# WHO consolidated guidelines on tuberculosis

## Module 2: Screening

## Systematic screening for tuberculosis disease

World Health Organization

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## Web annexes

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Holger Schünemann (McMaster University, Canada) served as the technical resource person on GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The following persons participated as observers at the GDG meetings: Sevim Ahmedov and Charlotte Colvin (United States Agency for International Development, USA), Draurio Barreira Cravo Neto (Unitaid, Switzerland), Olivia Bierman (Karolinska Institute, Sweden), Michael Campbell (Clinton Health Access Initiative, USA), Pierre-Marie David (Université de Montréal, Canada), Christopher Gilpin (International Organization for Migration, Switzerland), Brian Kaiser (Global Drug Facility, Switzerland) and Mohammed Yassin (Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland). Kerri Viney (WHO Global Tuberculosis Programme) contributed to the reviews on the accuracy of screening approaches in the general population. The document was edited by Miriam Pinchuk. The Global Tuberculosis Programme also thanks the Guideline Review Committee and its WHO secretariat for their review and approval of the guidelines.

# Abbreviations and acronyms

| | |
|---|---|
| **ART** | antiretroviral treatment |
| **CAD** | computer-aided detection of TB-related abnormalities on chest radiography |
| **CI** | confidence interval |
| **CRP** | C-reactive protein |
| **CXR** | chest radiograph (chest X-ray) |
| **ERG** | External Review Group |
| **GDG** | Guideline Development Group |
| **GRADE** | Grading of Recommendations Assessment, Development and Evaluation |
| **IPD** | individual patient data |
| **LF-LAM** | lateral flow urine lipoarabinomannan assay |
| **mWRD** | molecular WHO-recommended rapid diagnostic test |
| **NNS** | number needed to screen (to detect one person with tuberculosis disease) |
| **PICO** | population, intervention, comparator and outcomes (framework) |
| **RR** | relative risk |
| **TB** | tuberculosis |
| **TPT** | TB preventive treatment |
| **W4SS** | WHO-recommended four-symptom screen |
| **WHO** | World Health Organization |

# Definitions

The definitions below apply to terms as used in these guidelines, and they may have different meanings elsewhere.

**Active (tuberculosis) case-finding (ACF)**: Provider-initiated screening and testing in communities by mobile teams, often using mobile X-ray and rapid molecular tests. The term is sometimes used synonymously with "systematic screening".

**Computer-aided detection (CAD):** The use of specialized software to interpret abnormalities on chest radiographs that are suggestive of TB. The results are expressed as abnormality scores. CAD may be used for screening or triage.

**Enhanced (tuberculosis) case-finding**: Health information or education, or awareness campaigns to provide information about what type of health-seeking behaviour is appropriate when people experience symptoms of TB; this type of case-finding may be combined with improving access to diagnostic services. Enhanced case-finding may or may not be combined with screening.

**Initial screening**: The first screening test, examination or other procedure applied in the population eligible for screening.

**Number needed to screen (NNS)**: The number of persons that need to undergo screening in order to diagnose one person with TB disease.

**Passive case-finding**: A patient-initiated pathway to TB diagnosis involving: (1) a person with TB disease who experiences symptoms that he or she recognizes as serious; (2) the person having access to and seeking care, and presenting spontaneously at an appropriate health facility; (3) a health worker correctly assessing that the person fulfils the criteria for presumptive TB; and (4) successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB.

**Repeat screening**: This refers to rescreening the same population at a given interval.

**Risk groups**: Any group of people in which the prevalence or incidence of TB is significantly higher than in the general population.

**Screening test, examination or procedure for tuberculosis disease**: A test, examination, or other procedure used to distinguish people with a high likelihood of having TB disease from people who are highly unlikely to have TB. A screening test is not intended to be diagnostic. People with positive results on a screening test should undergo further evaluation, depending on the screening algorithm used.

**Second screening**: A second screening test, examination or other procedure undergone by persons whose results were positive during the initial screen.

**Systematic screening for TB disease**: The systematic identification of people at risk for TB disease, in a predetermined target group, by assessing symptoms and using tests, examinations or other procedures that can be applied rapidly. For those who screen positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments. This term is sometimes used interchangeably with "active tuberculosis case-finding". It should be distinguished from testing for TB infection (with a TB skin test or interferon-g release assay).

**Triage**: The process of deciding the diagnostic and care pathways for people based on their symptoms, signs, risk markers and test results. Triaging involves assessing the likelihood of various differential diagnoses as a basis for making clinical decisions. It can follow more- or less-standardized protocols and algorithms, and it may be done in multiple steps.

**Triage test for TB**: A test that can be rapidly conducted among people presenting to a health facility to differentiate those who should have further diagnostic evaluation for TB from those who should undergo further investigation for non-TB diagnoses.

**Tuberculosis disease**: The disease state caused by *Mycobacterium tuberculosis*. It is usually characterized by clinical manifestations, which distinguish it from TB infection without signs or symptoms (previously referred to as latent TB infection). Also referred to as active tuberculosis.

# Executive summary

Tuberculosis (TB) is a leading cause of death from a single infectious agent, despite being largely curable and preventable. In 2019 an estimated 2.9 million of the 10 million people who fell ill with TB were not diagnosed or reported to the World Health Organization (WHO). The Political Declaration adopted by the United Nations General Assembly in September 2018 at the High-Level Meeting on the Fight Against Tuberculosis commits to, among other goals, diagnosing and treating 40 million people with TB by 2022. In order to achieve this ambitious target, there is an urgent need to deploy strategies to improve the diagnosis and initiation of care for people with TB. One of these strategies is systematic screening for TB disease, which is included in the End TB Strategy as a central component of its first pillar aimed at ensuring early diagnosis for all with TB.

To facilitate the implementation of TB screening at the country level, WHO published guidelines on *Systematic screening for active tuberculosis: principles and recommendations* in 2013. Since then, there have been important new studies evaluating the impact of screening interventions on both individual-level and community-level outcomes related to TB, as well as new research evaluating innovative tools for screening for TB – including the use of computer-aided detection of TB on digital radiographs, C-reactive protein and molecular WHO-recommended rapid diagnostic tests for TB – among important populations at high risk for TB disease.

In view of these new developments and due to requests by countries for more guidance, WHO convened a Guideline Development Group (GDG) in 2020 to examine the evidence and update the 2013 guidelines. The GDG met in virtual sessions between June and October 2020 and proposed several new and updated recommendations related to TB screening. WHO gratefully acknowledges the work of the GDG members, the evidence reviewers, representatives of national TB and HIV programmes, WHO colleagues, technical and funding partners, civil society representatives, patients and all others who contributed to the data used to inform this guideline update.

The evidence reviewed to address the guideline questions was derived from several trials and other studies, programmatic data, surveys and modelling work. The certainty of the evidence and the strength of the recommendations were assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method. Decisions about the strength of a recommendation and the evidence depend on the level of confidence in the estimates, as well as on other critical considerations, such as acceptability, feasibility, resource use and impact on health equity.

The use of **chest radiography** (chest X-ray, or CXR) as a screening tool for detecting TB disease in several populations was reviewed, including in the general public, people living with HIV, people younger than 15 years who are contacts of TB patients and other high-risk groups. Across all populations considered, CXR was found to be a sensitive screening tool that, while lacking sufficient specificity to confirm a TB diagnosis, has an important role in the early detection of TB in children and adults who are at higher risk of TB, as well as the potential to reduce the population burden of TB disease when combined with early treatment.

In recent years **computer-aided detection** (CAD) software packages have been developed and introduced to automate the interpretation of digital CXR images and produce a numerical score indicating the likelihood of TB. Three independent evaluations of CAD were reviewed to develop recommendations for both screening and triage for TB. The diagnostic accuracy and the overall performance of CAD software were similar to the interpretation of digital CXR by a human reader, in

both the screening and triage contexts. Evaluations showed substantial variation in diagnostic accuracy across different contexts, implying that the use of CAD will require calibration for the purpose and setting in which it will be implemented.

**C-reactive protein** (CRP) is an indicator of inflammation that can be measured using point-of-care tests performed on capillary blood collected via finger prick. The accuracy of CRP to detect bacteriologically confirmed TB in people living with HIV was assessed with a meta-analysis of individual patient data of people screened in high- and medium-burden settings. CRP was found to have similar sensitivity and higher or similar specificity to symptom screening in all subpopulations tested. CRP offers a clinically significant improvement in accuracy over the WHO-recommended four-symptom screen among ambulant people living with HIV who are newly in care and not yet on antiretroviral treatment, a subpopulation for whom the accuracy of the four-symptom screen is low.

**Molecular WHO-recommended rapid diagnostic tests for TB** (mWRDs; eg Xpert MTB/RIF) were reviewed for use as TB screening tools among different populations at high risk of TB. Evidence shows improved accuracy and effectiveness in people living with HIV and in other high-risk populations. The evidence is strongest for hospitalized patients with HIV in settings with a high burden of TB, given the limited value of symptom screening and the grave consequences of missing the opportunity to initiate TB treatment promptly in this patient group.

Based on these updates, a set of 17 new and revised recommendations for screening for TB disease have been developed (**Table 1**). The main changes from the previous WHO guidance are summarized in **Box 1**. The new guidelines replace all previous WHO guidance on TB screening. The recommendations are accompanied by updated operational guidance, the *WHO operational handbook on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*, that includes further details on target populations and tools to use for systematic screening, including revised algorithms and modelled estimates of their performance.

**Table 1. Recommendations in the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*, 2021**

| | **Screening for TB in targeted populations** |
|---|---|
| 1 | Systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher<br>(*updated recommendation: conditional recommendation, low certainty of evidence).* |
| 2 | Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care<br>(*existing recommendation: conditional recommendation, very low certainty of evidence*). |
| 3 | People living with HIV should be systematically screened for TB disease at each visit to a health facility<br>*(existing recommendation: strong recommendation, very low certainty of evidence).* |
| 4 | Household contacts and other close contacts of individuals with TB disease should be systematically screened for TB disease<br>(*updated recommendation: strong recommendation, moderate certainty of evidence*). |
| 5 | Systematic screening for TB disease should be conducted in prisons and penitentiary institutions<br>(*updated recommendation: strong recommendation, very low certainty of evidence*). |

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|---|---|
| **Screening for TB in targeted populations** | |
| 6 | Current and former workers in workplaces with silica exposure should be systematically screened for TB disease<br>(*existing recommendation: strong recommendation, low certainty of evidence*). |
| 7 | In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB who are either seeking health care or who are already in care<br>(*existing recommendation: conditional recommendation, very low certainty of evidence*). |
| 8 | People with an untreated fibrotic lesion seen on chest X-ray may be systematically screened for TB disease<br>(*existing recommendation: conditional recommendation, very low certainty of evidence*). |
| **Tools for screening for TB** | |
| 9 | Among individuals aged 15 years and older in populations in which TB screening is recommended, systematic screening for TB disease may be conducted using a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination<br>(*new recommendation: conditional recommendation, very low certainty of evidence for test accuracy*). |
| 10 | Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease<br>*(new recommendation: conditional recommendation, low certainty of evidence).* |
| 11 | Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases<br>(*existing recommendation: strong recommendation, moderate certainty of evidence*). |
| 12 | Among adults and adolescents living with HIV, C-reactive protein using a cut-off of >5mg/L may be used to screen for TB disease<br>(*new recommendation: conditional recommendation, low certainty of evidence for test accuracy*). |
| 13 | Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease<br>(*new recommendation: conditional recommendation, moderate certainty of evidence for test accuracy*). |
| 14 | Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease<br>(*new recommendation: conditional recommendation, moderate certainty of evidence for test accuracy*). |
| 15 | Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is > 10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test<br>(*new recommendation: strong recommendation, moderate certainty of evidence for test accuracy*). |

| | |
|---|---|
| 16 | Among individuals younger than 15 years who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both<br>(*new recommendation: strong recommendation, moderate to low certainty of evidence for test accuracy*). |
| 17 | Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient<br>(*new recommendation: strong recommendation, low certainty of evidence for test accuracy*). |

TB: tuberculosis.

**Box 1. Main changes to the guidance in the current update**

- ➔ Community-wide systematic screening using an accurate screening and diagnostic algorithm may be used in settings with a TB prevalence of 0.5% and higher, based on new evidence of public health benefit.
- ➔ Computer-aided detection (CAD) is being recommended for the first time as an alternative to human interpretation of digital chest X-ray (CXR) for screening and triage for TB. Its use should be limited to the interpretation of plain CXRs for pulmonary TB in individuals aged 15 years or older.
- ➔ Molecular WHO-recommended rapid diagnostic tests (mWRDs) may be used to improve the accuracy of symptom screening in populations at high risk of TB.
- ➔ When scaling up CXR and innovations such as CAD, C-reactive protein and mWRDs for screening, due consideration should be given to avoid creating inequities. The use of mWRDs needs to be prioritized for diagnostic testing for people with presumptive TB. Implementation of CAD will require thorough consideration of its infrastructure requirements, including the availability of digital radiography equipment, computers and internet access, as well as the costs to licence and use different CAD products.
- ➔ In adults and adolescents living with HIV:
  - screening with CXR improves the sensitivity of the WHO-recommended four-symptom screen (cough, fever, weight loss or night sweats) for detecting TB, including in people who attend HIV care services for antiretroviral treatment;
  - C-reactive protein may be used for TB screening in addition to the WHO-recommended four-symptom screen in all people living with HIV in settings with a high TB burden;
  - mWRDs may be used to screen for TB in all people living with HIV as well as in other high-risk populations in settings with a high TB burden. They offer a distinct opportunity to improve timely diagnosis and treatment in hospitalized patients with HIV in medical wards in settings with a high TB burden.

# 1. Introduction

## 1.1 Background

Tuberculosis (TB) is a leading cause of death from a single infectious agent, despite being largely curable and preventable. In 2019, an estimated 2.9 million of the 10 million people who fell ill with TB were not diagnosed or reported to the World Health Organization (WHO) *(1)*. WHO's End TB Strategy envisions a 90% reduction in TB incidence and a 95% reduction in TB deaths by 2035 *(2, 3)*, and the Declaration adopted by the United Nations General Assembly in September 2018 at the High-Level Meeting on the Fight Against Tuberculosis commits to diagnosing and treating 40 million people with TB by 2022 *(4)*. In order to achieve these ambitious targets, there is an urgent need to deploy strategies to improve the diagnosis and initiation of care for people with TB. One key strategy is systematic screening for TB disease, which is included in the End TB Strategy as a central component of its first pillar, aimed at ensuring early diagnosis for all with TB.

To help facilitate the implementation of TB screening at the country level, WHO published guidelines on systematic screening for TB in 2013 *(5)*. Since then, there have been important new studies evaluating the impact of screening interventions on both individual-level and community-level outcomes related to TB, as well as new research evaluating innovative tools for screening for TB among important populations at high risk for TB disease. In light of these new developments and continual requests by Member States for guidance on how to conduct effective TB screening, in 2020 WHO convened a Guideline Development Group (GDG) to examine the evidence in order to update WHO's guidelines and recommendations for screening for TB disease.

## 1.2 Definition and objectives of systematic screening for TB disease

For the purpose of this guideline, systematic screening for TB disease is defined as **the systematic identification of people at risk for TB disease, in a predetermined target group, by assessing using tests, examinations or other procedures that can be applied rapidly**. The screening tests, examinations and other procedures should efficiently distinguish people with a high probability of having TB disease from those who are unlikely to have TB disease. Among those whose screening is positive, the diagnosis needs to be established by diagnostic evaluation, consisting of one or more diagnostic tests, and clinical assessment, which together have high accuracy.

Systematic screening for TB disease is predominantly provider initiated. It may be conducted among people who do not seek health care because they do not have or recognize symptoms, they do not perceive that they have a health problem that warrants medical attention, there are barriers to accessing care, or for other reasons. It may also target people seeking health care who do or do not have symptoms or signs compatible with TB and who may not be identified by passive case-finding as possibly having TB. People seeking care who may be eligible for TB screening include people with medical conditions that constitute risk factors for TB (such as people living with HIV or diabetes mellitus) who may be seeking care for reasons other than symptoms compatible with TB.

There are two primary objectives of screening for TB disease: the first objective is to ensure that TB disease is detected early and treatment is initiated promptly, with the ultimate aim of reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB; the second objective is to reduce the community-level prevalence of TB disease, thus reducing transmission of *Mycobacterium tuberculosis* and averting future incident TB. Beyond TB disease, screening can also identify individuals who are eligible for and would benefit from TB preventive treatment (TPT) once TB disease is ruled out, thus further averting future incident TB.

Arising from these two primary objectives, there are two primary levels at which screening can augment standard TB care practices: that of the individual and the community. For individuals with TB disease, screening interventions can speed up and improve the probability of receiving a diagnosis and initiating treatment by bypassing many of the barriers to diagnosis and care that people suffering from TB disease can face, including *(6)*:

- lacking knowledge about the signs and symptoms of TB;
- not recognizing symptoms;
- being unable to seek care or lacking sufficient resources for care-seeking;
- lacking access to TB diagnostic and treatment services;
- seeking care from providers who lack sufficient knowledge of TB or in facilities where TB diagnosis and treatment services are not available or of sufficient quality.

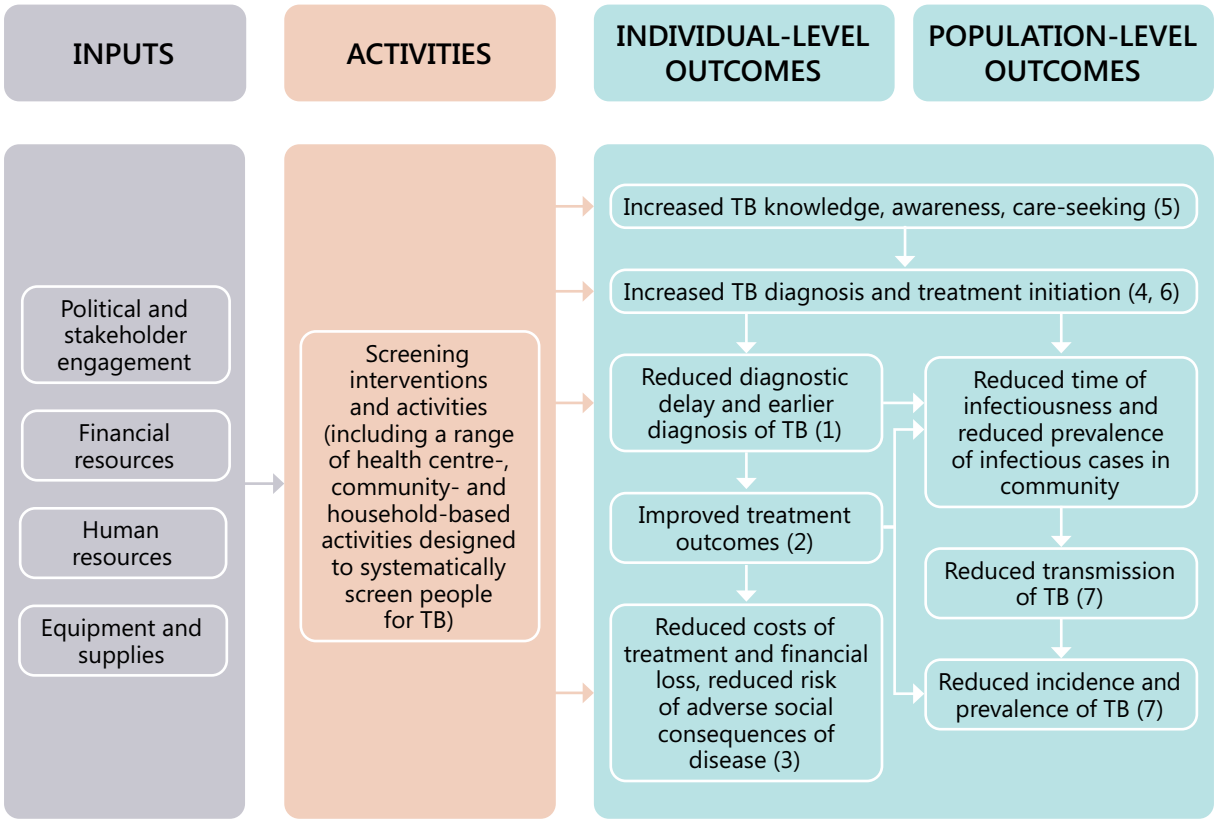
Beyond improving individual health and welfare, screening interventions for infectious diseases such as TB also address the epidemiology of the disease at the community level. By identifying and treating a proportion of the pool of individuals with TB disease in a given community, screening for TB seeks to reduce the prevalence, transmission and future incidence of the disease, with the long-term goal of eliminating the disease from the population.

The recommendations in this document apply to screening interventions that are conducted for the purpose of directly benefitting the individuals being screened by improving TB case detection and care and, thereby, benefitting the larger community by reducing the population burden of TB.

## 1.3 Scope of the 2021 update

**Fig. 1** summarizes the potential contribution of TB screening to standard TB care practices based on the above frameworks for TB screening and shows the conceptual framework that guided the 2021 update to the TB screening guidelines.

**Fig. 1. Conceptual framework for the 2021 WHO update to guidelines for systematic screening for TB. Numbers in parentheses refer to the PICO (population, intervention, comparator and outcome) questions that guided the evidence gathering**




A series of PICO (population, intervention, comparator and outcome) questions was established and systematic reviews were sought or commissioned for each of the PICO questions and the priority background questions.

The first PICO questions aimed at summarizing the evidence on the effectiveness of systematic screening interventions for TB disease to address individual and community outcomes.

1. Among people with TB disease, does TB screening identify people at an earlier stage of disease compared with passive case-finding?
2. Is there a difference in TB treatment outcomes between people with TB identified through screening interventions compared with people with TB identified through passive case-finding?
3. For people with TB disease and their families, does receiving a diagnosis and undergoing a course of treatment after case detection through screening have a different cost of illness and risk of adverse social consequences compared with receiving a diagnosis and undergoing a course of treatment after diagnosis through passive case-finding?
4. For people being screened who do not have TB disease, what are the consequences of TB screening?
5. Does TB screening used in addition to passive case-finding affect subsequent health-seeking behaviour compared with passive case-finding alone?

6. Does TB screening initially increase the number of people with TB detected compared with passive case-finding alone?
7. Does TB screening affect the epidemiology of TB in a community, including the prevalence, incidence and transmission, compared with passive case-finding alone?

A series of questions focusing on the diagnostic accuracy and performance of screening tools was also prioritized.

8. Among people living with HIV, what is the performance of a range of screening tools compared with a microbiological reference standard?
9. Among the general population and high-risk groups eligible for TB screening, what is the performance of a range of screening tools compared with a microbiological reference standard?
10. Among children and adolescents eligible for TB screening, what is the performance of a range of screening tools compared with a composite or microbiological reference standard?
11. What is the performance of computer-aided detection (CAD) software for automated reading of digital chest radiographs (CXRs) for the detection of TB disease in the screening- and the triage-use cases?
12. Among the general population and high-risk groups eligible for TB screening, what is the performance of molecular WHO-recommended rapid diagnostic tests (mWRDs) for screening for TB disease compared with a microbiological reference standard?

Lastly, in addition to the PICO questions assessing the accuracy and effectiveness of screening interventions, there was a series of background questions prioritized to inform the implementation of TB screening interventions.

13. Among the general public and high-risk populations, what is the number needed to screen (NNS) to detect one person with TB disease?
14. Among contacts of people with TB disease, what is the NNS to detect one person with TB disease?
15. What are the estimated relative risks of TB associated with a range of risk factors?
16. What are the costs and cost–effectiveness of implementing TB screening interventions?
17. What are the perceptions and attitudes of communities towards TB screening programmes?

## 1.4 Rationale for the guideline update

Since the publication of the first WHO guidelines on systematic screening for TB in 2013 *(5)*, there have been numerous studies, including reviews, randomized controlled trials, observational studies, modelling and cost–effectiveness research, evaluating the real or potential impacts of screening interventions on both individual-level and community-level outcomes related to TB. There have also been numerous prevalence surveys since 2013, which have shed new light on the magnitude of the burden of TB in several key countries. The majority of prevalence surveys have shown that the burden of TB is greater than previously thought.

## 1.5 Objectives of the guideline update

The specific objectives of the guideline update are:

1. to support Member States in implementing effective TB screening interventions by providing updated information about the expected impact of TB screening on patient-important outcomes and the epidemiology of TB, the expected yield of screening interventions and the expected performance of different screening tools and algorithms;

2. to contribute to finding more people with TB and finding them earlier in the course of disease in order to reduce disease burden, morbidity and mortality, and costs and financial hardship for people suffering from TB.

This update will allow policymakers in ministries of health to choose the best approach to planning and implementing screening and active case-finding activities, depending on the context. It will also provide a sound basis for developing or updating national guidelines for TB screening based on the epidemiology of TB and the health care delivery system in the country.

## 1.6 Target audience

This guideline is intended for personnel working in national TB programmes, national HIV/AIDS programmes or their equivalents, and other relevant national health programmes in ministries of health; other relevant ministries working in public health and screening; and for other health policymakers, clinicians and public health practitioners working on TB, HIV and infectious diseases in the public and private sectors. The recommendations provided here must be adapted to local settings. An accompanying operational handbook, *WHO operational handbook on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (7)* provides more detail and discussion of how screening recommendations can be adapted to address the conditions for and objectives of screening in specific contexts. National and subnational recommendations must be developed by national TB programmes and other national and subnational public health agencies and partners; recommendations developed by national and subnational agencies should guide health care staff working in specific settings.

# 2. Recommendations for systematic screening for TB disease in targeted populations

In this guideline, recommendations about systematic screening for TB disease are made for distinct populations for whom it is judged that the benefits and desirable effects of screening outweigh the potential harms.

Systematic screening for TB disease can be done for an entire population (community-wide screening) or it can be targeted at selected risk groups or subpopulations of people who may be at higher risk of being exposed to TB, developing TB disease or suffering poor outcomes from the disease, or some combination of these. It can target people who seek health care (with or without symptoms or signs compatible with TB) and people who do not seek care (because they do not perceive that they have a health problem that warrants medical attention, barriers make it difficult to access health care, or for other reasons). Furthermore, screening can help identify people who are at particularly high risk of developing TB disease and thus may require repeat screening, for example, people with an abnormal CXR compatible with TB but who are not diagnosed with TB disease at the time of screening or people for whom TPT is recommended. Combining screening for TB with screening for TB risk factors can also help map individual- or community-level risk factors, comorbidities and socioeconomic determinants that need to be addressed to more effectively prevent the disease.

Strong recommendations are made for those risk groups or subpopulations for which the desirable effects of adhering to the recommendation are judged to clearly outweigh the undesirable effects: for these recommendations, screening is judged to be feasible, acceptable and affordable in all settings. Conditional recommendations are made for those risk groups for which the desirable effects of TB screening probably outweigh the undesirable effects, but the trade-offs, cost–effectiveness, feasibility or affordability, or a combination of these, are uncertain. Reasons for uncertainty may include a lack of high-quality evidence to support the recommendation; limited evidence of benefit from implementing the recommendation; high costs or low feasibility or acceptability, or a combination of these.

It is important that TB is diagnosed promptly in groups that have a particularly high likelihood of undetected TB or a high risk of poor health outcomes, or both, in the absence of early diagnosis and treatment, even if direct evidence of benefit from screening is lacking. This is the rationale for making strong recommendations despite a lack of high-quality direct evidence for some risk groups. However, prioritization should also consider the risks associated with screening, including false-positive diagnoses, overtreatment and the opportunity costs of screening in terms of the resources required, both across risk groups and in relation to other interventions aimed at improving early diagnosis, treatment and prevention. Therefore, owing to the lack of high-quality direct evidence comparing benefits with harms and on the cost–effectiveness of screening in many of the populations considered, many of the recommendations made for screening in specific populations are conditional.

The degree of uncertainty about the trade-offs between the desirable effects and undesirable effects varies across settings, and it depends on the epidemiological situation and the health system. Therefore, a conditional recommendation in this guideline implies that the appropriateness of adhering to the

recommendation needs to be assessed in each setting, and there is a need to prioritize screening across risk groups in each setting.

For TB screening recommendations across all populations and in all settings, all people identified with presumptive TB disease should be offered HIV counselling and testing. In settings with a high prevalence of HIV, counselling and testing for HIV may be offered to all people screened for TB *(8)*. People identified through screening who have symptoms or abnormalities suggestive of TB but who are not diagnosed with TB disease should be counselled and supported to seek medical care if their symptoms continue, emerge, re-emerge or worsen. If possible, repeat testing for TB should be offered to these individuals.

People who are diagnosed with TB disease through screening should have nutrition screening and assessment. If malnutrition is identified, it should be managed according to WHO's recommendations on nutritional care and support for people with TB. Concerns about weight loss or failure to gain weight should trigger further clinical assessment (e.g. to determine whether there is resistance to TB drugs, poor adherence, comorbid conditions) and nutrition assessment in order to determine the most appropriate interventions *(9)*.

Screening population groups at higher risk for TB is ethically sound as long as it designed and conducted to improve individual and public health and wellbeing; in this way screening contributes to the common good and upholds the ethical principle of accountability. As such, screening should always be done with the intent to provide care to those who need it, and never to exclude entry or employment or discriminate against individuals *(10)*.

Nevertheless, screening population groups primarily based on risk raises a range of ethical issues *(10)*. First, most of the individuals offered screening will not have TB disease and are not contagious. This makes the ethical obligations different from those associated with testing people who seek care because they are ill. For example, the absence of an immediate risk of transmission makes it unethical to restrict the movements of someone who has been offered screening. Refusal of screening should be respected and should not introduce discrimination of any sort. A screening programme should not create inequities in access to care for TB disease or any other reason.

Second, a positive screening test carries uncertainties, and confirmatory tests should be available to ensure an effective diagnostic pathway. Informed consent requires effective communication with each person about these uncertainties (e.g. false-positive results, risk of overtreatment). Appropriate mechanisms to obtain informed consent should comply with international human rights standards and account for different languages, literacy skills and legal status. Risk and uncertainty must be communicated in a way that is culturally and linguistically appropriate, including to those whose first language is foreign to the local setting, children, as well as to people in prison.

Third, TB disproportionately affects individuals and groups that are already disadvantaged due to disease, their socioeconomic situation or legal status, among other disadvantages. Therefore, efforts must be made to address existing inequities in access to services and to uphold human rights, so that the vulnerability of targeted groups does not impede their access to screening and treatment or violate their rights. Any intervention for vulnerable groups – including migrants, prisoners and children – should include measures to minimize the risk of stigmatization. Testing positive on a screening test – as with a confirmed diagnosis of TB – should not influence an immigration procedure or be used to force migration or deny entry to a country. Screening done for migration or employment reasons must uphold ethical principles; this should be reflected in laws or other policy regulations *(10)*.

People should be offered screening in strict adherence to human rights and ethical considerations *(11)*. Policies should be evaluated from an ethical perspective by those who use the guidelines, and the views and experiences of affected populations should be gathered after implementation, both to consider possible unexpected effects and to ensure that the evidence on which they are based remains current and relevant *(12)*. Person-centred care entails, among other considerations, that it

is provided in an equitable fashion without placing marginalized and vulnerable populations at an added disadvantage; it focuses on the human rights aspects of screening so that there are appropriate safeguards in law, policy and practice to minimize any additional stigma, discrimination, violation of bodily integrity or restrictions on freedom of movement; and people who are offered testing and treatment should understand the associated uncertainties, which will help them make decisions about care options. Established human rights principles, such as consent, noncoercion, and confidentiality, should be respected.

## 2.1 Systematic screening for TB disease among the general population

1. Systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher

(*updated recommendation: conditional recommendation, low certainty of evidence*).

### 2.1.1 Summary of the evidence and rationale

Systematic screening in the general population is conducted on the premise that it bears dual benefit: to the persons diagnosed with TB and to the community in which screening is conducted. Individuals found to have TB may benefit from less diagnostic delay, improved treatment outcomes, and lower costs and financial losses associated with the disease. It also benefits public health by reducing the population prevalence of TB, thereby reducing further transmission of TB.

There is limited direct evidence of individual benefit from improved treatment success or reduced mortality when TB screening is performed in the general population. There is some evidence that systematic screening helps reduce delay in TB diagnosis and that it detects patients at an earlier stage of their disease. Data also show that screening interventions result in a reduction in costs for patients who are detected through screening and, most critically, a reduction in the risk of catastrophic costs for patients detected through screening and their families. However, some data show that the proportion of people who do not start treatment is higher among those identified through screening than among those who present with illness.

With respect to the benefits of screening for the community, there is inconsistent evidence that systematic screening for TB improves detection and notification in the general population, with none coming from randomized trials. There is, however, evidence of an effect on TB prevalence and transmission. A trial in Viet Nam in a population with an estimated prevalence of 0.35% that used 3 years of annual door-to-door sputum collection and testing using the Xpert MTB/RIF assay showed that systematic screening reduced adult TB disease prevalence *(13)*. An observational study in China conducted between 2013 and 2015 reported that three rounds of door-to-door symptom screening followed by CXR were associated with serial reductions in the absolute number of people with TB detected *(14)*. In addition, two trials showed lower frequencies of TB infection among children in clusters where TB screening was done compared with others without the intervention *(13, 15)*.

This is an updated recommendation: previously, systematic screening for TB disease in the general population was recommended in defined populations with extremely high levels of undetected TB, defined as a 1% prevalence or higher. Based on the updated evidence reviewed, the GDG concluded that the threshold of 1% recommended in the 2013 guidelines could be lowered, but considered that screening under programmatic conditions would not perform as well as was observed in the trial in Viet Nam and, therefore, proposed a 0.5% threshold to guide country implementation. Thus, the GDG recommended that general population screening may be considered in defined areas with a prevalence of undetected TB of 0.5% or more (see **Web Annex B**, Tables 1 and 2, and **Web Annex C**, Table 1).

### 2.1.2 Implementation considerations

The magnitude and balance of desirable and undesirable effects vary according the epidemiological conditions (the prevalence of TB and of risk factors) and the intensity of the screening intervention being implemented (the coverage of the population and the sensitivity of the screening test and algorithm). There is currently no evidence that population-wide screening using less sensitive screening algorithms that begin with symptom screening are effective at reducing the population prevalence or transmission of TB. However, there is limited evidence that screening utilizing symptom-based screening tools may benefit individuals who are diagnosed with TB by leading to earlier diagnosis with less severe TB disease, lower costs to the patient and lower risk of catastrophic costs associated with the course of disease. The balance of potential benefits and harms of screening may tip in favour of the intervention depending on factors such as the prevalence of TB in the population to be screened (particularly undetected TB), the accuracy of the screening and diagnostic tests used, the degree of current TB case detection and the vulnerability of the population being screened.

Screening should be conducted using the most sensitive and specific screening algorithm possible, with a screening test that identifies those with a higher likelihood of having TB and a diagnostic test to confirm the diagnosis. Highly accurate screening tests such as CXR and mWRDs have high sensitivity, specificity, or both; however, the feasibility of their use is affected by resource and implementation requirements. Symptom screening is less accurate (reduced sensitivity, specificity, or both), but is generally considered much more feasible to implement. Recent evidence suggests that reductions in the population prevalence of TB can be achieved with repeated annual screenings using a sensitive screening algorithm (mWRD followed by clinical evaluation) *(13)*. See **Section 3** for recommendations on tools for screening for more discussion on this topic.

While the implementation of a population-wide screening programme inevitably requires a significant investment of resources, overall there may be potential long-term savings to be made for health services through reduced future incidence. The costs of conducting community-wide screening will vary greatly, depending on the screening and diagnostic tests used and the population prevalence of TB. The cost–effectiveness of population-wide screening using a highly accurate algorithm is unknown, but the higher the prevalence, the more cost–effective the intervention will be. Using a highly accurate screening and diagnostic algorithm will inevitably require more resources than using symptom-based screening approaches, but it has a greater potential to reduce the population burden of TB.

The optimal frequency of screening in a general population to achieve individual- or community-level benefits remains unclear. There is also uncertainty about how people value the benefits expected from being screened. A review of qualitative studies of community perceptions of TB screening showed that, in general, screening was acceptable. However, resistance to screening was common, resulting from a combination of disparate factors, such as having a perception of being at low risk for TB among healthy participants, having little conviction in the effectiveness of screening, holding in poor regard TB services offered in the community, having concerns about confidentiality and the possible disclosure of diagnosis, and being anxious about the need to take TB medication.

Separate recommendations are made for select high-risk groups in the following sections. See the operational handbook for more details on the practicalities of implementing TB screening interventions using different tools and algorithms *(7)*.

## 2.2 Systematic screening for TB disease among people with structural risk factors for TB

> 2. Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care
>
> (*existing recommendation: conditional recommendation, very low certainty of evidence*).

### 2.2.1 Summary of evidence and rationale

Populations with structural risk factors for TB are those that are at increased risks of TB and of poor health outcomes from TB due to structural determinants in their environment, defined as the conditions that generate or reinforce social stratification (e.g. socioeconomic inequalities, population growth, urbanization), and therefore give rise to an unequal distribution of key social determinants of TB epidemiology, such as poor housing, poverty and malnutrition, which in turn influence exposure to risk, vulnerability and ability to recover after developing the disease *(16,17)*. Structural risk factors for TB include poverty; malnutrition; overcrowded and poorly ventilated living, working and gathering conditions; and limited or no access to health care. These risk factors are not mutually exclusive nor do they exclude the clinical risk factors described in other recommendations, and they often compound one another.

This recommendation has not been changed from the 2013 guidelines as, since the last GDG meeting, no new evidence was found to inform the question of the impact of systematic screening for TB disease compared with passive case-finding practices in these risk groups. Observational studies during 2013–2020 suggest that TB screening conducted among populations affected by structural risk factors may initially increase TB case notifications and decrease TB prevalence; however, all studies had a major risk of bias.

### 2.2.2 Implementation considerations

Due to the inherent lack of access to health care that defines the risk groups described in this recommendation, screening interventions would need to be conducted in and extended into the communities where members of these populations live and work in order to achieve effective reach and coverage.

The list of potential populations affected by structural risk factors included in this recommendation is not exhaustive, and this recommendation may apply to other groups with a high risk of TB and who have poor access to health care, including poor access to high-quality TB services.

There is no evidence about the effectiveness of different screening intervals; in the absence of such evidence, the choice of screening interval should be guided by feasibility. To the extent possible, community screening should be combined with screening for other diseases or risk factors and with health-promotion or social support activities. When screening is done in refugee camps and among displaced populations, consult *Tuberculosis care and control in refugee and displaced populations (18)* for recommendations on TB management and operational considerations.

## 2.3 Systematic screening for TB disease among people living with HIV

3. People living with HIV should be systematically screened for TB disease at each visit to a health facility

*(existing recommendation: strong recommendation, very low certainty of evidence).*

### 2.3.1 Summary of evidence and rationale

People living with HIV are approximately 19 times more likely to develop TB disease than those without HIV; in 2019, an estimated 44% of people living with HIV who also had TB disease did not reach care, and 30% of all HIV-related deaths were due to TB *(1)*. Thus, ensuring early detection and treatment for TB among all people living with HIV is crucial for reducing morbidity and mortality in this group.

This recommendation, which applies to people of all ages, was first published in 2011 in WHO's *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings (19)*, and it remains in place. The GDG placed high value on ensuring that TB is diagnosed early in this risk group, which has a high likelihood of having undetected TB and a high risk of poor health outcomes in the absence of early diagnosis and treatment.

### 2.3.2 Implementation considerations

Recommendations on specific tools to be used for screening people living with HIV are described in detail in **Section 3**. Persons living with HIV who have a positive or abnormal screening test should go on to have primary diagnostic tests to confirm or rule out TB disease including an mWRD and lateral flow urine lipoarabinomannan assay (LF-LAM), if eligible *(8)*. Once TB disease is ruled out, either through a normal screening test or after a negative diagnostic evaluation, people living with HIV should be evaluated for TPT as part of offering a comprehensive package of HIV care *(20)*.

## 2.4 Systematic screening for TB disease among household and other close contacts of individuals with TB disease

4. Household contacts and other close contacts of individuals with TB disease should be systematically screened for TB disease

(*updated recommendation: strong recommendation, moderate certainty of evidence*).

### 2.4.1 Summary of evidence and rationale

Household and close contacts of individuals with TB disease are at high risk of TB infection and developing TB disease. A systematic review conducted for the guideline update found the weighted pooled prevalence of TB disease among all close contacts of TB patients was 3.6% (95% confidence interval [CI]: 3.3–4.0), with a median NNS of 35 (95% CI: 17–65). Systematic screening has been strongly recommended since 2012 for contacts of individuals with TB disease *{21}*, given the high prevalence of disease in this population. At the GDG meeting, evidence was also presented on the individual- and community-level effects of screening of close contacts of TB patients. One trial of screening household contacts in Viet Nam showed a 2.5-fold increase in notification of contacts

diagnosed with TB resulting from the intervention (relative risk [RR]: 2.5; 95% CI: 2.0–3.2), along with a 40% reduction in all-cause mortality among household contacts (RR: 0.6; 95% CI: 0.4–0.8) *(22)*. Another trial of contact screening in South Africa and Zambia showed evidence that screening household contacts may reduce TB prevalence in the larger community after 4 years during which contact investigation is conducted, although this did not reach statistical significance (prevalence ratio: 0.82; 95% CI: 0.64–1.04); there was also a suggestion that the intervention reduced the transmission of TB, measured through the incidence of TB infection in schoolchildren (RR: 0.45; 95% CI: 0.20–1.05) (see **Web Annex B**, Table 3, and **Web Annex C**, Table 2) *(15)*.

Eligibility for TPT should be assessed among all TB contacts who are screened and found not to have indications of TB disease *(20)*. Children aged < 5 years who are household and close contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease after appropriate clinical evaluation or according to national guidelines should be given TPT even if testing for TB infection is unavailable. Children aged ≥ 5 years, adolescents and adults who are household and close contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease after appropriate clinical evaluation or according to national guidelines may also be given TPT. Contacts of TB patients who are living with HIV, no matter what their age, in whom TB disease has been ruled out, should receive TPT as part of a comprehensive package of HIV care *(20)*.

### 2.4.2 Implementation considerations

Contact screening should always be done when a person with TB has any of the following characteristics: bacteriologically confirmed pulmonary TB, proven or presumed multidrug-resistant TB or extensively drug-resistant TB, is a person living with HIV or is a child younger than 5 years. Among contacts of patients with bacteriologically confirmed TB, the weighted pooled prevalence of TB was 3.4% (95% CI: 2.9–3.8). Among contacts of patients with multidrug-resistant or extensively drug-resistant TB the weighted pooled prevalence of TB was 3.7% (95% CI: 2.4–5.3). The weighted pooled prevalence of TB among HIV-positive contacts was 11.6% (95% CI: 8.2–15.4), with a median NNS of 9 (95% CI: 5–13). The weighted pooled prevalence among contacts younger than 5 years was 3.9% (95% CI: 2.5–5.4), with a median NNS of 30 (95% CI: 12–62), while the prevalence among contacts aged 5–14 years was 2.4% (95% CI: 1.6–3.4), with a median NNS of 36 (95% CI: 17–61). Contact investigation may also be performed for TB patients with all other forms of disease.

The definition of a household or close contact can vary greatly across settings, and in some contexts there is no clear distinction between households; therefore, decisions about screening household and close contacts should be based on local definitions and policies, prioritizing contacts for screening based on an assessment of their level of exposure.

### 2.4.3 Subgroup considerations

Children and adolescents are of particular importance in contact screening, given the high prevalence found in the youngest age groups and the importance of rapid diagnosis and treatment owing to the risk of rapid disease progression in children younger than 5 years *(23)*, as well as the importance of initiating preventive treatment if TB disease has been ruled out (see **Section 2.4.2**).

Contacts who are persons living with HIV are also of particular importance in contact screening, given their extremely high prevalence of TB disease. Contacts living with HIV are also at increased risk for rapid progression to TB disease, and if they develop it, an increased risk of mortality. Contacts of TB patients who are also living with HIV are at a higher probability of themselves being HIV-positive, even they are unaware of their status. Thus, in settings with a high prevalence of HIV or when the index case is a person living with HIV, or both, all household contacts and close contacts should be offered counselling and testing for HIV. People living with HIV who are household contacts or close contacts of someone with TB disease and who, after an appropriate clinical evaluation, are found not to have TB disease should be evaluated for TPT.

## 2.5 Systematic screening for TB disease in prisons and other penitentiary institutions

5. Systematic screening for TB disease should be conducted in prisons and penitentiary institutions

(*updated recommendation: strong recommendation, very low certainty of evidence*).

### 2.5.1 Summary of evidence and rationale

People in prisons and other penitentiary institutions are at an increased risk for TB compared with the general population, and they often have limited access to health care services. The estimated incidence of TB among people residing in prisons is 23 times higher than that among the general population *(24)*. Data reviewed for the GDG meeting suggest that screening in prisons may improve early case detection, increase overall case detection and reduce TB prevalence. One observational study showed that a smaller proportion of TB patients in prisons whose disease was detected through screening were at an advanced stage of disease compared with those diagnosed through passive case-finding services *(25)*. Two observational studies showed that TB screening in prisons may reduce TB prevalence in the facilities *(26, 27)*. One trial showed that screening in prisons may increase case detection by more than 50% *(28)*.

Based on this new evidence and the high risk of TB in this population, the GDG felt that this risk group now merited a strong recommendation for TB screening (see **Web Annex B**, Table 4, and **Web Annex C**, Table 3). The GDG felt that implementing TB screening in prisons has the potential to increase equity in access to health care, particularly in settings where health services in prisons are suboptimal.

### 2.5.2 Implementation considerations

A prisoner is anyone held in a criminal justice facility or correctional facility during the investigation of a crime, anyone awaiting trial and anyone who has been sentenced. In addition, people residing in a correctional facility are almost always in close contact with several other inmates; thus, whenever a person residing in a prison is diagnosed with TB, prisoners who have been in close contact with that person should be investigated (see **Recommendation 4**). People who work in prisons and other penitentiary institutions are also at high risk of exposure to TB and should also be eligible for screening.

At a minimum, screening in prisons and other penitentiary institutions should always include screening when a person enters a detention facility, annual screening and screening upon release to prevent the reintroduction of TB into the broader community. Treatment and follow up after release should also be ensured.

Screening in prisons should be combined with efforts to improve living conditions and provide infection control measures. If possible, TB screening in prisons and other penitentiary institutions should be combined with screening for other diseases, including HIV, and health-promotion activities targeted towards people in these institutions. When starting screening, it is important to ensure that high-quality treatment and effective case management are in place, as well as effective mechanisms for continuing treatment after transfer or release. For recommendations on and operational aspects associated with TB care and prevention in prisons and other penitentiary institutions, see WHO's *Guidelines for the control of tuberculosis in prisons (29)*. However, even if TB management practices are suboptimal, screening may be initiated to assess the burden of undetected TB among inmates to provide a rationale for strengthening general diagnostic and treatment services for TB, as well as implementing measures to improve infection control and living conditions. In addition to systematic screening, any inmate who develops symptoms suggestive of TB should have easy access to diagnostic

testing. People identified through screening and presumed to have TB disease but in whom active TB has not been diagnosed, should be informed about the importance of seeking medical care if TB symptoms continue, emerge, re-emerge or worsen.

## 2.6 Systematic screening for TB disease among miners and others exposed to silica dust

6. Current and former workers in workplaces with silica exposure should be systematically screened for TB disease

(*existing recommendation: strong recommendation, low certainty of evidence*).

### 2.6.1 Summary of evidence and rationale

Exposure to silica dust and silicosis are among the strongest risk factors for TB, with a relative risk of 2.8–39 for silicosis, depending on the severity of the disease *(30)*. Silicosis is common in miners *(31, 32)*, which is a primary reason for the high incidence of TB among them, and this is often compounded by a high prevalence of HIV. TB patients with silicosis have an increased risk of death (RR: 3.0; 95% CI: 1.4–6.3) *(33)*. Thus, while the quality of the direct evidence is low for the benefit of TB screening in employees in workplaces where they are exposed to silica, the GDG placed high value on ensuring that TB is diagnosed early in this risk group, which has a high likelihood of having undetected TB as well as other pulmonary diseases that may be detected through screening. This recommendation has not been changed from the 2013 guidelines as no new robust evidence was found to inform the subject since the last guideline meeting.

### 2.6.2 Implementation considerations

There is limited evidence on the effectiveness of different screening intervals. The GDG suggests that the screening interval should be no longer than 12 months if possible, while an interval shorter than 12 months may be more beneficial. To the extent possible, TB screening should be combined with screening for other diseases and with health-promotion activities, as well as with efforts to improve working conditions (especially by reducing exposure to silica) and living conditions. During employment, screening should be considered to be the responsibility of the employer, and countries may have occupational health and safety legislation that addresses this.

## 2.7 Systematic screening for TB disease among people attending health care services who have clinical risk factors for TB

7. In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB who are either seeking health care or who are already in care

(*existing recommendation: conditional recommendation, very low certainty of evidence*).

8. People with an untreated fibrotic lesion seen on chest X-ray may be systematically screened for TB disease

(*existing recommendation: conditional recommendation, very low certainty of evidence*).

## 2.7.1 Summary of evidence and rationale

Several clinical characteristics, conditions and comorbidities can indicate an increased risk for developing TB disease or suffering worse outcomes from the disease, or both. Individuals identified as having untreated fibrotic lesions on CXR and who are not diagnosed with TB disease are at increased risk of developing TB disease *(34–37)*. These individuals are often identified through TB screening or clinical evaluation or during a clinical evaluation done for other reasons. Individuals with other risk factors for TB or risk factors for poor outcomes from TB often can be identified most easily in health care settings *(38–66)*. **Table 2** summarizes the evidence about the primary risk factors for TB and for poor health outcomes related to TB. Groups with other risk factors – such as people with malignancies and other disorders that compromise their immune system and people receiving immunomodulatory therapies – may also be prioritized, depending on the local epidemiology and capacity of the health system.

This recommendation has not been changed from the 2013 guidelines because since the last GDG meeting, no new, robust evidence was found about the impact of systematic screening for TB disease compared with passive case-finding for screening of individuals with risk factors.

**Table 2. Risk factors for tuberculosis (TB) to be considered when prioritizing TB screening among people attending for health care**

| Risk factor | Risk of TB or of poor outcomes |
|---|---|
| Fibrotic lesions on chest X-ray | Studies have shown an increased risk of developing TB disease among individuals with fibrotic lesions identified on chest X-ray but who are not diagnosed with TB disease.[a] |
| Diabetes mellitus (DM) | Systematic reviews have found that the risk of TB for patients with DM ranges from 1.5 to 2.0 to 3.1, with a decreasing risk in patients with well-controlled DM. Patients with DM were also at an increased risk of relapse, treatment failure and death.[b] |
| Previous TB | Patients with a history of TB are at increased risk of subsequent TB episodes, poor outcomes and developing drug-resistant TB.[c] |
| Chronic lung disease | Studies have found hazard ratios for developing TB among individuals with COPD ranging from 2.5 in China to 3.0 in Sweden.[d] |
| Smoking | Systematic reviews have found that people who smoke or who have a history of smoking have an increased risk of TB, with the RR ranging from 1.5 to 2.0 to 3.3; smokers are also at an increased risk of drug-resistant TB and poor outcomes from TB, including relapse and death.[e] |
| Alcohol use disorder | Systematic reviews have found a 1.35 to 1.9 RR associated with alcohol use and a 3 to 3.33 RR associated with alcohol use disorder, as well as increased risks of treatment failure and development of drug-resistant TB. An exposure–response analysis showed that for every 10–20 g of daily alcohol intake, there was a 12% increase in TB risk.[f] |
| Substance use disorder | People with substance use disorder are at increased risks of treatment failure, development of drug resistance, and mortality from TB due to low adherence and coincident clinical, socioeconomic and structural risk factors.[g] |
| Malnourishment | A systematic review found that lower BMI is associated with an increased risk of TB, with a reduction in TB incidence of 13.8% (95% confidence interval: 13.4–14.2) per unit increase in BMI within the range 18.5–30 kg/$m^2$. There are multiple pathways by which undernourishment can increase the risk of TB, including cell-mediated immunity and micronutrient deficiency, and other conditions can increase the risk of malnourishment and TB, including mental health and substance use disorders.[h] |

| Risk factor | Risk of TB or of poor outcomes |
|---|---|
| Pregnancy | A national registry study found IRRs for TB in pregnant women of 1.4 and of 1.9 for postpartum women compared with non-pregnant women. TB in pregnancy is associated with adverse outcomes and complications during birth. These outcomes include a roughly 2-fold increased risk of premature birth, low birthweight and intrauterine growth retardation, and a 6-fold increased risk of perinatal death.[i] |
| Immunocompromising conditions (organ transplant, renal failure, dialysis) | Systematic reviews have found that patients with immunosuppression for reasons other than HIV, including those undergoing organ transplantation or haemodialysis and those with renal failure, have a greatly increased risk of TB: one study found that the incidence of TB is 20–74 times higher in organ transplant patients compared with the general population; one study found that the incidence of TB is 10–25 times higher in dialyzed individuals compared with the general population; and one cohort study found that the incidence of TB is 100 times greater in persons undergoing dialysis compared with general population.[j] |
| Health care workers | A systematic review found the IRR of TB disease for health care workers was 2.94 compared with the general population.[k] |

BMI: body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; IRR: incidence rate ratio; RR: relative risk.

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## 2.7.2 Implementation considerations

This recommendation concerns interventions that should be undertaken in addition to passive case-finding practices, namely properly triaging and evaluating people seeking care who report signs or symptoms of TB, which should be done in all settings and is particularly important to implement rigorously among people who have risk factors for TB.

Groups should be prioritized based on their risk of TB, the risk of poor treatment outcomes if diagnosis is delayed and the size of the risk group in a given setting. People who are living with HIV, people who have had recent close contact with a person who has TB and people who have silicosis should always be screened for TB as described above (**Recommendations 3, 4 and 6**). Other risk factors that indicate an individual should be considered for screening are listed in **Table 2**.

For several of the clinical risk factors indicated above, TPT may be beneficial for the patient, subject to their exposure and eligibility *(20)*.

Health care workers are a specific group that merits consideration for screening in health facilities, given the potentially high level of occupational exposure and the risk of further transmission to patients.

# 3. Recommendations for tools for systematic screening for TB disease

TB screening tools are designed to distinguish people with a higher probability of having TB disease from those with a low probability and can be assumed to be free of TB disease. They are not intended to provide a definitive diagnosis. In general, they need to be able to be implemented easily and relay results rapidly in order to be informative in a screening context. Screening tests need to be followed by a diagnostic test, offered as part of a comprehensive clinical evaluation, to confirm or rule out TB disease in individuals who screen positive.

The most desirable screening strategy would be one with a high total yield of true-positive cases of TB, few false positives, low NNS, low cost, a rapid and simple algorithm and high client acceptability. In practice, many of these factors tend to run in opposite directions, so a multifactorial analysis is needed to decide which screening tools and algorithms to use.

In 2014, WHO released a report summarizing the desirable characteristics, or target product profiles, of screening tests for detecting TB disease *(67)*. The report highlighted that the minimal requirements for a target screening test would be an overall sensitivity of 90% and a specificity of 70% to detect pulmonary TB disease or rule it out in individuals being screened. Based on these benchmarks, an array of potential tools for screening for TB disease in different populations was considered by the GDG.

## 3.1 Tools for screening for TB disease among the general population and high-risk groups

9. Among individuals aged 15 years and older in populations in which TB screening is recommended, systematic screening for TB disease may be conducted using a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination

(*new recommendation: conditional recommendation, very low certainty of evidence for test accuracy*).

### 3.1.1 Summary of the evidence and rationale

The data used to inform this recommendation came from a systematic review of the diagnostic accuracy of using symptoms and chest radiography to detect TB disease among individuals aged 15 years and older with negative or unknown HIV status. The review included studies of screening conducted in the general population (including several prevalence surveys conducted in African and Asian countries), as well as screening conducted in high-risk groups (including contacts of TB patients, prisoners and others). Data from a separate review of the diagnostic accuracy of mWRDs used as a screening tool in individuals from high-risk groups aged 15 years and older (including contacts of TB

patients, prisoners and miners, all with negative or unknown HIV status) were also used to inform this recommendation. All data were pooled to estimate the sensitivity and specificity of each screening tool, as there was insufficient evidence to make estimates of accuracy for the screening tools in each high-risk group (the performance of tools among people living with HIV is presented later, in **Recommendations 11–15**). The reference standard used throughout was bacteriologically confirmed pulmonary TB. **Table 3** summarizes the diagnostic accuracy of the screening tools considered (see **Web Annex B**, Tables 5–10 for more details).

**Table 3. Diagnostic accuracy of symptoms, chest radiography, and molecular WHO-recommended rapid diagnostic tests for screening for TB disease**

| Screening test | No. of studies (no. of participants) | Sensitivity | No. of studies (no. of participants) | Specificity |
|---|---|---|---|---|
| WHO target product profile | NA | > 0.90 | NA | > 0.70 |
| Prolonged cough (≥ 2 weeks) | 40 (6 737) | 0.42 | 40 (1 284 181) | 0.94 |
| Any cough | 21 (2 734) | 0.51 | 21 (768 291) | 0.88 |
| Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss) | 28 (3 915) | 0.71 | 28 (460 878) | 0.64 |
| Chest radiography (any abnormality) | 22 (4 243) | 0.94 | 22 (1 012 752) | 0.89 |
| Chest radiography (suggestive abnormality) | 19 (2 152) | 0.85 | 19 (464 818) | 0.96 |
| Molecular WHO-recommended rapid diagnostic test | 5 (337) | 0.69 | 5 (8 619) | 0.99 |

NA: not applicable.

### 3.1.2 Implementation considerations for all tools

The GDG considered that all three approaches – symptom screening, CXR and mWRD – may have roles in screening for TB disease in the general population. The ranking of the tools according to accuracy proposed by the GDG is: first, CXR; second, mWRDs; third, screening for any TB symptom (higher sensitivity and lower specificity); and fourth, screening for any cough or cough lasting 2 weeks or longer (lower sensitivity and higher specificity). However, ease of implementation is highest by far for symptom screening, and less so for CXR and mWRDs with the requirement of additional equipment and resources. The GDG noted that factors related to patient selection, flow and timing may affect the measures of accuracy observed for CXR to detect TB. The inferences made about using mWRDs for screening in the general population relate primarily to pooled studies in high-risk populations and, therefore, there is uncertainty about whether the findings are directly applicable to a general population with a comparable burden of TB. See **Web Annex C**, Table 1, for more details of the recommendation.

The GDG noted that different symptom screening approaches have varying trade-offs in sensitivity and specificity. The feasibility of implementing symptom screening makes it a much more accessible option programmatically. Symptom screening is a standard part of a clinical workup and can be repeated as often as it is needed.

In contrast, additional resources are needed to undertake chest radiography and mWRDs. Radiography involves exposure to some ionizing radiation, which may increase the long-term risks of cancer. Innovations in radiography in recent years have substantially reduced radiation exposure levels. CXR is largely considered safe, with a radiation dose of 0.1 mSv, which corresponds to 1/30 of the average annual radiation dose from the environment (3 mSv) and 1/10 of the annual accepted dose of ionizing radiation for the general public (1 mSv). Pregnant women are especially vulnerable to ionizing radiation from radiography, and children have a longer life expectancy and, therefore, more time to develop radiation-induced health effects. However, for a pregnant woman and her fetus and for children, CXR has been deemed to not pose a significant risk, provided that good practices are observed, as the primary beam is targeted away from the pelvis *(68)*.

When used for screening, mWRDs have different accuracy than when they are used for diagnosis *(69)*, and different predictive values are associated with a positive test and a negative test due to differences in prevalence of TB in the populations being tested. Therefore, results should be interpreted appropriately, and those who screen positive for TB using an mWRD should receive a thorough clinical evaluation that may include further tests and procedures – such as CXR, repeat mWRD on additional sputum samples and other examinations – to establish a diagnosis of TB definitively prior to initiating treatment. These tests can be used on sputum only when a person can expectorate. Scaling up mWRDs for diagnosis should be prioritized (if full access has not yet been achieved) prior to scaling up mWRDs for screening. Using an mWRD as a screening tool requires significant resources, including increased capacity in and expansion of diagnostic and sample transportation networks. Depending on the feasibility and resources available, countries may choose to prioritize TB screening using mWRDs among certain subpopulations with a higher risk of TB.

Countries should position symptom screening, CXR and mWRDs within national TB screening and diagnostic algorithms, according to the goals and objectives of the screening, the populations being screened, the feasibility, resources available, and equity. A range of possible screening algorithms is presented in the operational handbook, including modelled performance of the expected yield.

## 3.2 Use of computer-aided detection software for automated reading of digital chest radiographs

10. Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease

*(new recommendation: conditional recommendation, low certainty of evidence)*.

### 3.2.1 Summary of the evidence and rationale

The use of CXR to screen for TB is a practice that goes back several decades. CXRs are also routinely used for triage of patients presenting to care who are displaying signs, symptoms or risk factors for TB to determine the most appropriate clinical pathway for proper evaluation. However, in many settings, the use of CXR for TB screening and triage for TB disease is limited by the unavailability of trained health personnel to interpret radiography images and by substantial intra- and inter-reader variability in its accuracy to detect abnormalities associated with TB *(70–72)*.

Numerous specific software packages that provide CAD, or automated interpretation of digital CXR images for the express purpose of determining the likelihood of TB disease, have been developed and offer a potential technological answer to the numerous implementation challenges inherent in human interpretation of CXRs.

The GDG considered the performance of CAD software separately for the screening- and triage-use cases. For this guideline, triaging is defined as the process of deciding the diagnostic and care pathways for people based on their symptoms, signs, risk markers and test results. Triaging involves assessing the likelihood of various differential diagnoses as a basis for making clinical decisions *(73)*. It can follow more- or less-standardized protocols and algorithms, and it may be done in multiple steps (*68*). A triage test for TB is one that can be rapidly conducted among people presenting to a health facility to differentiate those who should have further diagnostic evaluation for TB (those whose TB triage test is positive or abnormal) from those who should undergo further investigation for non-TB diagnoses (for those whose TB triage test is negative or normal) *(74)*. While there may be overlap between triaging and screening, there are several reasons to distinguish screening from triage when evaluating the performance of CAD software:

- The disease presentation may be different in screening populations in which one is more likely to encounter CXR findings of earlier TB than when compared with triage populations. Therefore, the same sensitivity and specificity point may not be achieved or may be achieved but with a different threshold score.
- TB prevalence will typically be much lower in screening populations (< 5%) than in triage populations (10–20%), which will impact a test's predictive values and the numbers of individuals correctly and incorrectly diagnosed.
- The ethical consequences of not detecting TB or other non-TB-related CXR findings (but clinically relevant abnormalities) that require follow-up examination are different for populations that do not seek care than for those that do *(11)*.

A previous assessment of using CAD for automated interpretation of digital CXRs for TB by WHO determined that in order to adequately assess diagnostic accuracy, it was necessary to evaluate CAD software using a standard panel of CXR files with associated demographic and clinical data, including TB diagnosis, drawn from a representative population for the corresponding use case for the technology. It was deemed essential that such evaluations ensure that CXR libraries used in an evaluation not be made available for CAD software development, training or evaluation *(68)*. For this GDG meeting, a scoping review for independent evaluations that met these criteria was conducted. Three independent evaluations for both the screening use case and the triage use case that assessed the performance of three distinct CAD programmes were identified and presented to the GDG, and they included all products that had received a CE mark (for Conformité Européenne, indicating a product's conformity with the European Economic Area's directives or standards) by January 2020.[2] The GDG was blinded to the brand names of the software programmes. A separate quality assessment of the evaluations was conducted and results presented to the GDG.

CAD programmes produce a numerical abnormality score for each digital image read that can then be compared to a threshold defined by the user to indicate if the patient is to be referred for further TB diagnostic evaluation. Because the abnormality scores produced are continuous, the sensitivity and specificity can vary from 0 to 100%, depending on where the threshold is set. For evaluation for the GDG, each software programme was set to a threshold that corresponded to 90% sensitivity for detecting pulmonary TB disease based on a microbiological reference standard. The resulting accompanying specificity for the software at that threshold was then reported and compared with the diagnostic accuracy of human readers interpreting CXRs in the same studies.

Due to specific methodological challenges, the estimates of CAD diagnostic accuracy were not able to be pooled across software programmes or across evaluations. Thus, the performances of CAD programmes and human readers from the included evaluations were presented as ranges (see **Table 4**). The three included evaluations assessed each programme's performance in different populations and in different settings (see **Web Annex B**, Tables 11 and 12, and **Web Annex C**, Tables 4 and 5).

[2] The three technologies that had received a CE mark by January 2020 and were included in all the evaluations are CAD4TB v6, Delft Imaging; Lunit Insight CXR, Lunit Insight; and qXR v2, Qure.ai.

**Table 4. Sensitivity and specificity ranges of computer-aided detection software and human readers interpreting digital chest radiographs for detection of bacteriologically confirmed TB across three software programmes, from three independent evaluations of the software in a range of populations and settings**

| Type of case and type of reader | Accuracy estimate range | |
|---|---|---|
| | Sensitivity | Specificity |
| WHO target product profile | > 0.90 | > 0.70 |
| **Screening use case** | | |
| CAD software | 0.90–0.92 | 0.23–0.66 |
| CXR with human reader | 0.82–0.93 | 0.14–0.63 |
| **Triage use case** | | |
| CAD software | 0.90–0.91 | 0.25–0.79 |
| CXR with human reader | 0.89–0.96 | 0.36–0.63 |

CAD: computer-aided detection; CXR: chest X-ray.

The results showed the variability of both human readers and CAD software programmes across different settings and populations. In comparing the range of accuracy of CAD to that of human readers interpreting CXRs and noting the variability of readers and the substantial overlap between the two ranges, the data suggested there is little difference between the two. Therefore, the GDG considered that CAD software programmes can be considered accurate when compared with human readers.

Other desirable effects beyond the accuracy of the technologies would likely include the possibility to scale up and thus increase the access to chest radiography, given the scarcity of radiologists in many settings. In addition, GDG members noted that in many settings, general practitioners or other providers without specific training in radiology are often tasked with interpreting chest radiographs, and they may not be as highly skilled as the readers used for comparison in the evaluations considered, thus indicating that the comparisons presented here may represent an underestimate of the true comparative accuracy of CAD software for detecting TB.

The drawback of using CAD interpretation in place of human readers for chest radiographs included the fact that it cannot detect other lung pathologies beyond TB. The capacity of CAD technologies to simultaneously screen for multiple pulmonary or thoracic conditions could be attractive for programmes, but no data on the performance of CAD for differential diagnosis were available to be assessed by the GDG.

CAD technologies have the potential to increase equity in the reach of TB screening interventions and in access to TB care if they facilitate the scale up of radiography for TB screening and triage and improve the interpretation of images.

The recommendation applies to software brands that upon external validation demonstrate a performance that is not inferior to the products reviewed by the GDG in 2020. The analysis for this recommendation was restricted to bacteriologically confirmed TB and, thus, the recommendation may not necessarily apply to other forms of TB (e.g. exclusively extrapulmonary TB, clinically diagnosed TB). This recommendation is specific to adults and adolescents aged 15 years and older. The recommendation applies only to the interpretation of anteroposterior or posteroanterior views of digital plain CXRs for pulmonary TB: it does not apply to the interpretation of lateral or oblique views, and its applicability to the interpretation of analogue CXRs is unknown.

### 3.2.2 Implementation considerations

The evaluations reviewed by the GDG demonstrated substantial variation in the diagnostic accuracy (sensitivity and specificity) of CAD programmes across settings, even when using the same technology set to the same threshold. Thus, it will be essential to calibrate the threshold to be used for any given software for each setting and population in which it will be used in order to ensure that the accuracy, predictive values, overall yield and requirements for further diagnostic testing are as expected. Further guidance on calibrating CAD in a new setting is provided in the operational handbook accompanying the guidelines, which links to a protocol for collecting the requisite data and a web-based tool to assist with the analysis of data and calculation of receiver operating characteristic curves and sensitivity and specificity values across a range of thresholds *(7)*.

The feasibility of implementing CAD depends heavily on the setting, including ensuring access to the required equipment for conducting digital radiography, a stable internet connection and required maintenance for the hardware and software. The required resources and the cost–effectiveness will depend on the setting, including the availability and salaries of human readers.

## 3.3 Tools for screening for TB disease among people living with HIV

11. Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases

(*existing recommendation: strong recommendation, moderate certainty of evidence*).

12. Among adults and adolescents living with HIV, C-reactive protein with a cut-off of > 5 mg/L may be used to screen for TB disease

(*new recommendation: conditional recommendation, low certainty of evidence for test accuracy*).

13. Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease

(*new recommendation: conditional recommendation, moderate certainty of evidence for test accuracy*).

14. Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease

(*new recommendation: conditional recommendation, moderate certainty of evidence for test accuracy*).

15. Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is > 10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test

(*new recommendation: strong recommendation, moderate certainty of evidence for test accuracy*).

### 3.3.1 Summary of the evidence and rationale

TB remains the primary cause of AIDS-related morbidity and mortality worldwide, despite impressive scale up of antiretroviral treatment (ART). In 2019, TB was associated with an estimated 208 000 (30%) AIDS-related deaths *(1)*. Global estimates show a 44% gap in case detection among people with HIV-associated TB *(1)*. A systematic review of postmortem studies of global AIDS-related deaths in adults found TB to be the primary cause of death in 37.2% of cases (95% CI: 25.7–48.7). TB was undiagnosed

prior to death in 45.8% of cases (95% CI: 32.6–59.1) *(75)*. Ensuring early detection and timely treatment of TB among people living with HIV is of paramount importance for reducing mortality.

A key component of the HIV care cascade is the WHO-recommended four-symptom screen (W4SS) for adults and adolescents living with HIV, comprising screening for a current cough, fever, night sweats or weight loss. This has been the only WHO-recommended TB screening strategy for people living with HIV since its introduction in 2011, and it is recommended for use at every patient encounter with a health care worker *(19)*. Designed primarily for ruling out active TB prior to the initiation of TPT, due to its high negative predictive value, the development of the W4SS was informed by a meta-analysis of individual patient data (IPD) from in observational studies conducted prior to 2010 and prior to the scale up of ART *(76)*. However, a more recent systematic review found that the pooled sensitivity of the W4SS among people living with HIV who were on ART was 51% (95% CI: 28.4–73.2) and the specificity was 70.7% (95% CI: 47.7–86.4) *(77)*. For people living with HIV who were not on ART, the sensitivity was 89.3% (95% CI: 82.6–93.9), and the specificity was 27.2% (95% CI: 17.3–40). In another study, the W4SS was found to have 42.9% sensitivity among pregnant women in Kenya attending services for prevention of mother to child transmission *(78)*.

Therefore, a systematic literature review and meta-analysis of IPD was undertaken to assess further the accuracy of the W4SS among people living with HIV overall and within important subgroups and to identify other screening tools and strategies that would enhance TB detection among people living with HIV. Screening tools and strategies reviewed by the GDG included the use of C-reactive protein (CRP), CXR and mWRDs as stand-alone tests, as well as in combination with the W4SS. Culture was the reference standard for assessing the accuracy of the different screening strategies. These recommendations apply to adults and adolescents aged 10 years and older living with HIV; for recommendation on children under 10 years living with HIV see **section 3.4**.

#### *3.3.1.1 WHO-recommended four-symptom screen*

The 2020 meta-analysis of IPD included 23 studies of 16 269 participants living with HIV, all of which reviewed the accuracy of the W4SS. The studies primarily focused on pulmonary TB disease. The unweighted average TB prevalence among participants within these studies was 9.2%, ranging from 1% to 26%; and 52% of people living with HIV screened positive on the W4SS. The sensitivity of the W4SS among all people living with HIV was 83% (95% CI: 74–89) and specificity was 38% (95% CI: 25–53). Estimates of the accuracy of the W4SS in different subgroups of people living with HIV are shown in **Table 5**. When used alone, the W4SS was found to have its lowest sensitivity among outpatients on ART and among pregnant women, and it had markedly low specificity among medical inpatients.

**Table 5. Diagnostic accuracy of the WHO-recommended four-symptom screen among different subpopulations of people living with HIV compared with culture as a reference standard**

| Population | No. of studies (no. of participants) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| WHO target product profile | NA | > 0.90 | > 0.70 |
| All people living with HIV | 23 (16 269) | 0.83 (0.74–0.89) | 0.38 (0.25–0.53) |
| Inpatients | 4 (672) | 0.96 (0.92–0.98) | 0.11 (0.08–0.14) |
| Outpatients on ART | 9 (4 309) | 0.53 (0.36–0.69) | 0.70 (0.50–0.85) |
| Outpatients not on ART | 19 (11 159) | 0.84 (0.75–0.90) | 0.37 (0.25–0.50) |
| CD4 ≤ 200 cells/μL | 22 (5 956) | 0.86 (0.77–0.92) | 0.30 (0.18–0.45) |
| Pregnant women living with HIV | 8 (1 937) | 0.61 (0.39–0.79) | 0.58 (0.39–0.75) |

ART: antiretroviral treatment; CI: confidence interval; NA: not applicable.

While there may be real-life limitations to the W4SS in terms of consistency and quality of delivery that might not be reflected in studies, it remains the simplest non-invasive tool to implement in any setting, requiring no infrastructure. However, the high proportion of W4SS positivity (94%) and very low specificity in medical inpatients living with HIV in settings where TB prevalence among study participants was > 10% gives it limited utility as a screen to rule in TB prior to diagnostic confirmation by mWRD in this very ill population.

The meta-analysis of IPD found no alternative screening tools or strategies that were significantly higher in both sensitivity and specificity than the W4SS or that met the WHO target product profile for a screening test on both parameters. In all cases, when sensitivity was higher and met the minimal requirements of the target product profile, specificity was compromised, and vice versa. Depending on a programme's decision to prioritize higher sensitivity or higher specificity, other tools or combinations of tools may be used to complement the W4SS.

### *3.3.1.2 C-reactive protein*

CRP is an indicator of general inflammation that can be measured using point-of-care tests performed on capillary blood collected via finger prick. The evidence reviewed for the performance of CRP included 6 studies from Kenya, South Africa and Uganda with a total of 3 971 participants (see **Web Annex B**, Table 13, and **Web Annex C**, Table 6). The average unweighted prevalence of TB among participants in the studies was 14%, ranging from 1% to 26%.

Data on the accuracy of CRP using a cut-off value of > 5 mg/L and of > 10 mg/L as indicators of TB disease were reviewed and both cut-offs were considered to have similar or superior accuracy when compared with the W4SS. The cut-off of > 5 mg/L was recommended because it is the lowest threshold indicating abnormality in many clinical settings, and it has higher sensitivity than the cut-off of > 10 mg/L. The choice of cut-off will depend on the availability of CRP technology in a given setting, the prevalence of TB and of other conditions that may increase CRP and the preference for increased sensitivity or increased specificity.

The IPD meta-analysis on CRP using a cut-off of > 5 mg/L reported similar sensitivity to and higher or similar specificity to the W4SS in all subpopulations assessed (see **Table 6**). When combined with the W4SS and used in parallel, whereby a positive screen for either tool led to a diagnostic test, it was found to have similar or higher sensitivity and specificity to the W4SS for all populations, depending

on the cut-off threshold used and the subpopulation assessed. CRP was found to be most accurate among outpatients who were not on ART, compared with the W4SS alone, which had a sensitivity of 0.84 (95% CI: 0.75–0.90) and specificity of 0.37 (95% CI: 0.25–0.50) in this subpopulation. When performed before the W4SS among people living with HIV, CRP with a cut-off of > 5 mg/L as an initial screening test was found to be as sensitive (0.78; 95% CI: 0.70–0.85) as the W4SS but to have significantly higher specificity (0.73; 95% CI: 0.66–0.79)in this subpopulation. Similar to the W4SS, the specificity of CRP for TB screening among inpatients living with HIV was found to be extremely low, likely due to competing comorbidities that would also result in raised CRP levels and the presence of symptoms (see **Web Annex C**, Table 6).

**Table 6. Diagnostic accuracy of C-reactive protein using a cut-off > 5 mg/L among different subpopulations of people living with HIV compared with culture as a reference standard**

| Population | No. of studies (no. of participants) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| WHO target product profile | NA | > 0.90 | > 0.70 |
| All people living with HIV | 6 (3 971) | 0.90 (0.78–0.96) | 0.50 (0.29–0.71) |
| Inpatients | 1 (400) | 0.98 (0.93–1.00) | 0.12 (0.09–0.17) |
| Outpatients on ART | 1 (381) | 0.40 (0.10–0.80) | 0.80 (0.75–0.84) |
| Outpatients not on ART | 4 (3 186) | 0.89 (0.85–0.92) | 0.54 (0.45–0.62) |
| CD4 ≤ 200 cells/μL | 6 (1 829) | 0.93 (0.87–0.97) | 0.40 (0.22–0.62) |
| Pregnant women living with HIV | 2 (62) | 0.70 (0.12–0.97) | 0.41 (0.12–0.78) |

ART: antiretroviral treatment; CI: confidence interval; NA: not applicable.

As a point-of-care biomedical test, CRP represents an opportunity for enhancing TB screening among people living with HIV. Health staff and patients might be more motivated to pursue a confirmatory diagnostic test following a positive screen for CRP. The specificity and predictive value of the test for detecting TB, however, will likely be reduced in settings with a lower TB prevalence than in those included in the meta-analysis.

### *3.3.1.3 Chest radiography*

CXR is recommended by WHO to be used in parallel with the W4SS where CXR is available to assist in ruling out active TB prior to initiating TPT among people living with HIV who are on ART. The GDG agreed that, due to the increased sensitivity, the evidence supported using CXR in addition to the W4SS as a parallel screening strategy in which a positive or abnormal result on either screen would indicate a referral for diagnostic evaluation. Data on "any abnormality" and an "abnormality suggestive of TB" detected by CXR were reviewed and either approach is recommended, depending on the context, the availability of radiological expertise, resources and preference towards higher sensitivity or higher specificity.

The evidence reviewed for the performance of CXR and the W4SS for all people living with HIV came from 8 studies conducted in Benin, Botswana, Brazil, Guinea, India, Kenya, Malawi, Myanmar, Peru, South Africa and Zimbabwe, with a total of 6 238 participants (see **Web Annex B**, Table 14, and **Web Annex C**, Table 7). The average prevalence of TB in all people living with HIV in the studies was 7%, ranging from 3% to 18%. Among outpatients on ART, the average prevalence was 2.6%.

CXR alone was found to have similar sensitivity to and similar or higher specificity than the W4SS across all subpopulations. When combined in a sequence whereby CXR followed a positive W4SS screen, CXR had a lower or similar sensitivity with higher or similar specificity. When combined and used in parallel with the W4SS, it had a higher or similar sensitivity and similar specificity (see **Table 7**). The IPD meta-analysis found this strategy to have the highest sensitivity (0.85; 95% CI: 0.69–0.94) compared with the W4SS (0.53; 95% CI: 0.36–0.69) and the other tools and strategies assessed for TB screening in outpatients on ART. While the data were limited for inpatients living with HIV, the combined strategy of CXR and the W4SS had a very low specificity (0.07; 95% CI: 0.03–0.19), similar to findings for using CRP or the W4SS alone (see **Web Annex C**, Table 7).

**Table 7. Diagnostic accuracy among different subpopulations of people living with HIV of the WHO-recommended four-symptom screen combined with chest X-ray (any abnormality) compared with culture as the reference standard and using a positive or abnormal result on either screen or both**

| Population | No. of studies (no. of participants) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| WHO target product profile | NA | > 0.90 | > 0.70 |
| All people living with HIV | 8 (6 238) | 0.93 (0.88–0.96) | 0.20 (0.10–0.38) |
| Inpatients | 1 (52) | 0.90 (0.33–0.99) | 0.07 (0.03–0.19) |
| Outpatients on ART | 4 (2 670) | 0.85 (0.69–0.94) | 0.33 (0.15–0.58) |
| Outpatients not on ART | 8 (3 516) | 0.94 (0.89–0.96) | 0.19 (0.09–0.34) |
| CD4 ≤ 200 cells/μL | 8 (2 232) | 0.94 (0.90–0.97) | 0.14 (0.07–0.25) |
| Pregnant women living with HIV | 1 (8) | 0.75 (0.11–0.99) | 0.56 (0.24–0.84) |

ART: antiretroviral treatment; CI: confidence interval; NA: not applicable.

#### *3.3.1.4 Molecular WHO-recommended rapid diagnostic tests for medical inpatients living with HIV in settings with a high TB burden*

TB is the main cause of hospitalization and mortality among people living with HIV. The assessment of the performance of an mWRD used as a combined TB screening and diagnostic strategy for medical ward patients with HIV included 4 studies in Ghana, Myanmar and South Africa with a total of 639 participants (see **Web Annex B**, Table 15, and **Web Annex C**, Table 8). The prevalence of TB in the included studies was 23.8%, ranging from 7% to 26%. The mWRD test assessed in the IPD was primarily the Xpert MTB/RIF assay.

Using the W4SS alone had 96% sensitivity and 11% specificity in the IPD meta-analysis of medical ward inpatients living with HIV, 94% of whom were positive on the W4SS. Thus, the difference in accuracy was minimal between the full screening and diagnostic strategy of using W4SS followed by mWRD and using mWRD alone. Therefore, the value of the W4SS was judged to have limited utility in screening for TB in this population prior to an mWRD test, and the GDG recommended that medical inpatients should be screened and tested with an mWRD, irrespective of symptoms, to inform a decision about whether to treat for TB. A 10% threshold TB prevalence among hospital inpatients living with HIV is recommended, taking into account the TB prevalence among the participants studied and striking a balance between ensuring rapid diagnosis in this critically ill population and the need to avoid overtreatment. In lower prevalence settings, a screening and diagnostic strategy with mWRD alone would give rise to higher numbers of false positives, with overtreatment and the related social and

economic consequences, including potential delay in starting ART. This recommendation may not be applicable to settings with a lower pretest probability of TB.

#### *3.3.1.5 Molecular WHO-recommended rapid diagnostic tests for all other people living with HIV*

The systematic review of the performance of an mWRD used to screen for TB among people living with HIV included 14 studies with a total of 9 209 participants (see **Web Annex B**, Table 16, and **Web Annex C**, Table 9). The Xpert MTB/RIF assay was the primary mWRD used in these studies. The prevalence of TB in the studies ranged from 1% to 26%. The average TB prevalence among participants attending outpatient facilities was 8.6%.

Using an mWRD alone was found to have sensitivity of 0.69 (95% CI: 0.60–0.76) and specificity of 0.98 (95% CI: 0.97–0.99) compared with using the W4SS followed by an mWRD as a diagnostic test, which had sensitivity of 0.62 (95% CI: 0.56–0.69) and specificity of 0.99 (95% CI: 0.97–0.99) (see **Table 8**). There were no significant differences in the accuracy of the mWRD between the different subpopulations when compared with using the W4SS followed by the mWRD.

Due to the increased sensitivity of mWRDs, but also in consideration of the likely challenges relating to access, high costs and feasibility in many countries, mWRDs are recommended as an option for screening for TB disease among all adults and adolescents living with HIV who are not medical inpatients in settings where the TB prevalence exceeds 10%. As with all screening tools, the GDG emphasized the importance in all settings of following up an mWRD screen with a diagnostic assessment to prevent the potential harm of overtreatment. In addition, due consideration should be made to prioritizing mWRDs as a diagnostic test for all people with presumptive TB before scaling up mWRD as a screening test.

**Table 8. Diagnostic accuracy of molecular WHO-recommended rapid diagnostic tests for screening for TB among different subpopulations of people living with HIV compared with culture as a reference standard**

| Population | No. of studies (no. of participants) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|
| WHO target product profile | NA | > 0.90 | > 0.70 |
| All people living with HIV | 14 (9 209) | 0.69 (0.60–0.76) | 0.98 (0.97–0.99) |
| Inpatients | 4 (639) | 0.77 (0.69–0.84) | 0.93 (0.89–0.96) |
| Outpatients on ART | 4 (2 645) | 0.54 (0.20–0.84) | 0.99 (0.97–1.00) |
| Outpatients not on ART | 10 (5 796) | 0.72 (0.64–0.79) | 0.98 (0.98–0.99) |
| CD4 ≤ 200 cells/μL | 12 (3 422) | 0.76 (0.68–0.82) | 0.97 (0.95–0.98) |
| Pregnant women living with HIV | 4/473 | 0.55 (0.33–0.75) | 0.99 (0.97–0.99) |

ART: antiretroviral treatment; CI: confidence interval; NA: not applicable.

### 3.3.2 Implementation considerations for all tools for screening people living with HIV

Countries should position the W4SS, CRP, CXR and mWRD in combination with diagnostic evaluation using mWRDs and LF-LAM *(8)* within national TB screening and diagnostic algorithms according to their feasibility, the level of the health facility, resources and equity. Algorithms exploring the available

screening tools are presented in the operational handbook, including modelled performance of accuracy and yield *(7)*. While all of the screening tools presented are recommended for all people living with HIV for ease of programming, evidence showed notable accuracy of CRP for TB screening in people not yet receiving ART and that CXR enhanced the sensitivity of the W4SS among people receiving ART, both of which might be considered when choosing algorithms.

Among inpatients on medical wards in settings with a high TB burden, evidence showed that the W4SS, CRP and CXR had limited accuracy, either due to extremely low specificity or suboptimal sensitivity. Therefore, using mWRD as an upfront screening and diagnostic test is warranted, particularly given the urgency of timely diagnosis in this population.

While there are minimal data on optimal frequency of screening across all tools, data presented to the GDG on results from the WHIP3TB trial (evaluating the effectiveness of weekly rifapentine plus isoniazid for 3 months compared with periodic rifapentine plus isoniazid for 3 months and 6 months of daily isoniazid in HIV-positive individuals) *(79)* underscored the need for more intensified routine screening in addition to the W4SS, even among those receiving ART who have received TPT. The GDG suggested that conducting more intensified screening in addition to the W4SS should occur at the time of an initial diagnosis of HIV or during the first antenatal care visit for pregnant women, and then annually thereafter. To reduce the burden on the patient, screening should be aligned with other routine HIV care visits, such as those for viral load monitoring or for ruling out TB disease prior to initiating TPT, depending on the setting and the national guidelines on HIV. Where applicable, the W4SS should also be conducted as part of a comprehensive clinical evaluation and to inform the need for increased infection control and for other diagnostic tests, such as LF-LAM. Otherwise screening with the W4SS alone should be carried out during all other interactions between patients and health care workers.

Consideration should also be given to the added benefit of including CRP for ruling out TB disease prior to initiating TPT among people living with HIV. In a setting of 1% TB prevalence, among 1 000 outpatients screened with the W4SS followed by CRP, 742 would be true negatives and eligible for TPT compared with only 416 found eligible by the W4SS. As is the case for using CXR for ruling out TB disease prior to initiating TPT, restricted access to CRP or CXR should not be a barrier to initiating TPT.

When considering using an mWRD as a TB screening tool among people living with HIV, it should be ensured that universal access to mWRD as a diagnostic test for everyone with presumptive TB is achieved first. The use of an mWRD as a screening tool requires significant resources for implementation, including increased capacity for diagnostic networks and expansion of sample transportation networks. Depending on the feasibility and resources available, countries may choose to prioritize TB screening using mWRDs among certain subpopulations, such as medical inpatients in settings where the TB prevalence is less than 10%, among other patients who are acutely unwell or among pregnant women living with HIV. Screening with an mWRD in lower prevalence settings than those included in the IPD meta-analysis may result in higher false positives should the diagnosis not be confirmed, with the associated overtreatment and related social and economic consequences, including potential delays in starting ART. Careful clinical assessment is recommended to ensure that TB is the primary cause of illness and that other conditions leading to the clinical presentation are also managed. A negative mWRD does not exclude TB. Patients in such settings who are mWRD negative but are manifestly sick may not be able to produce sputum of sufficient quality or may have extrapulmonary TB. For patients with a history of TB within the past 5 years, a positive result may be due to the presence of DNA detected from previously treated TB. Should the patient be unable to provide sputum, other biological specimens should be considered, as indicated *(69)*. The TB prevalence among people living with HIV in medical wards may be calculated as the percentage of people with HIV-related admissions during a 6–12-month period who are diagnosed with TB.

To inform programming and resource planning, countries are encouraged to monitor and evaluate the yield of TB screening among people living with HIV, disaggregated by screening tool.

# 3.4 Tools for systematic screening for TB disease among children and adolescents

16. Among individuals younger than 15 years who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both

(*new recommendation: strong recommendation, moderate to low certainty of evidence for test accuracy*).

17. Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient

(*new recommendation: strong recommendation, low certainty of evidence for test accuracy*).

## 3.4.1 Summary of the evidence and rationale

Case detection is a crucial step in the cascade of care for children with TB; however, for most children who die from TB, the disease is never diagnosed *(80)*. Children and adolescents who are younger than 15 years represented approximately 12% of incident cases but 16% of the estimated 1.4 million deaths from TB in 2019 *(1)*. This relatively higher share of mortality in children highlights the urgent need for improved case detection and subsequent access to preventive and curative treatment in this age group, particularly for those at highest risk.

These recommendations relate to the two subpopulations of children for whom TB screening is strongly recommended but for whom there is as yet no standard screening approach: children and adolescents younger than 15 years who are close contacts of individuals with TB, and children younger than 10 years who are living with HIV. Adolescents living with HIV who are aged 10–19 years are covered in previous recommendations for screening people living with HIV (see **Recommendations 11–15**), and screening of contacts 15 years of age and older is covered in the previous recommendation on screening tools (see **Recommendations 9–10**).

Data from a systematic review of the diagnostic accuracy of multiple screening tools used to detect TB disease among children and adolescents, which were compared against a microbiological or composite reference standard, were used to inform this recommendation. Because bacteriological testing for TB is difficult in children, a composite reference standard is often used when evaluating diagnostic accuracy in this age group.

### *3.4.1.1 Close contacts younger than 15 years*

The evidence reviewed about the performance of symptom screening among children and adolescents younger than 15 years who are close contacts of someone with TB included 4 studies with a total of 2 695 participants (see **Web Annex B**, Table 17, and **Web Annex C**, Table 10). In this population, a symptom screen involving any one of cough, fever or poor weight gain (where the presence of any symptom constitutes a positive screen), when compared against a composite reference standard, had a pooled sensitivity of 0.89 (95% CI: 0.52–0.98) and a pooled specificity of 0.69 (95% CI: 0.51–0.83).

The evidence reviewed about the performance of chest radiography among close contacts younger than 15 years of TB patients included 4 studies with a total of 2 550 participants (see **Web Annex B**, Table 18, and **Web Annex C**, Table 8). Compared with a composite reference standard, chest radiography using abnormalities suggestive of TB as a positive screen had a pooled sensitivity of 0.84 (95% CI: 0.70–0.92) and a pooled specificity of 0.91 (95% CI: 0.90–0.92).

Despite the absence of high-certainty evidence for test accuracy, the GDG felt that a strong recommendation was warranted for both of the tools being considered for close contacts younger than 15 years, given the high risk of disease and of mortality if the diagnosis is missed and TB is left untreated

#### *3.4.1.2 Children younger than 10 years who are living with HIV*

The evidence reviewed about the performance of symptom screening (any one of current cough, fever, poor weight gain or close contact with someone with TB) included 2 studies conducted in the outpatient setting with a total of 20 926 participants and including 20 3135 screens (see **Web Annex B**, Table 19, and **Web Annex C**, Table 10). In this setting, the combined symptom screen (where the presence of any symptom constitutes a positive screen) was found to have a pooled sensitivity of 0.61 (95% CI: 0.58–0.64) and a pooled specificity of 0.94 (95% CI: 0.86–0.98).

Again, despite the absence of high-certainty evidence, the GDG felt that a strong recommendation was warranted for symptom screening for children younger than 10 years who are living with HIV, given the high risk of disease and of mortality if the diagnosis is missed and TB is left untreated.

### 3.4.2 Considerations for screening children and adolescents

None of the screens investigated reached the target product profile of 90% minimum sensitivity in these high-risk subpopulations of children, although CXRs came the closest. Concerns were noted about the risk of incorporation bias when using a composite reference standard in this group, thus potentially inflating the estimates of accuracy observed. Concerns were also noted about the increased risk of false-positive diagnoses in children following a false-positive screening test compared with the risk in adults because children are more likely to be diagnosed using clinical evaluation rather than bacteriological confirmation, and the process of confirming a clinical diagnosis will weight the results of the screening test or tests. When screening high-risk groups of children, including close contacts and children living with HIV, the balance between the benefits of early case detection arising from true-positive screening results and the possible risk of overtreatment from false-positive screening results is in favour of screening. When screening populations of children with a lower risk of TB or in lower prevalence settings, the trade-off between early case detection and possible overdiagnosis will be different and should be carefully considered. In such situations, while a highly sensitive screening approach is important in order to maximize early case detection, health care workers must remain vigilant to possible false-positive diagnoses and monitor responses to treatment carefully, including evaluating children and adolescents for other potential diagnoses if symptoms or CXR abnormalities persist.

Given the high risk of TB and of mortality if TB is left untreated among children with HIV and among those in close contact with TB patients, there is an urgent need to utilize any and all available screening tests to increase timely diagnosis among these high-risk populations.

Children living with HIV represent an important group that should be considered for regular TB screening and the provision of preventive therapy, given their high risk of TB and of poor outcomes if not diagnosed in a timely manner. An essential minimum screening strategy for this group would be to ensure regular screening for TB symptoms at each visit to a health centre. While data were lacking to evaluate CXR as an initial screen for children living with HIV, CXR is a useful part of a diagnostic evaluation for TB in all children, including those living with HIV, especially younger children in whom bacteriological evaluation is commonly negative *(68)*. Children and adolescents who are close contacts of someone with TB likewise represent an important group for screening for TB disease and for the initiation of preventive therapy, given their high risk for developing TB and rapid disease progression.

For children at high risk of TB, countries should position symptom screening and screening chest radiography within national TB screening and diagnostic algorithms, according to their feasibility, level of health facility, resources and equity. Algorithms exploring the different screening tools are presented in the operational handbook *(7)*.

# 4. Monitoring and evaluation

In this section, we consider the monitoring and evaluation required to support the implementation of TB screening programmes. The operational handbook contains more details about the monitoring, surveillance and evaluation of TB screening interventions *(7)*.

When considering implementing screening in the general population, it is important to know the epidemiology of TB and the prevalence of undetected TB in the community. This will help to estimate the impact of any screening programme. TB disease prevalence surveys are used to assess the baseline occurrence of TB in high-burden settings *(81)*. However, these surveys represent a major undertaking and are not practical in all situations. Surveillance data based on TB notifications can be used as a starting point, but it must be carefully considered alongside other factors that affect the risk of TB and the likelihood of diagnosis, including the availability of health services and the prevalence of other risk factors for TB (e.g. HIV, diabetes mellitus, smoking, malnutrition, poverty, overcrowded living conditions, older age, substance use disorder, and other lung conditions, including silicosis or fibrotic chest lesions).

In settings that are generally considered to have a higher TB burden than is found in the overall population, such as prisons, careful monitoring and surveillance to assess TB prevalence and incidence should be done alongside TB screening. If the burden of TB is found to be low and sustained at a low level for a period of time, then TB screening can be discontinued. However, surveillance should be conducted to minimize the risks of TB disease and transmission.

## 4.1 Indicators

Continued monitoring can help programme managers assess the performance of the TB screening components that are within their purview. The following indicators should be considered for each targeted risk group:

1. the number of people eligible for screening;
2. the number of people screened (considering the first screening and second screening separately, if applicable);
3. the proportion of those eligible for screening who were screened;
4. the number of people with presumptive TB who were identified;
5. the number of people undergoing diagnostic investigation;
6. the number of people diagnosed with TB, stratified by type of TB;
7. the proportion of those undergoing diagnostic investigation who have TB;
8. the NNS to detect one person with TB;
9. the proportion of initial defaulters (that is, the number of people diagnosed with TB who do NOT start treatment divided by number of people diagnosed with TB);
10. the treatment success rate and the death rate (using standard cohort analyses).

Additional disaggregation may be done – for example, by age group and sex – but this requires that more detailed data are collected for each individual who is screened.

The uptake of screening in a risk group (the proportion of those eligible for screening who are actually screened) can be assessed only if the size of the target group has been well defined. It is normally possible to obtain the relevant information when screening is conducted within health facilities or closed settings (such as prisons) and through contact investigations. However, it is often difficult to obtain this information from outreach screening programmes – for example, when screening is done in the community – although the estimated population size of a targeted community may be used to obtain a rough estimate of the eligible population.

## 4.2 Routines for recording and reporting

In order to obtain the required information for the indicators described above, a TB recording and reporting system needs to include a minimal set of data elements. Although paper-based systems have been used to collect such data, it is now becoming increasingly feasible to collect data electronically, and this should be the standard aspired to for monitoring TB screening activities. The following strategies can be used to collect the necessary data:

- maintain a log of the number of people screened in each risk group. A special register with individual-level information for each person screened may be used to obtain more refined data about subcategories of persons within a risk group. Collecting these data is resource intensive, but it may be relevant when a screening programme is started as part of operational research. It may be feasible to implement this type of data collection on a continual basis for certain risk groups, such as people seeking care in medical facilities;
- maintain a register of all patients with presumptive TB who undergo further diagnostic evaluation (if a register is used to collect individual-level information for all people who are screened, then this information can be included in it);
- include a field in the laboratory register for noting whether the tested patient was identified through screening and to which risk group the patient belongs;
- include a field in the treatment register to note whether the patient was identified through screening and to which risk group the patient belongs.

## 4.3 Programmatic evaluations

A successful screening programme may lead to a diminishing yield, at least if the risk group is a fixed population. Over time, changes in the background burden of TB, as well as changes in the profile of TB patients in the community (e.g. a trend towards fewer patients with symptomatic TB) can lead to a reduction in the yield from screening, an increase in the NNS, a reduction in cost–effectiveness and a change in the ratio of benefits to harms. Trends in all of these indicators need to be monitored, and the prioritization of risk groups, choice of screening approach and screening interval should be regularly reassessed. Criteria for stopping screening should be established before a screening initiative is implemented.

Monitoring the indicators discussed above may point to the need for a special assessment, for example, to explore the reasons for a low uptake of screening, an unexpectedly low proportion of people with presumptive TB that was identified through screening, a low proportion of those with presumptive TB undergoing a diagnostic investigation and a higher than expected NNS. Additional quantitative and qualitative analyses may be needed to determine whether there are barriers to screening and to identify opportunities to improve the screening approach.

## 4.4 Initial calibration for computer-aided detection technologies

When CAD is implemented, local calibration is advised to customize the score thresholds to the requirements of the programme (see the operational handbook for more details about how this can be done) *(7)*. After this initial calibration, ongoing monitoring and analysis of CAD performance should be carried out to assess the correlation with human readers' interpretations and with bacteriological confirmation, and with the proportion of images read as abnormal and requiring further investigation.

# 5. Research gaps

## 5.1 Screening for TB in targeted populations

### 5.1.1 The general population and high-risk groups

Well-designed trials and rigorous quasi-experimental studies in different settings are required to investigate the effects of population-wide systematic screening for TB on individual-level outcomes (diagnostic delay, treatment outcomes, costs to patients, social consequences) and population-level outcomes (TB prevalence, incidence, transmission), as well as to guide implementation choices (including the method of delivery, screening algorithms, the duration of screening intervals and frequency of screening, and the mode of delivering the intervention).

Research on the longer-term impacts of screening, including any potential evidence of averted morbidity or mortality, is not necessarily captured in the existing data. Research on the cost–effectiveness of screening is needed, using a longer time horizon to adequately capture all potential costs and longer-term effects, including potential reduced future prevalence and incidence.

Observational research and programmatic evaluations reporting the impact of community-wide screening on TB case notification rates – which provide an important source of evidence on the impacts of screening under programmatic conditions – must be carefully designed and analysed to minimize bias.

Studies of screening interventions should incorporate both qualitative and quantitative assessment of the indirect effects of screening, given the importance of health-seeking behaviour in TB care engagement and the potential impact of population-wide screening to change it and the importance of assessing any unintended mental, social or economic consequences of screening (including adverse effects, the burden of the test and downstream outcomes of clinical management that is guided by the outcomes of test results).

### 5.1.2 People living with HIV

Well-designed clinical trials are needed to strengthen the evidence about the accuracy, effectiveness (including the impact on patient-important outcomes such as mortality), feasibility and cost implications of using the W4SS, CRP, CXR and mWRD to screen for TB across all HIV subpopulations in settings with low, medium and high burdens of HIV and TB with and without high ART coverage.

Subpopulations of people living with HIV for whom further investigation is required would include, but not be limited to, inpatients, acute care service attendees, patients for whom ART has failed, patients newly diagnosed as HIV-positive enrolling in ART clinics, stable patients established on ART, pregnant women and children and adolescents living with HIV.

More data are needed on the effectiveness, cost–effectiveness, feasibility and acceptability, frequency and optimal periodicity of routine, regular screening with the W4SS, CRP, CXR and mWRD among people living with HIV. Specifically, more studies are needed that explore the optimal placement of mWRDs for screening in antenatal care settings versus within ART clinics. Lastly, more research is needed on the potential for screening people living with HIV with mWRDs using specimens other than sputum.

### 5.1.3 Children and adolescents

The GDG considered data on using mWRDs for screening children and adolescent outpatients accessing health care. They felt that the data, which included 2 studies with 787 participants and had results demonstrating substantial heterogeneity, represented insufficient evidence to establish an accurate and reliable estimate of the diagnostic accuracy of mWRDs, and, thus, the GDG decided not to issue a recommendation for or against their use as a screening tool for children and adolescents. This highlights as a research priority the need for more rigorous studies evaluating the use of mWRDs for screening children and adolescents.

Also highlighted is the urgent overall need for more research and the development of better screening tools and approaches for use in this population, including more data on screening approaches that target specific and distinct age ranges including infants younger than 12 months, children younger than 5 years, children up to the age of 10 years and those aged 10–19 years. More data are needed to determine the frequency with which screening should be conducted among the subpopulations of children at highest risk of TB, and further research is needed from well-designed clinical trials to provide evidence on patient-important outcomes for TB screening in children.

## 5.2 Tools for screening for TB

### 5.2.1 Computer-aided detection

Further evidence is needed about the performance of CAD software stratified according to the characteristics of the individual being evaluated (e.g. by smear status, HIV status, age cohort, history of TB, smoking status, sex) to allow for better setting-specific and patient-specific calibration of CAD programmes.

More research on users' perspectives is needed about CAD technologies in TB screening and triage, including their perceived acceptability to patients, providers and other stakeholders.

The development and evaluation of CAD programmes for automated detection of TB in children is urgently needed, as CXR is an important tool for detecting pulmonary TB in children and adolescents, given the difficulty of bacteriological testing and diagnosis.

### 5.2.2 C-reactive protein

For people living with HIV in settings with different TB prevalences, more research is needed to evaluate the accuracy and predictive value of measuring CRP above any cut-off higher than 5 mg/L for TB screening, when it is used either alone or in combination with other screening tests.

### 5.2.3 Screening algorithms

Across all populations and tools, more research is needed to evaluate the accuracy and effectiveness of complete screening and diagnostic algorithms, including symptom screening, CXR, CRP and mWRDs used in various combinations with diagnostic evaluation. Research into their effectiveness should include measures of the impacts on patient-important outcomes, such as mortality and treatment success.

## 5.3 Operational research

Standard monitoring and evaluation procedures may be complemented by operational research aimed at improving the performance of screening in the local setting as well as research aimed at improving the global evidence base for screening. Topics that may be explored include:

- assessing the accuracy and performance of different algorithms for screening and diagnosis;
- identifying operational challenges and solutions;
- identifying the best ways to improve acceptability and minimize the harms of screening;
- establishing the effectiveness and cost–effectiveness of screening in different risk groups and in different epidemiological situations;
- establishing local calibration of CAD software for the specific case of a programme.

There is a need for more, larger and better randomized trials to assess the short-term and long-term effectiveness and cost–effectiveness of screening. Implementing such studies requires careful planning and considerable resources.

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# Supplementary Table

## Summary of changes to existing recommendations

| 2013 Recommendation | 2021 Recommendation |
|---|---|
| Household contacts and other close contacts should be systematically screened for active TB (*strong recommendation, very low-quality evidence).* | Household contacts and other close contacts of individuals with TB should be systematically screened for TB disease (*strong recommendation, moderate certainty of evidence).* |
| People living with HIV should be systematically screened for active TB at each visit to a health facility *(strong recommendation, very low-quality evidence).* | People living with HIV should be systematically screened for TB disease at each visit to the health facility *(strong recommendation, very low certainty of evidence).* |
| Current and former workers in workplaces with silica exposure should be systematically screened for active TB *(strong recommendation, low-quality evidence).* | Current and former workers in workplaces with silica exposure should be systematically screened for TB disease (*strong recommendation, low certainty of evidence*). |
| Systematic screening for active TB should be considered in prisons and other penitentiary institutions (*conditional recommendation, very low-quality evidence*). | Systematic screening for TB disease should be conducted in prisons and penitentiary institutions (*strong recommendation, very low certainty of evidence*). |
| Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion (*conditional recommendation, very low-quality evidence*). | People with an untreated fibrotic lesion seen on chest X-ray may be systematically screened for TB disease (*conditional recommendation, very low certainty of evidence*). |
| In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for active TB should be considered among people who are seeking health care or who are in health care and who belong to selected risk groups (*conditional recommendation, very low-quality evidence*). | In settings where the TB prevalence in the general population is 100/100,000 population or higher, systematic screening for TB disease may be conducted among people with a risk factor for TB who are seeking health care or who are in health care (*conditional recommendation, very low certainty of evidence*). |
| Systematic screening for active TB may be considered for geographically defined subpopulations with extremely high levels of undetected TB (1% prevalence or higher) (*conditional recommendation, very low-quality evidence*). | Systematic screening for TB disease may be conducted among the general population in areas with an estimated TB prevalence of 0.5% or higher (*updated recommendation – conditional recommendation, low certainty of evidence).* |

| 2013 Recommendation | 2021 Recommendation |
|---|---|
| Systematic screening for active TB may be considered also for other subpopulations that have very poor access to health care, such as people living in urban slums, homeless people, people living in remote areas with poor access to health care, and other vulnerable or marginalized groups including some indigenous populations, migrants and refugees (*conditional recommendation, very low-quality evidence*). | Systematic screening for TB disease may be conducted for subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons , and other vulnerable or marginalized groups with limited access to health care (*conditional recommendation, very low certainty of evidence*). |
| Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases. (*strong recommendation, moderate quality of evidence*) | Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases (*strong recommendation, moderate certainty of evidence*). |

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