnosis, with potentially increased morbidity and mortality *(27)*. Not all types of TB can be readily confirmed bacteriologically. For example, childhood TB is primarily paucibacillary with a strong immunological component, complicating bacteriological confirmation. Similarly, HIV-associated TB may be more difficult to diagnose, although new WRDs perform considerably better than sputum smear microscopy. Nonetheless, highly sensitive tests are available for most adults with pulmonary TB, and the diagnoses of these individuals should be bacteriologically confirmed.

Application: A clinically diagnosed TB case is one that does not fulfil the criteria for bacteriological confirmation but was diagnosed as TB disease by a clinician or other medical practitioner, who decides to give the patient a full course of TB treatment *(28)*. This group includes both patients with a clinical diagnosis of TB despite a negative bacteriological test result and those whose TB was diagnosed without testing. The latter would not be included in the numerator.

Numerator

Number of patients notified with pulmonary TB tested with a WRD, irrespective of results, before starting treatment

Denominator

Total number of patients notified with pulmonary TB, both bacteriologically confirmed and clinically diagnosed

***Application for non-NTP or private-sector health facilities:** Clinical and CXR diagnosis of TB are often more common in the private sector because of differences in clinical practice and the higher cost of WRD testing in this sector. Access to tests at regulated prices is addressed in Benchmark 4. Bacteriological confirmation is equally important, irrespective of the entry point (public, private or non-NTP), particularly for pulmonary disease. The same numerator and denominator should be used, but data should be derived only from the non-NTP or private sector.

Benchmark

STEP 1 Identifying presumptive TB — 1 2

STEP 2 Accessing testing — 3 4 5 6

STEP 3 Being tested — 7 8 9

STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 4: Receiving a diagnosis

Benchmark

11 All districts monitor the test positivity rate to optimize the impact of screening and testing strategies

Gap to be addressed: Testing the right population and finding those with TB early are critical. The test-positivity rate is defined as the percentage of initial WRD tests with positive results in a defined period. The test-positivity rate varies widely by region and country. A low rate may indicate lack of precision in case finding, while a high rate may indicate suboptimal case finding. Because of the wide variation globally, median test-positivity rates are presented rather than average rates. The medians presented are the mid-points (50th centile) of the distribution of the test-positivity rates by country, while the interquartile range (IQR) represents the values for the 25th and 75th quartiles. The median test-positivity rate in 2021 was 17% (IQR 9–26) globally and 11% (IQR 8–25) in the African Region, 14% (IQR 8–21), in the European Region, 18% (IQR 11–24) in the Region of the Americas, 18% (IQR 13–23) in the South-East Asia Region, 26% (18–34%) in the Eastern Mediterranean Region and 27% (IQR 15–32) in the Western Pacific Region *(2)*. The percentages are influenced by the testing strategy used, particularly if WRD was not used as the initial test (e.g. to detect RR TB in smear-positive patients). The African Region had a higher testing coverage rate, and the median value may reflect an appropriate test-positivity rate. Monitoring of trends in the test-positivity rate over time can indicate whether the implementation strategy should be investigated and adjusted to maximize case finding, such as by refining screening strategies or using more sensitive tools.

Application: The total number of tests may include repeat tests, as this is not expected to skew the overall test-positivity rate significantly. The rate is based on laboratory data and is not programmatically useful without disaggregation of populations (e.g. district or province). Test-positivity rates in facilities are not interpretable if the volume of tests is too small, and a stable test-positivity rate would have to be calculated for a longer period. No acceptable positivity rate is recommended, as it depends on many factors. Trends over time and comparisons among subnational regions with similar characteristics are appropriate for assessing the usefulness of case finding. Evidence of such activities showing the trends could be documented in quarterly reports or presented at scheduled meetings to discuss trends.

Numerator
Number of districts that monitor test-positivity rate

Denominator
Total number of districts

Benchmark

STEP 1 Identifying presumptive TB — 1 2
STEP 2 Accessing testing — 3 4 5 6
STEP 3 Being tested — 7 8 9
STEP 4 Receiving a diagnosis — 10 11 12

Navigation

STEP 4: Receiving a diagnosis

Benchmark

12 All TB testing laboratories achieve a turn-around time of ≤ 48 h for ≥ 80% of samples received for WRD testing

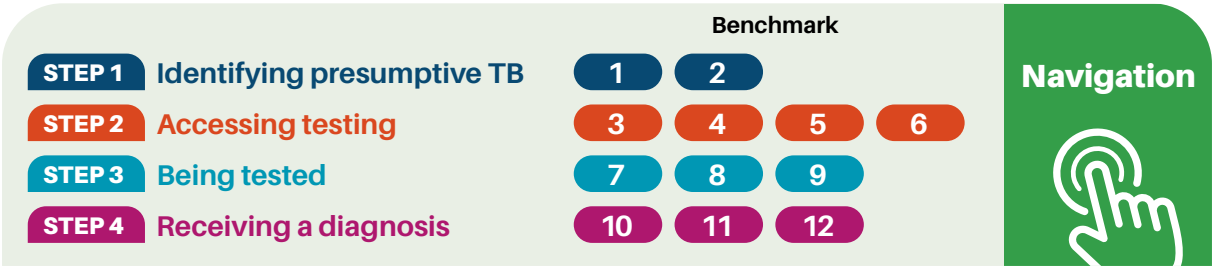
Gap to be addressed: Timely availability of results is an important patient-centric element. Delays in diagnosis can increase morbidity and mortality. Current technologies are highly accurate and provide results within hours. Nevertheless, their application in health settings with poor systems can negate their advantages; anecdotal reports indicate delays of receiving results of ≥ 1 week. Ideally, results should be available before a person leaves a health facility. This is not always possible with the current technologies, as the delay depends on the volume on a given day, the capacity of the instrument and the time interval between patients who require a test. Sample transport is appropriate if timely results can be achieved.

Application: Ideally, TAT is calculated from the time between first presentation of the patient to the start of treatment, with further disaggregation by delivery of the result and the start of treatment. TAT calculation can be difficult as time points a teach step, are often not captured reliably, and a pragmatic approach is proposed. For this purpose, TAT is defined as the time between sample collection and reporting of results by the laboratory. Data should be available in laboratory registers or on specimen request forms. The TAT will only include the first leg of the referral (i.e. not the return), and the time in the laboratory to generate a result. Although not all the steps are included, the method is practical and provides useful, actionable information. TAT is best calculated in a digital system. In the absence of a digital system, an audit of data (e.g. 10 rows of data over 5 days) at each TB testing site can be used as an alternative. The audit should be repeated at least quarterly, and the average used in annual reporting.

Numerator
Number of laboratories that achieve a TAT of ≤ 48 h for ≥ 80% of samples received for WRD testing

Denominator
Number of WRD testing laboratories

In view of the heterogeneity within and among countries, an absolute criterion for TAT cannot be established. To accommodate variation due to spatial heterogeneity, hard-to-reach settings and service gaps over weekends, the benchmark is for 80% of results to be available within 48 h, for all tests (on site and by sample referral). The proportion should be increased over time (to, e.g. 90%) and the period reduced (e.g. 36 h). The results of on-site testing should be available within 24 h, and the maximal time for WRD results to become available should not exceed 7 days when samples are referred from remote, hard-to-reach settings. Disaggregation of TAT by on-site and sample referral would be useful. The TAT for other test methods should also be monitored *(25)*.



PART 2

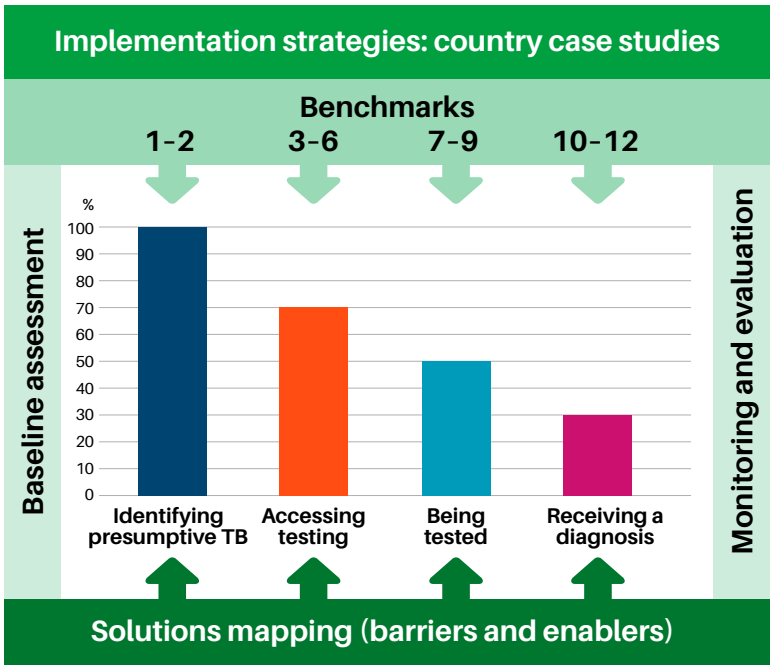
IMPLEMENTING THE WHO STANDARD

WHO GUIDANCE ON TB DIAGNOSIS

The *WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (6)* provide background, justification and recommendations on WHO-endorsed TB diagnostic technologies. They are accompanied by an operational handbook *(7)* that provides practical information on existing and new tests recommended by WHO, step-by-step advice on implementing them and scaling up testing for local and national impact and model diagnostic algorithms, which are updated with the latest recommendations. An overview of budgetary considerations and information sheets on each of the newly recommended tests is also included. Manuals on implementation of WRDs are also available from the Global Laboratory Initiative *(24)* and implementing partners, which cover considerations for selection of a WRD, tools for laboratory budgeting, sample referral systems, laboratory procedures and laboratory strengthening, including quality assurance, digital connectivity and test-specific procedures. Experience during implementation has shown, however, that there are still many practical barriers. Over the past decade, many enablers and examples of good practices to overcome the barriers have been published.

The WHO standard presented in part 1 outlines a systematic approach to achieving universal access to TB diagnostics, with 12 benchmarks. Fig. 5 shows the interplay between the benchmarks (part 1) and the supporting components (part 2) in the cascade of care. The benchmarks link the four steps in the cascade. To support countries in achieving the standard, Part 2 presents solutions and approaches that address barriers at each step of the cascade, which have been mapped, including a section on cost considerations. In addition, two case studies provide real-world examples of how two countries moved towards achieving universal access to WRDs and DST. A baseline assessment should be performed, followed by regular monitoring and evaluation.

Fig. 5. Illustrative example of the WHO standard: universal access to rapid tuberculosis diagnostics and implementation components



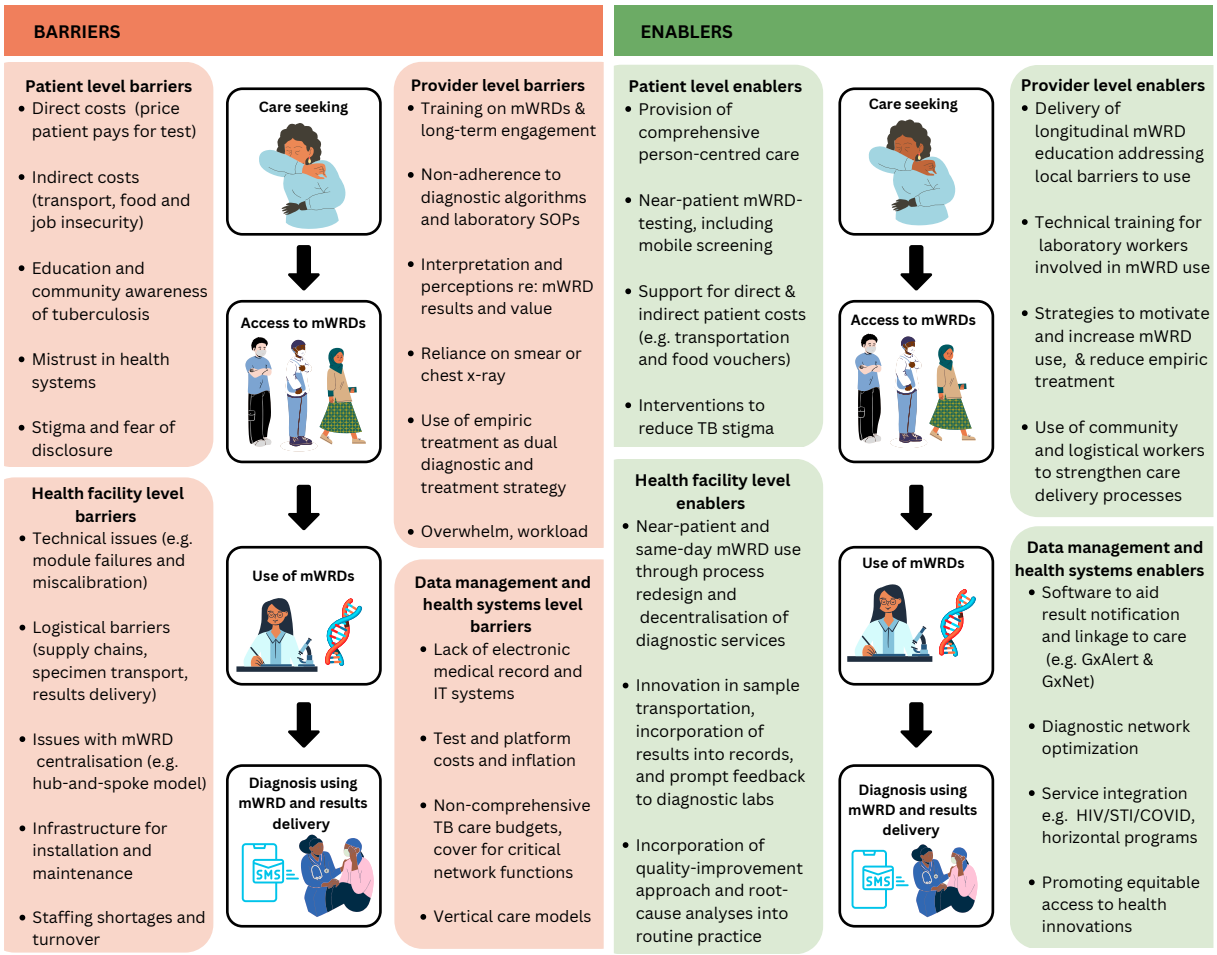
BARRIERS, ENABLERS, APPROACHES AND STRATEGIES FOR SCALING UP ACCESS TO AND USE OF WRDS

Information about barriers and enablers for the use of WRDs in the high-TB burden countries was collected in a systematic review and in a qualitative study to identify solutions and implementation strategies. In a mixed-methods systematic review, data from quantitative, qualitative, mixed-methods implementation studies and operational reports were analysed. Perspectives on use of WRDs were collected in a qualitative study of stakeholders in high-burden countries. The findings are summarized here; the full reports are available as a web annex A.

Barriers and enablers

Diagnosis remains the weakest link in TB care. Although context is important for conducting WRDs, there are common barriers and enablers in all settings, which can be stratified by patient, provider, health facility and data management and health systems (Fig. 6). The enablers shown are examples of activities or interventions that have been used to overcome barriers and facilitate WRD implementation.

Fig. 6. Barriers and enablers to use and implementation of WRDs at patient, provider, health facility, data management, and health systems levels



Implementation strategies in the diagnostic cascade

Strategies for scaling up use of WRDs were identified and mapped to each step of the diagnostic care cascade (Fig. 7). This showed the importance of combining high-quality, person-centred TB care with multicomponent strategies to address barriers at each level. Clear evidence was found for the importance of longitudinal stakeholder engagement, leveraging innovative solutions such as improving diagnostic networks, digital health technologies and iterative redesign to improve quality in response to the results of operational research.

Fig. 7. Implementation solutions along the cascade of care from the systematic review

Enablers identified by key stakeholders

A series of stakeholder consultations was conducted to collect perspectives and experiences in the use and extension of WRDs for TB in high-TB burden countries. Solutions for introducing WRD were found in projects for infrastructure, logistics, cost savings, policy and public–private integration. A highlight of the identified enablers was the importance of knowledge exchange among implementers in different settings and contexts.

Selected examples of enablers are discussed below. The full list of enablers that were identified is provided in the web annex B.

Use of solar panels:

As electricity was the single most commonly discussed barrier, solutions to the problem were proposed frequently. They included generators, inverters and high-capacity solar panels. One implementer reported:

> For facilities where we could see that the air-conditioning is now optimal, and the refrigerators are in order and they have high-capacity solar panels, we saw that those facilities are working optimally without problems. But for those that are yet to be upgraded, we still have the same issues. My machine broke down today. It's breaking down again tomorrow. Then the refrigerator is not working because there is no power to our refrigerators … All these are power dependent. So, without an ultimate power backup plan, we're not making any headway.

He concluded that high-capacity solar panels could enable use of WRD in many contexts.

Refresher training and incentives:

Video-based refresher training, which was introduced in response to COVID-19-related travel restrictions, also overcame some of the challenges created by staff turnover and idiosyncratic instrument operation. Several countries reported lower error rates after video-based modular training provided by test suppliers.

Some stakeholders reported that paying a small bonus to laboratory staff for effective performance of WRD tests helped to reduce user error and the TAT, and that laboratory staff were willing to run a test that might require staying after their normal working hours.

> We give incentive of about [US$ 0.11] per test. That has really, really, really increased the testing that we have in country by WRD in the last year. Testing has increased astronomically because of that little money we give [to the lab technician] for a successful[ly run] test.

Network access according to the local context: Many stakeholders suggested that tools and strategies for optimizing networks had been and could be leveraged for better use of machines. They noted that WRD tools worked best when programmes had recognized the importance of optimization in their context. One leader explained,

> If we want to improve equity of access, probably we would need to think of placing machines. Even though there is a lot of emphasis on utilization of machines, I think the emphasis should be on providing access to the patients…probably we need to place two module machines there [in low work load settings]. But then I have to think about what happens if one goes out of order.

In her view, optimization tools were very useful as long as agreement had been reached on the definition of "optimal" in each system. Additional suggestions were repeating assessments of network optimization and even changing to real-time feedback on network status.

Communication:

Stakeholders emphasized that effective communication platforms are important enablers of WRD. They reported using social media, email, SMS and other tools to share information about programme operations. Tools that facilitate sharing of WRD test results with patients, physicians and others increased the efficiency of WRD tools.

Market diversification:

Stakeholders suggested that diversification of the tools used and their availability on the market might make users less vulnerable to shifts in the market that resulted in changes in the prices or availability of instruments. One participant suggested that production of new instruments in high-burden countries might both stabilize the market and keep costs down. He said,

> Let's provide that opportunity for other platforms as well to be tested and be adopted in the lab system. There are risks to one platform, as we saw...during the pandemic when there's cartridge stockouts, they have to ration cartridge orders to countries. ... [high burden] countries will be in a disadvantaged position once those things happen.

Governance:

Stakeholders also suggested that creation of national groups to address challenges together had enabled scaling up of WRD. One laboratory member explained,

> What has worked well? Implementation partners of the TB programme do weekly reports on GeneXpert utilization. So, during these weekly reports, there are presentations...and during that you account.

Such forms of cooperation, in which local, regional and national administrators and implementers, users and clinicians identify and solve issues together, were reported to be enablers.

Integrating the public and private sectors:

In many contexts, NTPs, in collaboration with donors, have placed WRD instruments in private-sector hospitals and laboratories, reimbursed the tests conducted or brought the prices of instruments and consumables into an affordable range for private laboratories and patients. One civil society stakeholder explained the importance of this flexibility for positivity rates:

> We have established 28 Xpert sites in private-sector. We have engaged the large private hospitals in the private sector and established 28 Xpert sites there. Where the machines are established, we see a proportion of the positive cases, that is more than 50%. We have established a specimen transportation mechanism and in 50 districts, so specimens are transported to Xpert sites to the private-sector, where the machines are established in private-sector. If the machines are not established at private-sector, the specimens are transported to the public sector machines.

Public-sector activities also benefited from integration with the private sector, in which they sent samples to private laboratories in cases of breakdown or other delays. Similarly, by placing publicly supported machines in private laboratories, the large packet of inputs necessary to avoid infrastructural challenges such as an unstable electrical supply were avoided.

Key findings from the systematic review and stakeholder consultations

1. Equitable access and person-centred diagnosis and care are core components of optimization.
2. Multicomponent strategies for WRD implementation are enablers.
3. Strong communication among stakeholders and creation of fora in which stakeholders can exchange solutions ensure continuous improvement and targeted responses.
4. Multi-disease testing approaches can increase access, lower costs and strengthen health systems.
5. Longitudinal, accessible training for stakeholders can facilitate implementation of multicomponent WRDs.
6. Integration and movement of samples, information and patients between public- and private-sector services increase access and improve the quality of services in both sectors.
7. Use of data management and communication software in laboratory systems allows strong monitoring and rapid delivery of results to patients.
8. Iterative improvement of the diagnostic network can increase access and efficiency.
9. Strengthened global, national and subnational resource mobilization and national research capacity accelerate expansion of WRD services.

COUNTRY CASE STUDIES

Models of implementation have evolved over the years. Some countries with strong political commitment extended testing to all individuals with presumptive TB from the onset, starting in high-burden districts and progressively reaching all districts (e.g. in South Africa). Others initially limited access to high-risk groups, resulting in low coverage, and subsequently extended eligibility, leading to rapid increases in access (e.g. in Zambia). Yet others increased access by extending the diagnostic network by improving sample referral systems (e.g. in Uganda). Extension of access to affordable, quality-assured testing to the non-NTP sector also had a significant impact (in India) *(29)*. Such country case studies are important for implementation. Short summaries of two country case studies are presented below as examples of successful WRD implementation. Full details are available in the web annex B.

Nigerian case study
Beyond the instrument

Summary

- In Nigeria, a complex network of international, national and local public and private stakeholders offer TB diagnostics and treatment services.
- Poor infrastructure in health facilities throughout the country challenges optimization of WRDs as the first tests for TB.
- Stakeholders developed a WRD "package" to address the challenge, which consists of various equipment, actors and resources with WRD instruments.
- To mitigate machine system failure and loss of patients to follow up, a web-based platform has been developed to connect all WRD instruments in the country.

The Nigerian TB programme, supported by WHO and international stakeholders, conducted a pilot programme in which eight GeneXpert machines were installed in eight health-care institutions in 2016 *(30)*. Since then, use of WRD has been scaled up significantly *(31)*; in 2022, about 500 four-module GeneXpert machines were located in Nigeria's 36 states. As of October 2022, about 70% of people with signs and symptoms of TB were offered a WRD as an initial test for TB.

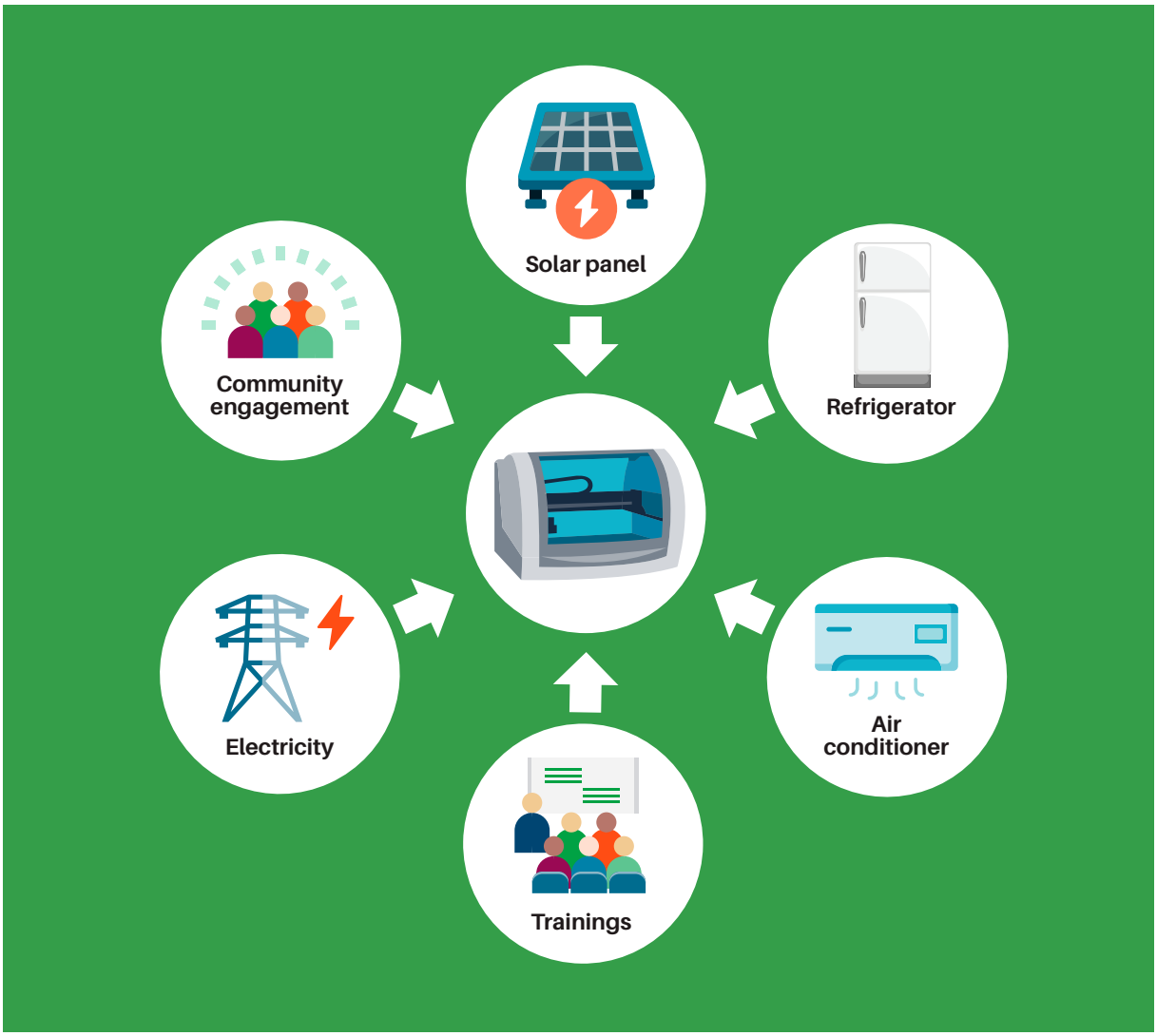
More than just a machine

One medical doctor said:

> We must think beyond the instrument. Instruments are not a solution on their own. So, the first thing, any country, that wants to roll it out, they need, make sure that if they have steady power supply, look at the supply management system, look at the connectivity, look at training of the clinicians, but look at the civil society, look at patient groups, look at your demand creation. You need to look at it now as a complete package.

Like many high-TB-burden countries, Nigeria faces significant suboptimal environmental and infrastructure conditions for increasing uptake of WRDs, including insufficient infrastructure and human resources, few or no sample transport networks and complications for machine distribution and maintenance. The lack of just one item in the package could lead to error, modular failure and delayed diagnosis. Therefore, various additional tools were included in the implementation package (Fig. 8), including solar panels so that WRD instruments could be used without a steady supply of electricity.

Fig. 8. The WRD package in Nigeria



Building networks

Awareness of TB varies, and many people with presumed TB seek care from private hospitals, pharmacies and traditional healers *(32)*. The implementers therefore recruited these sectors such as pharmacists and others to refer patients for TB testing with a WRD and encouraged them to facilitate taking of specimens for transport, thereby extending the network of stakeholders that provide access to WRD testing. The extension of sampling, however, posed a problem, as there were insufficient WRDs for maximum coverage, and the implementers adopted a hub-and-spoke model, as described previously *(33)*. The network solved some of the issues in samples reaching an instrument but created other organizational challenges, particularly sample storage, sample transport, loss of samples and delay in retrieving results. The latter was addressed through use of Internet-based connectivity to retrieve results.

Philippines case study Building the diagnostic network

Summary

- Introduction of WRD in the Philippines involved extensive, repeated evaluations of the diagnostic network to inform network expansion and specimen transport strategies.
- Use of specimen transport riders (STRiders) is a patient-centred innovation that obviates travel of patients for sputum sample collection and links facilities with laboratory infrastructure.
- The Philippines' health reforms prioritize an integrated approach to disease management, with which WRD machines and supporting infrastructure are aligned.

Context

Molecular tests for TB have been introduced for specific groups of patients in the public sector in a stepwise manner since 2012. In 2020, the national diagnostic algorithm was simplified by recommending molecular tests universally as the first tests for TB diagnosis *(34)*. This was rapidly translated into practice, with 63% of notified new and retreatment TB patients being tested with WRDs in 2020, exceeding the national target *(35)*. By 2021, there were 840 GeneXpert machines and 3616 operational GeneXpert modules in the country. Devolved health governance and geographically isolated, disadvantaged areas pose challenges and opportunities for continued extension of molecular tests for TB.

Repeated network analysis and optimization to improve service delivery

During the introduction of WRDs to the Philippines, emphasis was placed on replacing smear microscopy with WRD as the initial test. There were, however, significant costs associated with procuring the instruments necessary to supply the country's 3531 public and 3946 private health facilities *(35)*, and policy-makers observed that a single machine could be shared by facilities in a broader diagnostic network.

An initial assessment of optimization of the TB diagnostic network was made to consider machine placement and to design referral networks that could link facilities. In a project supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria, use of "specimen transport riders" (STRiders, Fig. 9) was pilot-tested, to obviate movement of patients

between health facilities. Since the success of the project, the current STRiders programme has a national network of 370 motorcycle riders who transport specimens from health-care facilities that do not have on-site access to WRD tests. They have become a core part of the TB diagnostic network.

Fig. 9. A STRider in action

Photo credit: Courtesy of Philippine Business for Social Progress TB Project

When reflecting on lessons learnt in establishing a TB diagnostic network, the implementers noted that network analysis should be repeated and not be considered a one-off strategy. They also recommended that national planning and modelling be balanced by consultation and coordination with local implementers, who provide information on the terrain and other local conditions. While an optimized network may prioritize use of machines, health equity in remote areas might require machines that run fewer tests but offer faster results to the local population.

Expansion of the STRider specimen transport programme is an example of integration among programmes for several diseases, as STRiders also deliver TB treatment and HIV antiretroviral therapy to patients in hard-to-reach areas as well as transport specimens for COVID-19, HPV and HIV testing. Implementers are also planning to use the STRiders programme to increase access to WRD technology in the private sector.

INVESTING IN UNIVERSAL ACCESS TO TB DIAGNOSTICS

Although diagnostics are central to TB care, they are often undervalued, and price is cited as a barrier. Costs that should be considered include all elements to perform testing for health programmes and patient sided elements including travel *(36)*. The required diagnostic capacity is the basis for improving the quality of services, including decreasing the time to diagnosis and achieving successful clinical outcomes. Diagnostic costs should be seen from the perspective of the full value chain.

Implementation costs for WRDs were a concern after initial recommendations were made by WHO in the early phase, and the concern persists. COVID-19 has highlighted the critical importance of diagnostics for early detection of disease, and this is a fundamental, non-negotiable pillar in the response to TB. Furthermore, lessons from COVID-19 show that global availability and high volumes can half the prices of tests *(37)*. The case for TB is even stronger, as highly effective, shortened treatments are available to cure both drug-susceptible and -resistant TB disease, and shorter, patient-friendly preventive therapies are also available. Long-term morbidity and mortality due to post-TB disease are often underestimated but are significant *(38)* and could be averted by early diagnosis and treatment.

Investments in TB diagnostics have benefitted the pandemic response in many parts of the world *(39)*. Similarly, the expansion of diagnostics for pandemic preparedness must include multi-disease testing options, which could improve access to TB diagnostic tests. Many testing platforms could be used for other diseases, including COVID-19, HIV, hepatitis, human papillomavirus infection, sexually transmitted infections and others.

The cost of microscopy is often perceived to be low. Several factors should be considered, however: patients will be missed if the sensitivity of microscopy is low, particularly for childhood and extra-pulmonary TB. Furthermore, two tests are required, so that patients often have to return for a second smear with an increased risk of loss to follow-up before treatment. Staff time for processing samples and maintenance of the necessary skills are additional costs. Furthermore, microscopy cannot be used to detect resistance to RIF.

Although countries are making progress in scaling up use of WRDs, it has taken more than 10 years to achieve 16 million tests per year in 2021 *(2)*. In the same year, only 38% of notified TB patients received a WRD as the initial test, implying that, in order to test everyone who requires it, more than 40 million tests will be required each year *(1)*. The four financial justifications for scaling up TB diagnostics are as follows with further details provide in web annex C.

The benefit–cost ratio for TB

TB control provides a better return on investment for governments than other major health priorities. The median cost–benefit ratio of TB control is even higher than those of HIV, hepatitis B, hypertension and diabetes in low- and medium-income countries *(40)*.

Lessons from programmes for the control of other priority diseases

Recent examples of care for patients with COVID-19 and HIV show that governments and donors can massively scale up testing and spending, even in resource-limited settings *(41)*. In the second quarter of 2020, the COVID-19 Diagnostic Consortium received orders from 44 countries for over 17 million automated and manual polymerase chain reaction (PCR) tests *(42)*, which exceeds the total number of TB PCR tests procured annually by high-burden countries even 10 years after scaling up. HIV control programmes currently conduct over 20 million PCR tests for HIV viral load each year to monitor patients on treatment, and HIV programmes spend US$ 7–10 per test annually for every patient on antiretroviral therapy to ensure appropriate care.

Proportion of spending on TB diagnostics in overall health-care spending

Diagnostics account for less than 3% of the US$ 5.3 billion spent annually on TB and overall health care. As total annual health-care expenditure in low- and medium-income countries is US$ 1.8 trillion, even a 10-times increase in spending on WRDs for TB at current prices would still represent < 0.15% of total health-care spending *(43)*.

Price reductions as volumes increase

Price reductions for diagnostic commodities over time are usually the result of an increase in volume, which enables further investment. Although the global access price for the TB market leader has remained unchanged for 12 years, it has been proposed that this price could reasonably and sustainably be reduced as countries continue to increase the volume requested *(44)*. The price of tests for HIV viral load on the same platform dropped by 40–60% when the volume increased from 2 to 10 million tests, and many suppliers secured reasonable market shares. Governments and global partners could therefore ensure rapid improvement by accelerating plans for testing with high-quality WRDs. Concessional pricing for high-burden countries must include all sectors in those countries (i.e. public, private and nongovernmental organizations) and not be limited to public or nongovernmental sectors.

CONSIDERATIONS FOR THE FUTURE

Next-generation of tests for TB – reaching primary health care

Use of current WRDs will not fill all the gaps in diagnostics. Technologies are required that can be decentralized, with simpler sample types, suitable for use in primary health care, which are affordable, sustainable and deliver results before an individual leaves the health facility. These would include instrument-free rapid tests or instruments that are fit for purpose, affordable and robust enough for use in the most basic facilities. The next-generation LF-LAM technologies being developed by several manufacturers are promising, with a sensitivity expected to be better than that of current smear microscopy and simple and fast enough for use during a clinical consultation. Other technologies in development include a low-cost, battery-operated rapid nucleic acid amplification test that provides results within 30 min at an expected price well below the US$ 10 threshold and suitable for sample types that are simpler to collect (e.g. tongue swabs).

These next-generation tests will probably come onto the market by 2025 and is expected to close the last third of the gap towards universal access. These tests will allow testing closer to communities but may be less sensitive and not include testing for resistance, therefore necessitating referral to diagnostic sites with the current generation of WRDs to complete diagnosis. Extending access to existing WRDs is therefore essential to address the weak diagnostic linkage that limits care today while preparing laboratory networks and health systems for next-generation solutions. Several other exciting methods, such as those that include a face mask or another novel collection device and alternative methods for detection, are being developed, although it is too early to evaluate their potential.

Solutions are required urgently, even if they are not perfect. Improving diagnostic networks will provide a platform to ensure that the next generation of tools can close the remaining gaps to reach all patients with TB and truly achieve the goal to End TB.

Closing diagnostic gaps between 2023 and 2025

Provided government commitment, funding and support for implementation are available, adoption of this *WHO standard: universal access to rapid tuberculosis diagnostics* will increase the number of newly notified TB cases tested with a WRD at initial diagnosis and in the number of bacteriologically confirmed TB cases, which represent the pool of infectious cases that are a priority for testing. Scaling up of WRDs will automatically increase testing for RIF resistance, an important step towards universal DST and quality-assured testing.

COVID-19 has highlighted the central role of diagnostics in the public health response. Health systems should transition from use of outdated diagnostic technologies such as smear microscopy and over-reliance on clinical diagnosis to use of WHO-recommended rapid diagnostics that are highly accurate, reduce the time to diagnosis, improve outcomes that are important to patients and are cost-effective *(6)*.

Up-front investment will accelerate universal health coverage, result in better health for all and reduce the unacceptable rate of mortality due to a curable, preventable disease such as TB. Strong political will and funding commitments in countries and by international agencies are necessary to ensure universal access to WRDs and universal DST.

REFERENCES

1. The End TB strategy. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/331326, accessed 10 May 2022).
2. Global TB report. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/346387, accessed 10 May 2022).
3. Tuberculosis data. Geneva: World Health Organization; 2022 (https://www.who.int/teams/global-tuberculosis-programme/data, accessed 4 January 2022).
4. Technical specifications series for submission to WHO prequalification – diagnostic assessment (TSS17). Geneva: World Health Organization; 2022 (https://extranet.who.int/pqweb/sites/default/files/documents/220805_TSS17_MBTC-NAT.pdf, accessed 4 January 2022).
5. FAQ: TB diagnostics – GTB Recommendations and PQ. Geneva: World Health Organization; 2022 (https://extranet.who.int/pqweb/sites/default/files/documents/FAQ_TB-IVDs_PQ_March2022.pdf, accessed 10 May 2022).
6. WHO consolidated guidelines on tuberculosis. Module 3: Diagnosis – Rapid diagnostics for tuberculosis detection – 2021 update. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/rest/bitstreams/1354562/retrieve, accessed 10 May 2022).
7. WHO operational handbook on tuberculosis. Module 3: Diagnosis –Rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/rest/bitstreams/1354706/retrieve, accessed 10 May 2022).
8. Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N et al. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754. doi:10.1371/journal.pmed.1002754.
9. Daniels B, Kwan A, Pai M, Das J. Lessons on the quality of tuberculosis diagnosis from standardized patients in China, India, Kenya, and South Africa. J Clin Tuberc Other Mycobact Dis. 2019;16:100109. doi:10.1016/j.jctube.2019.100109.
10. Cazabon D, Alsdurf H, Satyanarayana S, Nathavitharana R, Subbaraman R, Daftary A et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. Int J Infect Dis. 2017;56:111–6. doi:10.1016/j.ijid.2016.10.016.
11. WHO consolidated guidelines on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/rest/bitstreams/1336771/retrieve, accessed 10 December 2022).
12. WHO operational handbook on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/rest/bitstreams/1336777/retrieve, accessed 10 December 2022).
13. Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, Floyd K. National tuberculosis prevalence surveys in Asia, 1990–2012: an overview of results and lessons learned. Trop Med Int Health. 2015;20(9):1128–45. doi:10.1111/tmi.12534.
14. Law I, Floyd K, African TB Prevalence Survey Group. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308–27. doi:10.1111/tmi.13485.
15. Hanson C, Osberg M, Brown J, Durham G, Chin DP. Finding the missing patients with tuberculosis: Lessons learned from patient-pathway analyses in 5 countries. J Infect Dis. 2017;216(suppl_7):S686–95. doi:10.1093/infdis/jix388.

16. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022. (https://apps.who.int/iris/rest/bitstreams/1414329/retrieve, accessed 15 December 2022).
17. Primary health care. Geneva: World Health Organization; 2021 (https://www.who.int/news-room/fact-sheets/detail/primary-health-care, accessed 15 February 2023).
18. Standardised instrument for TB laboratory networks assessment. Geneva: World Health Organization; 2010 (https://www.who.int/publications/m/item/standardised-instrument-for-tb-laboratory-networks-assessment, accessed 15 February 2023).
19. Assessment of TB diagnostic networks: a new tool. Washington DC: United States Agency for International Development; 2018 (https://www.teachepi.org/wp-content/uploads/Courses/ADV-2018/APiatek_adv_TB_diag2018June20.pdf, accessed 8 January 2023).
20. Diagnostic network optimization: a network analytics approach to design patient-centred and cost-efficient diagnostic systems. Geneva: FIND; 2022 (https://www.finddx.org/tools-and-resources/access-and-implementation/diagnostic-network-design-and-optimization/, accessed 7 January 2023).
21. Nalugwa T, Shete PB, Nantale M, Farr K, Ojok C, Ochom E et al. Challenges with scale-up of GeneXpert MTB/RIF® in Uganda: a health systems perspective. BMC Health Serv Res. 2020;20(1):162. doi:10.1186/s12913-020-4997-x.
22. Kebede A, Beyene D, Yenew B, Diriba G, Mehamd Z, Alemu A et al. Monitoring quality indicators for the Xpert MTB/RIF molecular assay in Ethiopia. PLoS One. 2019;14(11):e0225205. doi:10.1371/journal.pone.0225205.
23. Gomathi NS, Singh M, Singh UB, et al. Multicentric validation of indigenous molecular test Truenat™ MTB for detection of *Mycobacterium tuberculosis* in sputum samples from presumptive pulmonary tuberculosis patients in comparison with reference standards. Indian J Med Res. 2020;152(4):378–85. doi:10.4103/ijmr.IJMR_2539_19.
24. Data to Care. Brussels: Savics SRL; 2022 (http://datatocare.org/analysis, accessed 17 February 2023).
25. Global Laboratory Initiative, World Health Organization. Practical manual on tuberculosis laboratory stregthening. 2022 update. Geneva: World Health Organization; 2023 (https://apps.who.int/iris/rest/bitstreams/1484351/retrieve, accessed 23 February 2023).
26. Global Laboratory Initiative. Guidance and tools. Geneva: World Health Organizaion, Global TB Programme; 2022 (https://stoptb.org/wg/gli/gat.asp, accessed 8 January 2023).
27. Floyd S, Klinkenberg E, de Haas P, Kosloff B, Gachie T, Dodd PJ et al. Optimising Xpert-Ultra and culture testing to reliably measure tuberculosis prevalence in the community: findings from surveys in Zambia and South Africa. BMJ Open. 2022;12(6):e058195. doi:10.1136/bmjopen-2021-058195.
28. Abdullahi O, Moses N, Sanga D, Annie W. The effect of empirical and laboratory-confirmed tuberculosis on treatment outcomes. Sci Rep. 2021;11(1):14854. doi: 10.1038/s41598-021-94153-0.
29. Definitions and reporting framework for tuberculosis. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf), accessed 23 February 2023.
30. Dabas H, Deo S, Sabharwal M, et al. Initiative for promoting affordable and quality tuberculosis tests: a market-shaping intervention in India. BMJ GlobHealth. 2019;4(6):e001539. doi:10.1136/bmjgh-2019-001539.
31. Gidado M, Nwokoye N, Ogbudebe C, Nsa B, Nwadike P, Ajiboye P et al. Assessment of GeneXpert MTB/RIF performance by type and level of health-care facilities in Nigeria. Niger Med J. 2019;60(1):33–9. doi:10.4103/nmj.NMJ_12_19.

32. Draft 2019 annual TB report. National TB and Leprosy Control Programme. Abuja: Federal Ministry of Health, Department of Pub;ic Health; 2020 (https://www.health.gov.ng/doc/Draft-2019-NTBLCP-Annual-report-22032020.pdf, accessedd 23 February 2023).
33. Oga-Omenka C, Boffa J, Kuye J, Dakum P, Menzies D, Zarowsky C. Understanding the gaps in DR-TB care cascade in Nigeria: A sequential mixed-method study. J Clin Tuberc Other Mycobact Dis. 2020;21:100193. doi:10.1016/j.jctube.2020.100193)
34. Cattamanchi A, Reza TF, Nalugwa T, Adams K, Nantale M, Oyuku D et al. Multicomponent strategy with decentralized molecular testing for tuberculosis. NEJM. 2021;385(26):2441–50. doi:10.1056/NEJMoa2105470.
35. Updated Philippine strategic TB elimination plan phase 1: 2020–2023. Manila: Department of Health; 2020 (https://doh.gov.ph/node/24443, accessed 8 January 2023).
36. Infectious disease detection and surveillance. Tuberculosis diagnostic network analysis for the Philippines. Washington DC: United States Agency for International Development; 2022.
37. Nirros P, Claudia MD, Wayne Van G, Madhukar P. New TB tools need to be affordable in the private sector: The case study of Xpert MTB/RIF. J Epidemiol Glob Health. 2018;8(3–4):103–5, doi:10.2991/j.jegh.2018.04.005.
38. Cost of rapid COVID-19 tests halved as global investment ensures availability of high volumes for low- and middle-income countries. Geneva: Unitaid; 2021 (https://unitaid.org/news-blog/cost-of-rapid-covid-19-tests-halved-as-global-investment-ensures-availability-of-high-volumes-for-low-and-middle-income-countries/#en, accessed 10 June 2022).
39. Menzies NA, Quaife M, Allwood BW, Byrne AL, Coussens AK, Harries AD et al. Lifetime burden of disease due to incident tuberculosis: a global reappraisal including post-tuberculosis sequelae. Lancet Glob Health. 2021;9(12):e1679–87. doi:10.1016/S2214-109X(21)00367-3.
40. Existing HIV and TB laboratory systems facilitating COVID-19 testing in Africa. Geneva: World Health Organization; 2020 (https://www.who.int/news/item/26-11-2020-existing-hiv-and-tb-laboratory-systems-facilitating-covid-19-testing-in-africa, accessed 12 May 2022).
41. Fleming KA, Horton S, Wilson ML, Atun R, DeStigter K, Flanigan J et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet. 2021;398(10315):1997–2050. doi:10.1016/S0140-6736(21)00673-5.
42. Our role in the ACT-Accelerator. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2022 (https://www.theglobalfund.org/en/act-accelerator/, accessed 5 October 2022).
43. WHO Diagnostics Consortium dashboard. Geneva: World Health Organization; 2022 (https://app.powerbi.com/links/r1ep2ImCjW?ctid=f610c0b7-bd24-4b39-810b-3dc280afb590&pbi_source=linkShare, accessed 12 July 2022).
44. Global health expenditure database. Geneva: World Health Organization; 2022 (https://apps.who.int/nha/database/Select/Indicators/en, accessed 21 September 2022).
45. Campaign: Time for $5. Geneva: MSF Access Campaign, Médecins sans Frontières; 2019 (https://msfaccess.org/time-for-5, accessed 8 January 2023).

For further information, please contact:

Global Tuberculosis Programme
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

Web site: www.who.int/tb

9789240071315