WHO operational handbook on tuberculosis

Module 2: Screening

Systematic screening for tuberculosis disease

World Health Organization

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Abbreviations and acronyms

ART   antiretroviral treatment

CAD   computer-aided detection of TB-related abnormalities on chest radiography

CXR   chest radiograph (chest X-ray)

LF-LAM   lateral flow urine lipoarabinomannan assay

mWRD   molecular WHO-recommended rapid diagnostic test

NNS   number needed to screen

ROC   receiver operating characteristic

TB   tuberculosis

TPT   TB preventive treatment

W4SS   WHO-recommended four-symptom screen

Definitions

Active (TB) case-finding: 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". It is referred to as "intensified case-finding" when conducted in health-care facilities and as "enhanced case-finding" when conducted in communities.

Close contact: A person who does not live in the household but who shared an enclosed space, such as a social gathering place, workplace or facility, with the index patient for extended periods during the day during the 3 months before the current disease episode commenced.

Computer-aided detection (CAD): refers to 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.

Contact: Any person who has been exposed to a person with TB disease.

Contact investigation: systematic identification of people with previously undiagnosed TB disease and TB infection among the contacts of an index TB patient in the household and in comparable settings in which transmission occurs. It consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease). This term is often used synonymously with "contact tracing"; however, in the context of TB, action beyond identifying contacts is critical.

Household contact: A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index patient during the 3 months before the start of current treatment.

Index patient (index case): A person of any age with new or recurrent TB initially identified in a specific household or comparable setting in which others may have been exposed. An index patient is the person on whom a contact investigation is centred but is not necessarily the source.

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

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

Passive TB 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.

Patient-initiated health care pathway: The patient-initiated pathway to TB diagnosis relies on patients seeking care and on health systems to respond quickly and appropriately. Some people may access care after exposure if they are very well informed, but most people will seek care only once they experience symptoms severe enough to merit attention. They may experience delay due to access barriers. On accessing care, they may experience delays until they are referred to a service that can make a TB diagnosis, and there may be further delays and barriers before a diagnosis is made and appropriate treatment is initiated.

Provider-initiated TB screening pathway: The provider-initiated TB screening pathway systematically targets people at high risk of exposure or of developing TB disease and screens them by assessing symptoms, using tests, examinations or other procedures to identify those who might have TB, following up with a diagnostic test and additional clinical assessments to make a definite diagnosis. This approach can target people at different stages of TB, for example by screening those at high risk of exposure (e.g. high TB burden communities or settings such as prisons) or those who are exposed to TB (e.g. contacts of a TB patient), or those who have high risk of developing TB (e.g. people living with HIV). Screening programmes must include an appropriate pathway for diagnostic confirmation, treatment and care and further management.

Repeat screening: Re-screening in the same population at a given interval.

Risk group: 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 TB: 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.

Systematic screening for TB disease: 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 may be done in multiple steps.

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

Tuberculosis (TB): The disease state caused by *Mycobacterium tuberculosis*. It is usually characterized by clinical manifestations, which distinguishes it from TB infection without signs or symptoms. In this document, it is referred to simply as "TB" or "TB disease". It should be distinguished from "TB infection" (previously referred to as "latent TB infection" or LTBI, a term that incorporated generations of TB bacilli that are not dormant). Pulmonary TB involves the lungs and is the most common form of TB. Extrapulmonary TB involves organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones or meninges). The two forms may coexist in the same patient.

Tuberculosis preventive treatment: Treatment offered to individuals considered to be at risk of TB disease in order to reduce that risk. Also referred to as "treatment of TB infection" and previously treatment of "latent TB infection".

WHO four-symptom screen: The presence of either cough, fever, weight loss or night sweats used as a screening test in people living with HIV.

Chapter 1. Introduction

1.1 Rationale for systematic screening for TB disease

Tuberculosis (TB) is a major yet preventable airborne infectious disease. About one fourth of the world's population is infected with TB bacilli, the vast majority of whom have no disease *(1, 2)*. In 2019, an estimated 10 million new TB cases emerged worldwide, and more than 1.4 million people died of TB, making it the leading single infectious disease cause of death that year *(2)*. Of the estimated 10 million people who fell ill with TB in 2019, TB was not diagnosed in an estimated 2.9 million, and they were not enrolled in quality-assured TB treatment *(2)*. Additionally, many people delay seeking care for their illness or are misdiagnosed before they are eventually diagnosed and treated *(3)* (see also **Web Annex B** of the screening guidelines).

The aim of screening (or active TB case finding) is to detect TB disease early in order to minimize avoidable delays in diagnosis and initiation of treatment, thereby reducing the risk of unfavourable treatment outcomes, health sequelae and the adverse social and economic consequences of TB for individuals and their families. In addition, screening reduces TB transmission in a household, workplace, school or other community setting by removing people with prevalent disease and shortening the duration of infectiousness. This reduces the incidence of TB infection and consequently the incidence and prevalence of TB disease. When implemented with an effective algorithm for screening and diagnostic testing and when integrated with TB preventive treatment (TPT) for people without TB disease at risk of progression, there is a higher likelihood that the health of individuals and the community will be improved. Testing for TB infection with a TB skin test or interferon-g release assay to inform decisions about TPT is not part of screening and is discussed in separate normative documents *(4, 5)*.

Detecting TB only among people who present to health facilities is not enough to find all people with TB disease. The remaining case-detection gap, particularly in certain vulnerable populations, and the persistence of diagnostic delays and resulting continued transmission in the community, indicate the need for a more active approach to early detection of TB. This justifies systematic screening of selected risk groups and populations for TB disease.

The WHO End TB Strategy includes systematic screening for TB disease in high-risk groups as a central component of its first pillar, to ensure early diagnosis of all persons with TB *(6, 7)*. In 2021, WHO has updated the TB screening guidelines from 2013 to help countries in implementing this critical programmatic component. This operational handbook accompanies *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease* and provides additional practical details for applying the guideline recommendations by identifying priority risk groups and selecting the appropriate screening approaches in the light of new evidence. The updated recommendations are summarized in Table 1.1.

Table 1.1 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 *(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 *(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 *(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 *(updated recommendation: strong recommendation, moderate certainty of evidence).*
5	Systematic screening for TB disease should be conducted in prisons and penitentiary institutions *(updated recommendation: strong recommendation, very low certainty of evidence).*
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).*
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).*
	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 *(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 *(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 *(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 *(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).*
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).*

TB: tuberculosis.

1.2 Principles of TB screening

Systematic screening for TB fulfils the classic screening criteria *(8)*. The following key principles are to be considered in planning a TB screening initiative:

- Principle 1: TB screening should always be done with the intention to follow up with appropriate medical care and ideally implemented where high-quality TB diagnostic and treatment services are available. If a community lacks access to appropriate follow-up care but would benefit from TB screening, this should be an impetus for investment by national TB programmes in TB diagnosis and treatment services, in order to complement TB screening.
- Principle 2: Screening should reach the people at greatest risk of developing TB disease, including high-risk groups and communities with a high prevalence of TB. Prioritization of risk groups for screening should be based on an assessment for each group of the potential benefits and harm, the feasibility and acceptability of the screening approach, the number needed to screen (NNS) and the cost–effectiveness of screening. The benefits and harm of TB screening in different groups and populations need to be carefully assessed to maximize the common good while minimizing harm to individuals. TB threatens the health not only of an affected individual but also of their communities and the broader population.
- Principle 3: TB screening should follow established ethical principles for screening for infectious diseases, including obtaining voluntary informed consent before proceeding with screening individuals and observing human rights, and be designed to minimize the risks of discomfort, pain, stigmatization and discrimination. Informed consent is a basic right and an important means of respecting an individual's autonomy.

- Principle 4: The choice of algorithm for screening and diagnosis is based on an assessment of the accuracy of the algorithm for each risk group, as well as the availability, feasibility and cost of the screening tests. After a positive screening test result, the diagnosis of TB should be confirmed before TB treatment is started.
- Principle 5: TB screening should be synergized with the delivery of other health and social services. Synergies are best identified during the development and implementation of screening approaches for different target populations, which may have particular patterns of use of health and social services.
- Principle 6: A screening strategy is expected to maximize coverage and frequency of screening to achieve its aims. Regular monitoring is necessary to inform any re-prioritization of risk groups, resource use, adaptation of screening approaches and discontinuation of screening. This includes the assessment of risk of false-positive diagnoses resulting from screening.

1.3 Objectives of the operational handbook

This document provides practical guidance on translating WHO's recommendations for screening into a national or local strategy with clear objectives, prioritization of risk groups and definition of the most appropriate screening approaches.

The specific objectives are:

- to support Member States in implementing effective TB screening by supporting policymakers in ministries of health in choosing the best approach to planning and implementing screening and active case-finding, depending on the context;
- to provide a sound basis for development or updating of national guidelines for TB screening according to the epidemiology of TB in different risk groups and the health care delivery system in the country; and
- to contribute to finding people with TB who may be missed by standard case-finding approaches and finding people with TB earlier in the course of disease to reduce transmission, morbidity, mortality and financial hardship for people suffering from TB.

Six essential steps in the cycle of designing and implementing a TB screening programme are discussed in Chapter 2: 1) assessing the situation; 2) setting goals and specific objectives; 3) identifying and prioritizing risk groups; 4) choosing algorithms for screening and diagnosis; 5) planning, budgeting and implementing and 6) monitoring, evaluating and modifying the programme. These six steps are an iterative process, which may lead to revision of the strategy, as necessary. The process should be followed throughout screening and integrated with overall national TB and health systems activities (Fig. 1.1).

Fig. 1.1 The six essential steps in the cycle of designing and implementing a TB screening programme
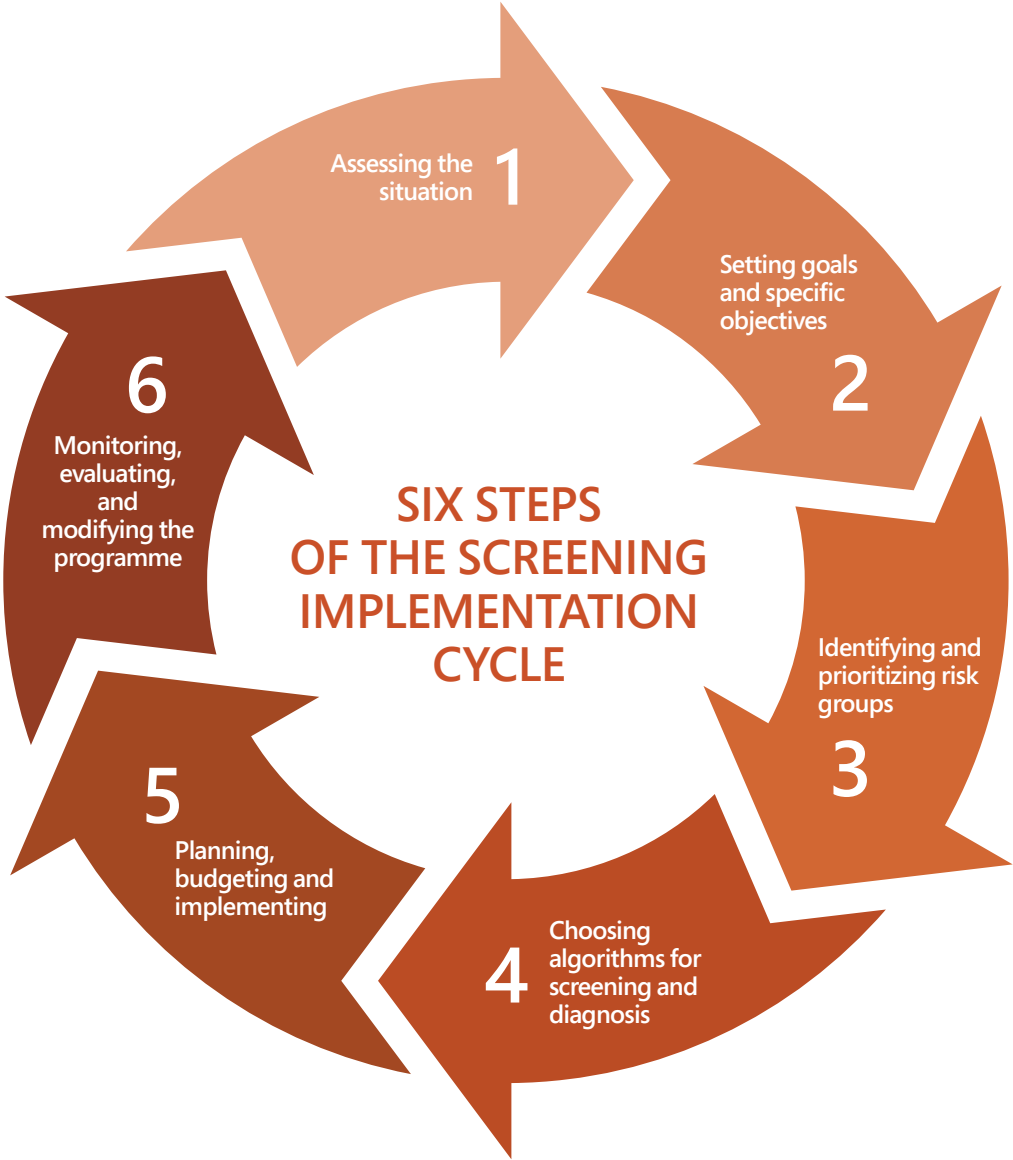
Details of different screening tools and their performance in different populations and of algorithms for screening and diagnosis are described in Chapter 3. Most of the approaches proposed in this handbook are for detecting pulmonary TB, the predominant form of the disease worldwide, which is directly transmissible and for which most evidence exists. This does not diminish the importance of extrapulmonary TB as a public health concern in many countries and in certain subpopulations (e.g. children). About 16% of new and relapsed TB patients reported globally in 2019 had exclusively extrapulmonary forms of TB, presenting an additional challenge for detection. Screening for extrapulmonary TB is therefore an important gap that should be filled by research and guidance. The screening tools described here include assessment of symptoms and chest X-ray (CXR), which have traditionally been used for TB screening, and tools that are newly recommended for screening, including computer-aided detection (CAD) technologies for automated interpretation of digital CXR, C-reactive protein (CRP) for screening people living with HIV and use of WHO-recommended rapid molecular diagnostic tests (mWRDs) for screening. Algorithms that combine various screening and diagnostic tools in order to optimize accuracy and ensure a feasible implementation strategy are also discussed. As algorithms perform differently in different populations, an online tool, ScreenTB,

has been developed to assist in prioritizing risk groups for screening and choice of algorithm. It is described in Chapter 3.

CAD software packages for automated interpretation of digital CXR images of TB are recommended for screening for the first time by WHO. Chapter 4 provides suggestions on implementation of CAD technologies in new settings, including selection of CAD technologies and protocols for operational research to facilitate implementation. This chapter also provides a description of an online tool, CAD for TB, for the analysis and interpretation of data for CAD calibration. Chapter 5 specifically addresses TB screening in people living with HIV, describing the different subpopulations (outpatients receiving antiretroviral treatment (ART), outpatients newly enrolling in ART care, inpatients with HIV and pregnant women living with HIV), who have specific needs and in whom screening tests perform differently. Because new screening tools are recommended for TB screening in people living with HIV, including CRP and mWRD, specific consideration is given to how these tools and associated algorithms might be integrated into HIV services with additional tests like lateral flow urine lipoarabinomannan assay (LF-LAM) for people with advanced disease.

Chapter 6 addresses operational factors specific to the new recommendations on screening in children, including a discussion of implementation specifically for different subpopulations of children by age group and risk population.

1.4 Target audience of the operational handbook

The operational handbook is intended for personnel in national TB programmes and 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; other health policy-makers, implementing partners including technical and funding agencies, civil society and representatives of affected communities, clinicians and public health practitioners working on TB and HIV and infectious diseases in the public and private sectors.

Chapter 2. The six steps in the planning and implementation cycle

2.1 Introduction

The two complementary approaches for improving early detection of TB are illustrated in Fig. 2.1 The primary approach is to optimize the patient-initiated pathway to TB diagnosis and treatment (for details see 2.1.1). This approach does not constitute screening and is a passive form of case detection. Because it relies on initiation by people with TB disease and on health systems to respond, this approach is beset with delays associated with societal norms, stigmatization and discrimination, illness behaviour, limitations in health coverage, barriers to accessing services, and constraints of resources and capacity at health service entry points and referral pathways within the health system. The other approach to enhance case detection is screening, or the provider-initiated screening pathway to TB diagnosis and is the focus of this operational handbook.

Fig. 2.1 Comparison of the provider-initiated TB screening pathway with the patient-initiated health care pathway for TB
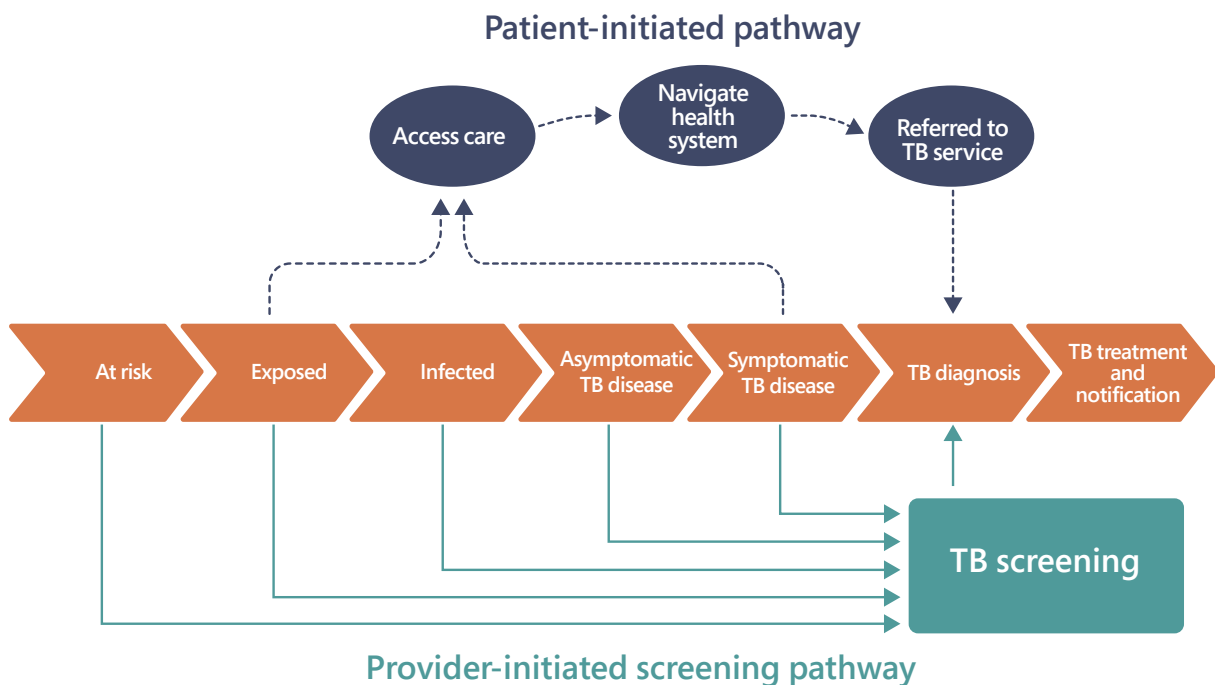
2.1.1 Enhancing the patient-initiated pathway to TB diagnosis

The patient-initiated pathway to TB diagnosis can be enhanced by:

- *improving access to care*, including reducing the direct and indirect costs to patients associated with seeking care and addressing the specific needs of vulnerable groups by strengthening primary health-care services, extending diagnostic and testing services and providing social protection schemes where possible and necessary.
- *improving the acceptability of care*, by ensuring privacy and providing fast-tracking through outpatient departments and faster services to reduce waiting times and to ensure that daily wage-earners do not lose income. Incorporating "care" aspects, by including emotional care in addition to diagnosis and treatment in training curricula help to ensure empathetic, compassionate and patient-centred care *(9)*.
- *community engagement and demand generation*, by education and awareness campaigns (including on exposure and risk) for the general public and in communities that are at higher risk of TB to increase the likelihood that those who have been exposed and/or have TB disease will seek care at facilities with the capacity to diagnose and treat TB.
- *training and capacity-building of health-care workers*, by providing additional training and equipping all health-care workers in the health system, in both the public and the private sectors, in primary care, at entry points to health care and lay community workers and volunteers *(10)* to increase the likelihood that individuals with symptoms of TB who seek care are recognized and referred for appropriate evaluation and care.
- *reassessing the definition of a person with possible TB*, by broadening the indications for diagnostic testing for TB, in accordance with the local epidemiology of the disease and the epidemiology of the most common risk factors for TB to help ensure that the appropriate people are targeted for evaluation.
- *improving access to testing and diagnostics*, by increasing the capacity of mWRDs, ensuring sufficient laboratory requirements, including human resources, improving links between the private and public sectors and improving the system of reporting results from the laboratory to the clinician.
- *making any other changes to current approach to passive case detection*, as such changes may result in more patients identified in facilities. Greater use of CXR, mWRDs and other accurate tools for diagnosing TB may increase the number of people with TB detected.

Additional approaches to increasing the capacity for TB care and prevention include:

- improving the integrated management of respiratory conditions in primary health care *(11)*;
- scaling up mWRD testing (e.g. Xpert MTB/RIF, Truenat MTB and MTB-RIF Dx) *(12, 13)*;
- scaling up sputum collection and transport systems;
- improving the diagnosis of bacteriologically negative TB, extrapulmonary TB and TB in children;
- providing access to CXR services and CAD; and
- improving referrals and notifications by all care providers *(10)*.

2.1.2 The provider-initiated screening pathway to TB diagnosis

The provider-initiated screening pathway to TB diagnosis entails systematic identification of people with possible TB disease in a predetermined target group with tests, examinations or other procedures that can be applied rapidly. In those with a positive screening test result, the diagnosis must be established by one or several diagnostic tests and additional clinical assessments, which together are highly accurate.

Provider-initiated systematic screening requires careful planning in order to target the specific characteristics and needs of populations. Key stakeholders should be involved in planning, including district or regional managers, who are often familiar with specific implementation challenges, as well as stakeholders from the groups targeted for screening, to create a more people-centred approach *(14)*.

Screening in low-risk groups has the potential to cause more harm than benefit – for example, by detecting more false-positive cases than true-positive cases and potentially overwhelming a stretched diagnostic service and diverting resources for more likely and symptomatic cases. Therefore, after relevant risk groups that potentially would benefit from screening have been identified, those groups at the highest risk should be prioritized. It is also necessary to choose the appropriate screening and diagnostic tests and algorithms for each risk group and for each epidemiological situation. A systematic, carefully planned approach avoids wasting resources and optimizes individual and public health benefits.

2.2 Assessing the situation

The epidemiology of TB in each setting and the social and the health-system contexts will inform decisions on a TB screening strategy, *including how risk groups are prioritized, which screening approach to choose and whether screening of specific risk groups is feasible*. Therefore, before embarking on detailed planning, a baseline assessment of the following features should be undertaken:

- the existing screening and outreach activities, to assess the potential and readiness for intersectoral collaboration (for details, see 2.2.1);
- the societal context, to assess whether screening in specific communities or risk groups would be feasible, acceptable and valuable to the community (for details, see 2.2.2);
- the epidemiology of TB, to identify gaps in case detection, current case-finding activities and the size and distribution of risk groups that might be targeted for screening (for details, see 2.2.3);
- the national TB programme and the general health-care system, including the private health sector and other nongovernmental providers, to assess their preparedness for screening and their capacity to manage a potential increase in evaluation, diagnosis, monitoring and treatment of patients with TB, providing TPT and referring people with symptoms of other respiratory ailments or health conditions identified during TB screening (for details, see 2.2.4);
- health-care coverage and access to health services, to determine whether all people diagnosed with TB will have equitable access to high-quality care (for details, see 2.2.5); and
- protection from stigmatization, discrimination and harm, to ensure that people do not experience negative consequences from screening or any eventual TB diagnosis and its implications for the rights to employment, education and freedom of movement, among others (for details, see 2.1.6).

The specific questions to be addressed in a situation assessment are listed in Table 2.1 Different methods may be used to answer these questions, including analysis of existing data, literature reviews, site visits and interviews.

Table 2.1 Questions to be addressed in a situation assessment before implementing screening for TB

Area to be assessed	Questions
Existing screening and outreach activities that may allow intersectoral collaboration	• Which populations are already being screened for TB? • Which other health conditions are already being screened for? • What links exist among health care services (e.g. integrated TB/HIV services)? • Do any of the potential collaborating agencies have experience in screening for TB or caring for vulnerable populations? • Is there infrastructure that could be used for TB screening? • Where does the funding come from for the other programmes? • Are there already known locations and trained human resources that can be involved in TB screening? • Are there social support programmes that could collaborate?
Distribution of TB burden and risk factors; size and distribution of gaps in case detection	• What is the current distribution of the estimated TB burden in this setting (as inferred from TB notification and case-finding, prevalence and mortality) and specifically for different subpopulations or risk groups? • What is the current gap in case detection, and what are the specific causes of missed or delayed diagnosis for each subpopulation or risk group? • Which subpopulations or risk groups have the highest risk that TB will remain undetected? • Which subpopulations or risk groups make the greatest contribution to undetected TB? • What are the differences in gender with regard to TB burden, TB risks and barriers to care? • Which types of TB are most likely not to be detected? (e.g. extrapulmonary TB) • What are the main reasons for gaps in case detection? • What are the HIV burden and ART coverage?
Current case-detection activities	• What is the level of knowledge about TB among health-care staff and others who provide care? • What is the current definition of presumed TB, and to what extent is it applied in practice? • Which algorithms and diagnostic tests are used to screen for and diagnose different types of TB? • To what extent are mWRDs available, and which individuals are eligible? What is the yield in different settings? • Are CXRs available, and what is the level of access in hospitals, community health centres and mobile health units? Are the CXRs of good quality? Is the interpretation of the CXRs of good quality? How are CXRs used for TB screening and diagnosis? • What is the availability of CAD or the willingness to introduce it for TB detection? • What is the trend in the number of people being tested for TB, by subpopulation? • What is the trend in the proportion of people testing positive for TB among those tested, by subpopulation?

Area to be assessed	Questions
Role of different providers	• When do people go to a provider, and what type of provider do they go to? Do people go to public or private providers? • What diagnosis and treatment services are offered by different providers (for example, in the public and private sectors; among formal or informal providers such as traditional healers; by health-care or other providers; by community or civil society organizations)? • Are services affordable?
TB awareness and health-seeking behaviour	• What barriers prevent access to diagnostic and treatment services for the targeted community? • What is the level of knowledge about TB disease and TB care in the targeted community? • What is the level of knowledge about TB risk, transmission, exposure and prevention in the targeted community? • What are the main reasons for delays in seeking health care in the targeted community? • What are the perceptions of members of the targeted groups regarding TB services?
Risk group size, distribution and special challenges	• What are the sizes and geographical distribution of the different TB risk groups? • Which specific barriers to accessing care affect the different groups? • What are the specific challenges to initiating and adhering to treatment in each group?
Previous and present experience in improving early TB detection	• What were the results of any previous effort to improve the patient-initiated pathway to ensure earlier detection of TB? • What were the outcomes and lessons learnt from previous systematic screening initiatives in different risk groups?
Stigmatization, discrimination, coverage, access, catastrophic costs	• What are the existing frameworks for protecting human rights, and to what extent are they enforced? • What sort of stigmatization or discrimination might people screened for TB and people diagnosed with TB experience, what are the possible consequences, and what can be done to mitigate those risks? • Which groups are at particular risk of stigmatization or discrimination and its consequences, and what can be done to mitigate those risks? • What is the legal status of migrants screened for TB and/or diagnosed with TB?

2.2.1 Existing screening and outreach activities

The cost of screening, especially as an outreach activity, can be high. The opportunity cost must be considered and compared with other means for improving early TB detection, such as improving the patient-initiated pathway to TB diagnosis (see 2.1.1). The efficiency of a screening programme can be increased by collaboration with other health and social programmes. Outreach activities such as health promotion, social support or screening the targeted population for other health conditions may already be in place and may serve as platforms for TB screening within a broader, more integrated approach.

Identification of appropriate entry points for screening is critical, and this requires mapping the healthcare and social-service providers for relevant groups, such as endocrinology departments caring for people with diabetes or nongovernmental organizations providing social support for

vulnerable groups. The private health care sector plays an important role in providing services to a large proportion of patients with TB, and, by involving them in TB screening, they may provide an entry point to TB care and treatment that would otherwise not be available.

Table 2.2 lists the programmes, services and stakeholders that could collaborate in screening activities.

Table 2.2 Services, programmes and stakeholders that could collaborate in systematic screening programmes for TB

Services	Programmes and stakeholders
Health services	• HIV programmes, clinics offering voluntary counselling and testing for HIV, clinics delivering ART, programmes to prevent mother-to-child transmission of HIV • Diabetes or endocrinology clinic screening initiatives, within the broader platform for preventing noncommunicable diseases • Maternal and child health and antenatal care programmes • Immunization clinics and campaigns and vaccination programmes • Smoking and alcohol cessation programmes • Malnutrition treatment programmes • Clinics and outreach programmes for people who use or inject drugs • Dialysis centres • Infection control providers and programmes, e.g. COVID-19 screening programmes • Community health services and outreach services such as community health workers and volunteers, or community health posts, including those run by community or civil society organizations or nongovernmental organizations • Other (community) screening programmes, such as for HIV, sexually transmitted infections, visceral leishmaniasis, or leprosy
Social services	• Outreach and community support or development programmes in remote rural areas or poor urban communities • Programmes and institutions that support homeless people or house insecure individuals and families or other vulnerable populations • Programmes that provide social support for sex workers • Programmes that provide social services for immigrants and refugees • Social protection programmes for youth, orphans or other vulnerable populations • Programmes that address food insecurity • Other partner agencies working with affected or vulnerable populations
Other government services	• Prison health services • Military • Occupational health services (especially for miners, health-care workers and workers in other high-risk occupations) • One Health initiatives
Civil society organizations	• Nongovernmental organizations and others that provide social support for vulnerable groups
Private health-care providers	• Private providers • Informal providers • Pharmacies

2.2.2 Societal context

The acceptability and feasibility of screening for those who will be screened and those who will provide screening should be assessed. Whether screening is accepted depends on how the programme is designed and implemented. Acceptability is therefore difficult to predict from evidence for other sites or for other subgroups. The acceptability of screening may be assessed in advance by organizing focus groups of target populations, preferably with a risk profile and an age and sex distribution that matches that of the populations at highest risk. Consulting and working with affected communities and local civil society organizations that support them throughout the development and implementation of TB screening interventions will help to ensure that they meet the needs and expectations of communities and that they are accepted.

Some people may accept screening more readily than others, depending on the perceived cost and inconvenience, as well as the adverse consequences of participating in screening or of a TB diagnosis (such as stigmatization or discrimination) as compared with the perceived benefits. TB screening is generally acceptable to most people (see more information in **the Web Annexes B** and **C** of the screening guidelines).

Certain risk groups are more difficult to reach than others. To some extent, the structure of health and social services determines which risk groups can be reached most easily. Generally, it is more feasible to conduct screening in well-defined risk groups that can be reached in a specific location, such as clinical risk groups within health facilities, people living in institutions (such as prisons) and people working in high-risk locations (such as mines). A screening intervention should not reduce health equity throughout the health services; therefore, any effort to screen hard-to-reach populations should be matched with appropriate resource mobilization.

2.2.3 Epidemiology of TB

The main purpose of an epidemiological assessment is to identify gaps in TB case detection and opportunities for addressing those gaps through screening. The assessment should account for potential benefits, risks and costs of systematic screening, particularly in relation to other possible interventions. The analysis should be disaggregated by age, sex and geographical location, and special attention should be paid to vulnerable groups that are at high risk for exposure and/or progression to TB disease or are likely to face barriers to accessing TB services, or both. Systematic TB screening is recommended in geographical areas with an estimated TB prevalence of 0.5% or more. Such areas may be informal peri-urban settlements and slum areas, where entire neighbourhoods could harbour a large burden of TB. Epidemiological techniques like geographical information systems could be used to plot "hotspots" for targeted action.

Potential data sources include:

- surveillance data (including laboratory data);
- location of all TB diagnosis and treatment facilities, including in the public and the private sector;
- data from TB prevalence and HIV incidence surveys;
- evaluations of previous or continuing activities to improve case-finding, including screening;
- national health and demographic statistics (including vital statistics and programmatic data); and
- the findings of research.

Box 1 lists WHO references on collecting data.

2.2.4 National TB programmes and the general health-care system

High-quality services for TB diagnosis, treatment and management and support services for patients should be in place before or scaled up at the same time as systematic screening for TB disease. The availability of high-quality TB services will minimize the risk of negative effects of screening, including the risk of a false-positive result and the accompanying anxiety, the risk of a false-negative diagnostic test and unnecessary treatment and delay in receiving an appropriate diagnosis (especially if the quality of TB diagnostic services is suboptimal) or worsening of TB treatment outcomes if treatment services are suboptimal and not properly tailored to the vulnerable groups that may be targeted through screening. Moreover, systematic screening in the context of poor-quality general services raises ethical concerns and may reduce the confidence of the population in the services provided. In addition, the capacity of specific health institutions and health staff to take on additional functions related to TB screening should be carefully assessed to avoid undermining the quality of TB and other services. Where people would benefit from systematic screening for TB but high-quality services and health system capacity for TB diagnosis, treatment, management and support are not in place, the gaps should be identified and should serve as an impetus for investment to improve TB services and capacity in those areas.

The critical conditions to be met or strengthened when implementing systematic screening are listed below.

• Quality-assured diagnostic services are available, including specimen transport from the community to the nearest health facility for onward transport or to the nearest laboratory. The services should include the capacity to deal with anticipated increased demand in diagnostic testing.
• Regular, reliable supplies of anti-TB medicines are available, and there is the capacity to treat the anticipated rise in cases of drug-susceptible as well as drug-resistant cases among adults and children.

- Regular, reliable supplies of TPT medicines are available, as those who are screened and do not have TB may be eligible for TPT.
- There should be sufficient integration between TB and HIV services to ensure that all people with possible TB are tested for HIV.
- The performance of TB diagnostic and treatment services must be considered acceptable by decision-makers, and processes should be in place to monitor and maintain quality.
- There are sufficient mechanisms to provide social support for diagnosed patients, and there is capacity to tailor treatment programmes to the specific needs of the population to be screened.
- If mWRDs are used to assess drug resistance, there is adequate capacity for further drug-susceptibility testing and for programmatic management of drug-resistant TB.
- A mechanism should be in place to ensure that access to tests (mWRDs, radiography, other) for diagnostic purposes is appropriately prioritized in relation to tests for screening.
- Adequate financial and human resources can be made available for screening without adversely affecting other key functions of the health-care system.

2.2.5 Health-care coverage and access to health services

Before screening is started, it is essential to ensure that people with diagnosed TB have access to affordable, high-quality TB care. This may not be the case for certain vulnerable groups, such as migrants, refugees and homeless people, who may lack identity papers or health insurance. Inclusion criteria for screening, coverage of health insurance (where applicable) and access to health services should be assessed. The system should ensure that people do not pay out of pocket for screening and do not suffer financial hardship as a result of screening.

2.2.6 Protection from stigmatization, discrimination and harm

Discrimination based on gender, sexuality, ethnicity or caste or against populations such as sex workers and people who use or inject drugs, can severely limit access to treatment, which may be reinforced by the lack of a framework for protecting human rights. **The existing frameworks for protecting human rights and the extent to which they are enforced must be reviewed before systematic screening is implemented.**

Possible stigmatization of and discrimination against people screened for TB and people with diagnosed TB can create risks for people undergoing screening. For example, people with diagnosed TB may lose their jobs temporarily or permanently or be expelled from school or forced to divorce. The legal protection of the rights to care and to maintain employment must be considered. The legal status of migrants should be carefully considered when designing a screening plan, with regard to both their access to health services and their risk of expatriation if they are diagnosed with TB. If lack of protection of rights or other social risks affect people and communities that are at high risk of TB, measures must be taken to mitigate those risks as part of any systematic screening programme, and informed consent must be sought. While informed consent for TB screening is ethically required in all cases, it is especially important for populations who may face repercussions from a TB diagnosis.

2.3 Setting goals and specific objectives

The **primary goal of TB screening** is to reach people who are not reached by the patient-initiated pathway and to detect TB disease early, thereby improving outcomes for individuals and reducing transmission and incidence at population level.

Secondary goals of TB screening are to:

- rule out TB disease in order to identify people who are eligible for TPT *(4, 5)*;
- identify people who are at particularly high risk of developing TB disease and thus may require repeated screening, such as people with an abnormal CXR (e.g. fibrotic lesion) that is compatible

with TB but who were not diagnosed with TB disease at the time of screening, people living with HIV, health-care workers and prisoners; and

- better characterize TB risk factors by combining screening for TB with screening for TB risk factors (such as HIV, diabetes mellitus, chronic obstructive pulmonary disease, undernutrition or smoking) to map individual or community-level risk factors and socioeconomic determinants that should be addressed to prevent the disease more effectively. This may be an additional objective in settings where information about the prevalence and distribution of TB risk factors is lacking.

Specific objectives can be based on those goals and according to a country's priorities and situation assessment. They may be based on specific targets or gaps identified in the situation assessment. The objectives should be specific, measurable, achievable, relevant and time-bound (SMART).

2.4 Identifying and prioritizing risk groups

Risk groups include groups at high risk of exposure to TB or of progression to TB disease or who have limited access to TB services. The following risk groups should always be systematically screened for TB:

- household and close contacts of people with TB,
- people living with HIV,
- people exposed to silica (mainly some miners) and
- people in prisons and penitentiary institutions.

For these four risk groups, the focus should be on *how* to screen and on the quality of screening, not *if* to screen. The assessment should include the size and distribution of the group, the TB burden in the group, past and current screening experience and any remaining considerations and challenges to be addressed to optimize screening.

Other risk groups (Table 2.3) should be prioritized for screening according to local epidemiology and the goals and objectives of screening. Systematic screening for TB disease in children is challenging, as both the screening and the diagnostic tools are less accurate in children than in adults; therefore, there is a higher risk that large number of diagnostic tests will be required, with large numbers of false-positive cases that are unnecessarily started on TB treatment. In principle, **only children who are close contacts of a person with TB and children living with HIV should be *systematically* screened for TB**. Other children, including malnourished and internally displaced children, are to be assessed according to diagnostic algorithms for paediatric TB as part of standard clinical management. As TB may occur in contacts exposed 2 years or more previously, contact investigation may have to be extended in time beyond freshly diagnosed index TB patients.

Table 2.3 Additional risk groups to be considered for TB screening

Potential site of screening	Risk group
Community	Populations of geographical areas with a high prevalence of TB (estimated to be 0.5% or higher)
	Subpopulations with limited access to health care and with structural risk factors for TB, including those living in poor urban communities, homeless communities, communities in remote or isolated areas, indigenous or tribal communities or other vulnerable or marginalized groups with limited access to health care
Outpatient and hospital inpatient departments and primary health-care centres	People previously treated for or exposed to TB
	People with an untreated fibrotic lesion shown on CXR
	People with chronic respiratory disease
	People presenting with pneumonia
	People with diabetes mellitus
	People who smoke
	Undernourished people or people with a body mass index ≤ 18
	People who have had a gastrectomy or jejuno-ileal bypass
	People with alcohol use disorder or drug use disorder
	People with chronic renal failure
	People on treatments that compromise their immune system
	Older people (60 years and older)
	Women who are pregnant (and up to 3 months postpartum)
	General outpatients and inpatients (in settings where the prevalence of both TB and of TB risk factors is high, it may be logistically more feasible to screen all health centre attendees)
	People in mental health clinics or institutions
Residential institutions	People living in shelters
	Other congregate institutions (such as the military)
	Immigrants from settings with a high prevalence of TB
Immigration and refugee services	People in refugee camps
	Internally displaced persons
	Migrant workers
Workplaces with high occupational exposure	People working in TB or veterinary medicine laboratories
	Prison guards and other workers in penitentiary facilities
	Other workplaces with a high prevalence of TB
	Health-care workers

Screening should be designed to reach the people at greatest risk of TB, including high-risk groups and communities with a high prevalence of TB; indiscriminate mass screening regardless of risk should be avoided. Risk groups should be prioritized for screening after assessment of the potential benefits and harm in relation to costs. Screening offers benefits for the individual (see 2.4.1) but may also be a risk and cause harm (see 2.4.2). The benefits of screening may also be seen at population level, as a reduction in prevalence and transmission (see 2.4.3). The balance between benefits and costs is further determined by the total potential yield (see 2.4.4), the NNS to detect a true case of TB (see 2.4.5), the feasibility of the initiative and the acceptability of screening to the group (see 2.2.2).

Prioritization may also depend on which stakeholder is responsible for screening. For example, a national TB programme under the auspices of a ministry of health may have other mandates, priorities and resources than health services that are managed by a ministry of justice, ministry of labour, an immigration authority, a nongovernmental organization, a private health-care provider or an employer.

A tool has been developed to assist in prioritizing risk groups for screening, which provides estimates of the potential yield of true- and false-positive TB results and the cost of screening, according to the risk group(s) targeted and the screening algorithm(s) used (see 3.3).

2.4.1 Potential benefits for the individual

The benefits include the health, social and economic benefits of early diagnosis and treatment. In principle, the potential benefits are greater for persons who are at highest risk of delayed or missed diagnosis because they meet barriers in obtaining health care (for example, people living in poor communities or remote areas) and especially *those at highest risk of unfavourable treatment outcomes when diagnosis is delayed* (for example, because their immune system is compromised, such as people living with HIV and children).

When someone is screened for TB, *other conditions that require treatment may be identified* (such as lung cancer or chronic obstructive pulmonary disease. Although the screening team may not be responsible for offering treatment for other conditions, links must be forged with other health programmes to address these cases.

2.4.2 Potential risks and harms for the individual

The screening procedure itself may be inconvenient and have direct or indirect costs for the individual, which may vary with both the risk group and the screening approach. *Harm associated with the results of screening include the unintended negative effects of a correct diagnosis (such as stigmatization or discrimination) and the harm caused by a false-positive or a false-negative screening test or diagnosis.* Particular attention should be paid to harm to groups such as migrants, who may risk deportation if TB is diagnosed or presumed, and employees who lack legal protection against dismissal if they are diagnosed with TB. These risks should be identified, actively addressed and mitigated by the screening programme (see 2.2.6). The risk that screening leads to costs for the person being tested should also be reduced as much as possible, by ensuring that screening and potential further diagnostic testing and TB treatment is covered by insurance or the public health system.

The risk of a false-positive screen or a false-positive diagnosis depends on the prevalence of TB in the screened group and on the screening and diagnostic algorithm used. The harm due to a false-positive screening test result includes stress, anxiety and further diagnostic workup. Harm due to false-positive diagnostic test result includes unnecessary treatment and events. Screening of groups with a low TB prevalence can result in a large proportion of false-positive results. *Therefore, as a general rule, screening of low-risk groups should be avoided.* The importance of choosing an appropriate screening and diagnostic algorithm to minimize the number of false-positive outcomes is further discussed in 2.5 and in Chapter 3.

Potential harm is often due to inappropriate implementation. Contextual considerations are therefore important to ensure that screening is well designed and implemented and that both the potential benefits and harm are considered throughout the screening and diagnostic pathway *(25)*.

2.4.3 Potential impact on prevalence and transmission

The potential of screening to affect transmission is theoretically highest in congregate settings, such as prisons or overcrowded urban slums, where there is a high rate of transmission and where there is also substantial in-migration and out-migration. In a study in Viet Nam, 3 years of community-wide screening decreased the prevalence of pulmonary TB *(26)*. In principle, the larger the total yield of screening, the larger the potential impact on TB transmission in the community. However, when the TB burden is concentrated in a few high-risk groups, the largest impact on overall transmission will be generated by screening carefully selected groups, even if the overall impact may be relatively small.

2.4.4 Potential total yield of true TB cases

Fig. 3 shows the potential yield of screening in a range of hypothetical risk groups with a range of relative risks of TB (assuming 100% coverage, acceptance of screening, sensitivity and specificity of screening). As illustrated in Fig. 2.2, the yield of TB screening in a specific risk group (in terms of the number of TB cases detected; y axis) depends on both the size of the risk group (i.e. the prevalence of the risk factor in the general population; x axis) and the relative risk of TB for that risk group (z axis). The yield is also affected by the acceptance of screening in the risk group (see 2.2.2) and the sensitivity of the approach (see Chapter 3).

Fig. 2.2 Potential yield of screening as a function of the prevalence of the risk factor in the population and the relative risk of TB in the risk group (baseline incidence, 1000 cases in a population of 1 000 000)

Prevalence of TB as a function of the prevalence of a risk factor and the increased risk for TB associated with the risk factor
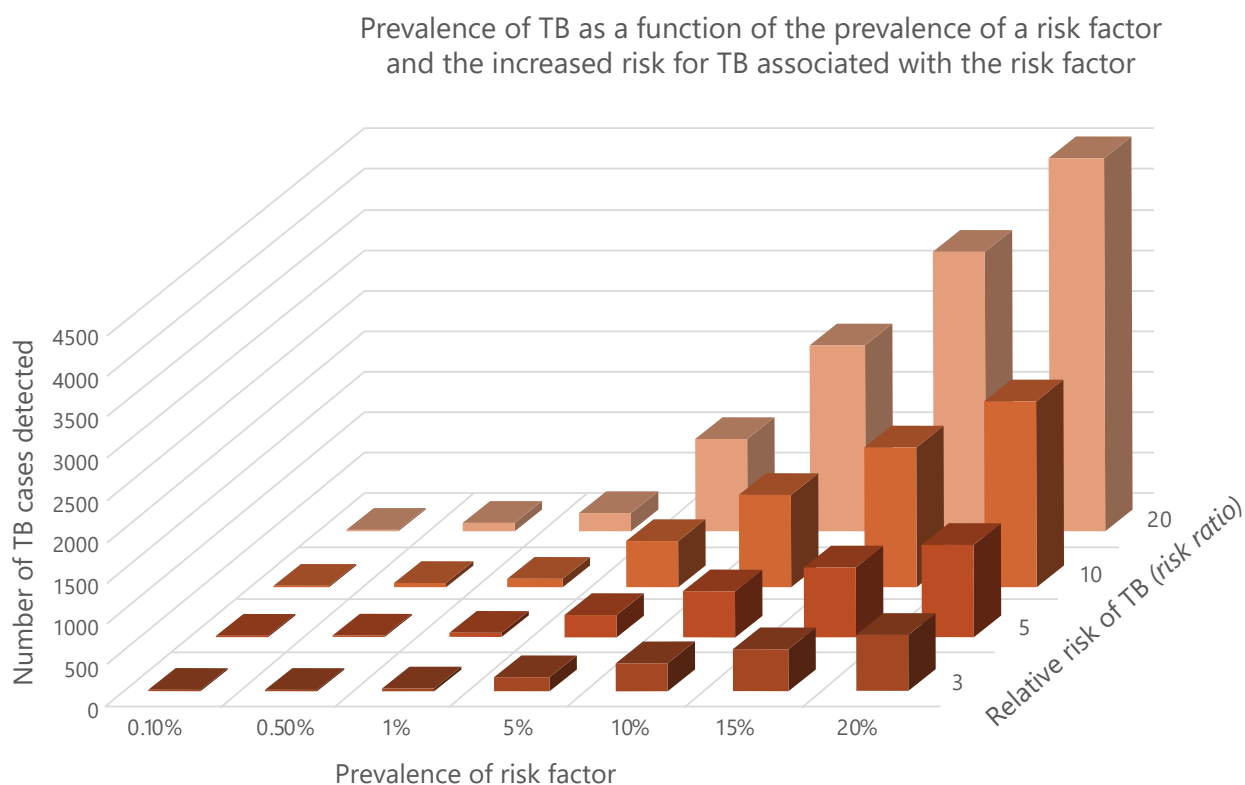
Often, the groups at highest risk of TB are also the smallest, and groups with only a moderately elevated risk may be very large. For example, the population prevalence of HIV, which is associated with an increase in risk of up to 20 times, is usually less than 1% (except in some countries in sub-Saharan Africa), and the total number of close contacts of someone with TB (who also have a dramatically elevated TB risk) is usually a very small fraction of the total population. Nevertheless, risk factors such as having diabetes or undernutrition or living in a crowded slum, which usually pose moderate relative risks for TB (in the range of 2–3) could affect more than 10% of the total population.

Therefore, screening the highest-risk groups often gives a low total yield in terms of the absolute number of TB cases detected. A high overall yield from screening may be possible only by achieving very high coverage of screening in large groups that have a moderate increase in the risk of TB; however, screening of these groups will generally require a higher NNS and might result in a higher cost per case detected than screening of groups at very high risk. The risk of a false-positive diagnosis is also higher in these groups. Therefore, there is often a difficult trade-off between the desire to achieve a large total yield and cost–effectiveness. Table 2.4 shows the NNS for TB disease with different screening approaches by burden setting, as estimated from the studies reviewed for the latest guidelines on TB screening. Similar estimates for other risk groups are given in **Web Annex C** of the screening guidelines.

Table 2.4 Number needed to screen (NNS) for TB disease in general populations and in community-based screening

Primary screening strategy	Weighted mean NNS (range) (number of studies)	
	Low or moderate TB incidence[a]	Medium or high TB incidence[a]
Symptoms	4424 (2417–6031) n=1	1058 (31–4085) (n=22)
CXR	3016 (n=1)	475 (186–605) (n=3)
Symptoms or CXR	1567 (23–2857) (n=3)	426 (125–763)[b] (n=18)
mWRD (Xpert MTB/RIF)	–	1002 (338–1010) (n=2)

[a] Low or moderate TB incidence (up to 100/100 000 population), medium or high TB incidence (> 100/100 000 population)

[b] 15 studies with 18 cohorts

2.4.5 Number needed to screen to detect a person with TB

The NNS to identify one person with confirmed TB in a specific risk group is the inverse of the prevalence of detectable TB in that risk group, assuming 100% sensitivity of the screening and diagnostic tools being used. If a given risk group has a very low prevalence of detectable TB, many people will have to be screened in order to find one case of TB, and this will require a high NNS; however, if a given risk group has a high prevalence of TB that can be detected by the screening and diagnostic tools being used, fewer people will have to be screened for each case detected, resulting in a lower NNS. Fig. 2.3 illustrates the general concept of the NNS in a risk group.

Fig. 2.3 The number needed to screen (NNS) in order to diagnose one person with TB in any given risk group is roughly the inverse of the prevalence of the disease in that risk group
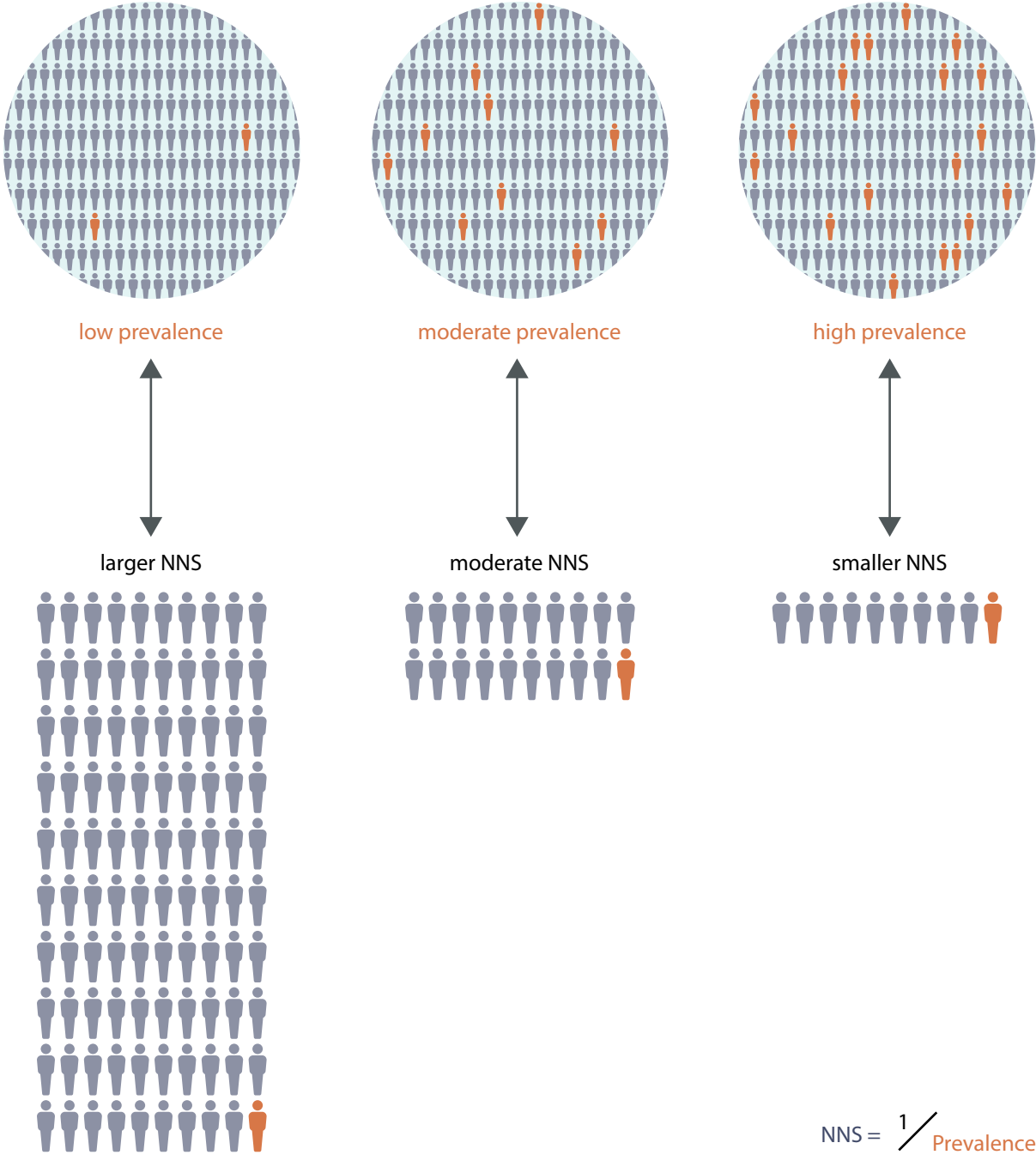
$$NNS = \frac{1}{Prevalence}$$

At a prevalence of 200/100 000 population, the NNS is at least 500 (in practice, it will be higher when the accuracy of the screening is suboptimal). The prevalence of undetected TB in the general population is often less than 200/100 000, even in countries with a high burden of TB; therefore, screening the general population is not usually cost–effective.

The NNS is a rough indicator of cost–effectiveness and of effort. Comparison of the NNS of risk groups provides a measure of relative cost–effectiveness if it can be assumed that the cost of screening and treatment and the benefits of early treatment are the same for all risk groups. This assumption is, however, rarely valid in practice. For example, an NNS of 50 for contact investigation might mean that

a person visits 12 different houses over 2 days. In contrast, in another situation, an NNS of 150 might be found by verbal screening in a slum area where that many people can be verbally screened in 4 h. Clearly, the effort and cost of screening are higher in the first example, even though the NNS is lower.

To guide prioritization of risk groups, the NNS should be estimated, even approximately, for each group being considered for screening, and it should be specific to the screening algorithms being used. This process is described in detail in Chapter 3.

2.4.6 Cost–effectiveness and cost–benefit analyses

Before implementation of a programme, its cost–effectiveness, or cost-benefit – in which costs and benefits are compared in monetary terms – can be modelled from estimates of the predicted number of additional true-positive TB patients detected, the reduction in morbidity, the reduction in the time that a person remains infectious and reductions in transmission, incidence and mortality. Cost will depend on the NNS, the algorithm used for screening and diagnosis, the method used to reach people for screening and the direct and indirect costs incurred by the screened individuals.

Models can be used to estimate how costs are related to the potential impact on TB transmission and epidemiology. Some empirical evidence on the impact of active community-wide screening on the prevalence of tuberculosis is beginning to emerge *(26)*. The ScreenTB tool can be used as a basic calculator of cost per case detected through screening (see 3.3).

2.5 Choosing algorithms for screening and diagnosis

Screening algorithms combine one or several screening tests and one or several diagnostic tests. The accuracy of different screening tests and potential algorithms for different populations and the considerations to be made when selecting algorithms, are discussed in detail in Chapter 3.

2.6 Planning, budgeting and implementing

2.6.1 Requirements for planning, human resources, commodities and budgeting

Consideration should be given to the extra resources, both human and financial, that will be necessary to prepare for, carry out and monitor screening activities and to accommodate the increased demand for testing of people with presumptive TB and the extra patients who may be identified by screening.

To determine which cadre(s) of staff should be involved in screening, current terms of reference, workload and the capacity of different staff should be reviewed, including supervisory staff and staff that provide commodities (e.g. equipment, software, consumables) for front-line screening workers. Programmatic experience in screening within health facilities and during outreach might provide lessons. There may be opportunities for task-sharing and task-shifting by involving communities (leaders, volunteers, ex-TB patients, civil society agencies, religious groups) and people in the target populations who may be trained in mobilization or even in some of the screening activities. The model of staffing and supervision may be highly context-specific (even within countries) and might vary between urban and rural settings and targeted risk groups.

New data collection systems, preferably electronic, may be required, and training will be necessary. Screening can be done by a variety of personnel, depending on the tests being used. For instance, symptom screening can be conducted by community health workers or volunteers. New diagnostic equipment or additional tests may be required for additional activities. In many cases, the logistics of gaining access to and testing the target population will also require significant resources. If one of

the goals of screening is to increase the number of people beginning treatment, it will be important to ensure that there is an adequate supply of medicines for treating TB disease and for prevention; it will also be important to ensure that patients receive adequate support during treatment.

2.6.2 Choosing a screening programme model

The choice of screening programme will have implications for the resources required and the potential reach and effectiveness of the programme. The decision on which model to use should be based on determining which approach will be most effective for reaching the targeted risk group with the resources available. The effort and resources required to reach the target population can be limited by screening in locations where people gather for other purposes, such as health centres or workplaces, although not all populations can be reached in this way.

Programmes that bring screening to places where people live or work can reach more vulnerable populations, particularly those for whom there are barriers to accessing care, but these programmes require more resources. Such programme models can include continuous community-based case finding or periodic event-based case-finding *(27)*. Examples include home visits, mobile outreach screening campaigns, community-based screening events with or without door-to-door mobilization, such as health fairs, and differentiated service delivery events, such as ART adherence meetings. Fig. 2.4 shows different forms of screening programme models.

Fig. 2.4 Screening programme models

Screening health centre attendees

Occupational screening or screening in prisons or places hosting refugees

Screening in the home

Mobile outreach screening campaign

Community-based screening events (health fairs)
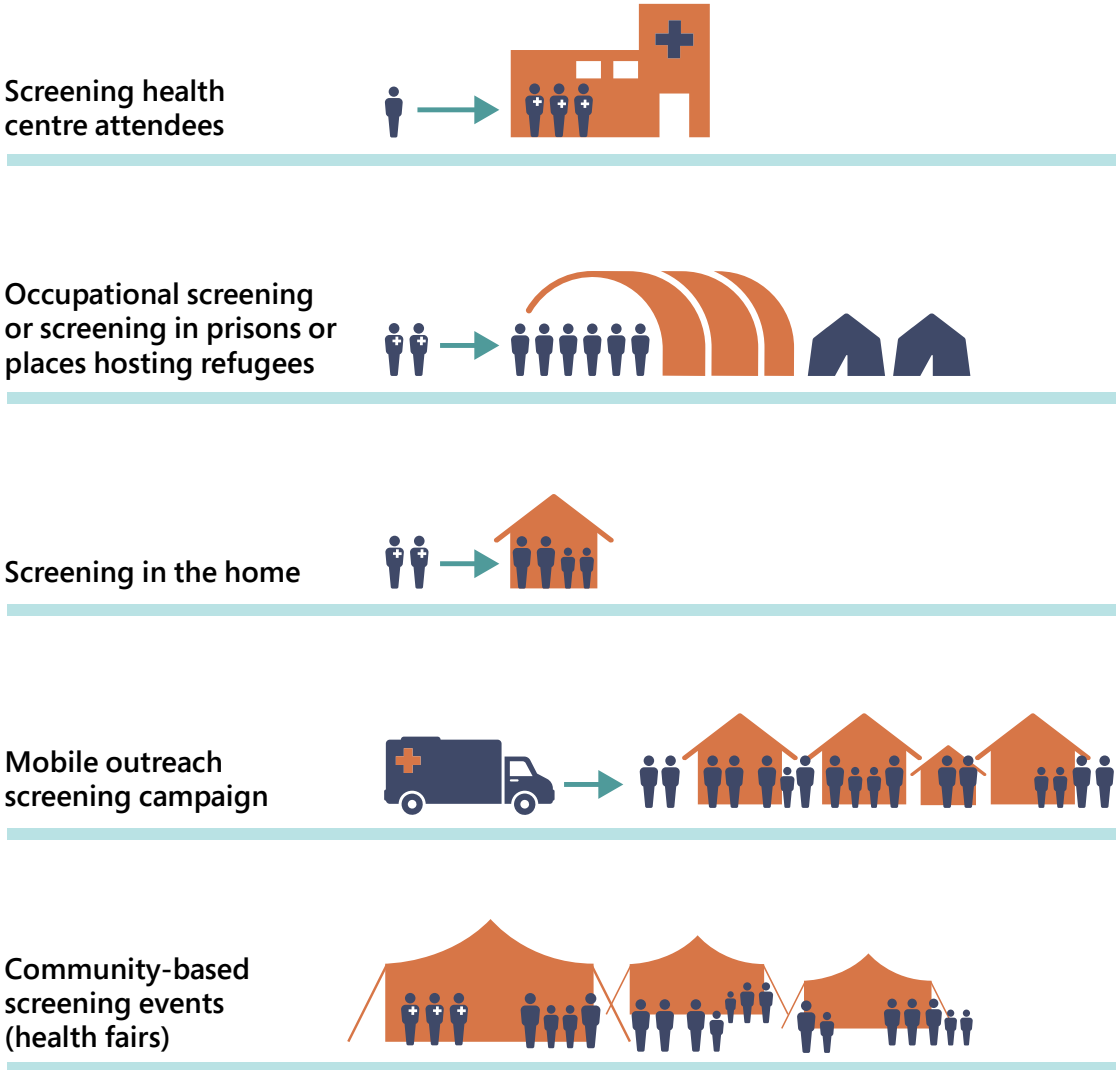
2.6.3 Ethical considerations

Ethical issues should be considered from the onset of planning and should involve end-users. The design of screening interventions for specific risk groups should involve risk groups and organizations that might work with these populations, especially groups that face specific access barriers or discrimination. This should help in arriving at user-friendly, acceptable, effective approaches and building demand for services and their use.

Those invited for screening should be provided with detailed information, including the benefits and risks, and verbal informed consent should be obtained. Refusal of screening should be respected and should not lead to discrimination of any sort. Informed consent requires effective communication with each person about the uncertainties associated with screening, such as false-positive results and risk of overtreatment. Appropriate mechanisms for obtaining informed consent should comply with international human rights standards and account for different languages, literacy and legal status. Risk and uncertainty must be communicated in a way that is culturally and linguistically appropriate, including to people whose first language is foreign to the local setting, to children and to people in prison. Confirmatory tests should be available to ensure an effective diagnostic pathway. The privacy and confidentiality of all information related to screening should be ensured.

The risks of discrimination and stigmatization should be carefully assessed before initiating screening. Depending on the risks identified for different target groups, measures may be adapted to minimize the consequences.

Further information on ethical considerations can be found in the WHO Ethics guidance for the implementation of the TB strategy *(28)*.

2.6.4 Involving stakeholders and partner organizations and establishing roles

Many different stakeholders and partners may be involved in screening for TB. It is important to involve communities and the target population when planning activities to ensure that the screening activities are feasible and acceptable. These stakeholders may also be able to plan mobilization and sensitization to inform the target population and motivate them to be screened. The programmes, services and stakeholders identified for collaboration in screening (see 2.2.1) should collaborate in the planning of screening.

Planning for the required financial and human resources should account for all possible stakeholders who may be involved. Similarly, planning should include stakeholders who may be involved in developing supply chains for tests and equipment, as well as referral chains to ensure that those who are found to have TB receive appropriate care. Good coordination among stakeholders is necessary to ensure complementarity and to avoid overlap or conflicting approaches.

2.6.5 Mobilizing resources

The goal of resource mobilization is to support the start-up, pilot-testing and maintenance of TB screening. In the initial phases, national TB programmes may not have allocated funding for new screening activities, and funds might have to be sought from alternative domestic and external sources *(14)*. Usually, once screening activities become routine and are shown to be effective, funding becomes available from mainstream domestic and external TB programme budgets. In the medium to long term, as the TB epidemic is better controlled, TB prevalence decreases and the NNS increases, and resource mobilization may have to shift to maintaining funding levels to find fewer and fewer people with TB. Once the TB epidemic reaches near-elimination, national TB programme budgets may be expected to be reduced while still maintain high-quality screening among at-risk groups.

2.6.6 Pilot-testing

It is critical to pilot-test a newly designed screening programme to ensure that it is operational. Pilot-testing is a valuable opportunity to refine new instruments (e.g. digital radiography, CAD and CRP), protocols, data systems and management structures. It also allows initial evaluation of the performance of the screening programme in terms of yield and costs to ensure that it has the intended effects on case detection, so that the design or the protocol can be modified if necessary.

2.7 Monitoring, evaluating and modifying the programme

A monitoring and evaluation plan should be part of any screening programme. General conditions and risk group-specific conditions for discontinuing screening should be established from the outset – for example, in relation to yield, contribution to overall case detection and improvement in treatment enrolment and outcomes, cost per case detected or some combination of these. Indicators should be chosen, and digital forms created for collecting data or adapted to the specific objectives and local conditions. To monitor yield and the NNS in each targeted risk group, an appropriate information system should be developed to generate data about the number of people diagnosed with TB in relation to the number of people approached, screened and tested. This information should be assessed periodically and the mix of approaches adjusted appropriately.

The general epidemiology of TB, the importance of different risk groups and the epidemiology of TB in each group may change over time, and prioritization for screening will have to be adapted accordingly. As some members of a particular risk population will eventually find their way to diagnosis through the patient-initiated pathway if they are not screened, it is of interest to evaluate the impact of screening a particular group on overall additional notifications in a larger basic management unit or group of basic management units. This will require analysis of notification trends, preferably with comparisons to control areas.

It is also important to measure whether screening is simply concentrating case-finding in a few facilities, which may be the case if a specific intervention is seen as beneficial and information about it spreads through the community. This can result in increased notification in one area and decreased notification in another.

As one objective of screening is early detection, it may be useful to measure delays in diagnosis and treatment, which will require special surveys. Treatment outcomes and mortality rates among detected TB patients can, however, be captured and evaluated more easily.

2.7.1 Developing a plan for monitoring and evaluation

Monitoring and evaluating systematic screening should be incorporated into the monitoring and evaluation programmes used in the national TB programme. The programme will determine the roles of the people involved in monitoring and its characteristics (e.g. frequency of monitoring, methods used, how the information collected will be fed back to adjust screening). Targets should be set for the expected caseload and yield, the NNS and costs in relation to benefits. Targets should be based on the estimated under-detection in different settings but should also account for programme realities. Screening interventions that are expected to require additional funding and resource mobilization should be appropriate to the need.

2.7.2 Proposed indicators

Approaches to screening will depend on each group, and intervention-specific indicators should be developed for each approach. In general, however, the data on indicators shown in Fig. 2.5 should

be collected for each targeted risk group, such as all close contacts of TB patients or all people living with HIV in care.

Fig. 2.5 Data to be collected for systematic screening programmes for TB

A	Number of people eligible for TB screening
B	Number of people screened for TB
C	Number of people with presumptive TB identified
D	Number of people evaluated for TB disease
E	Number of people diagnosed with TB
F	Number of people initiated on TB treatment
G	Number of people successfully completing TB treatment
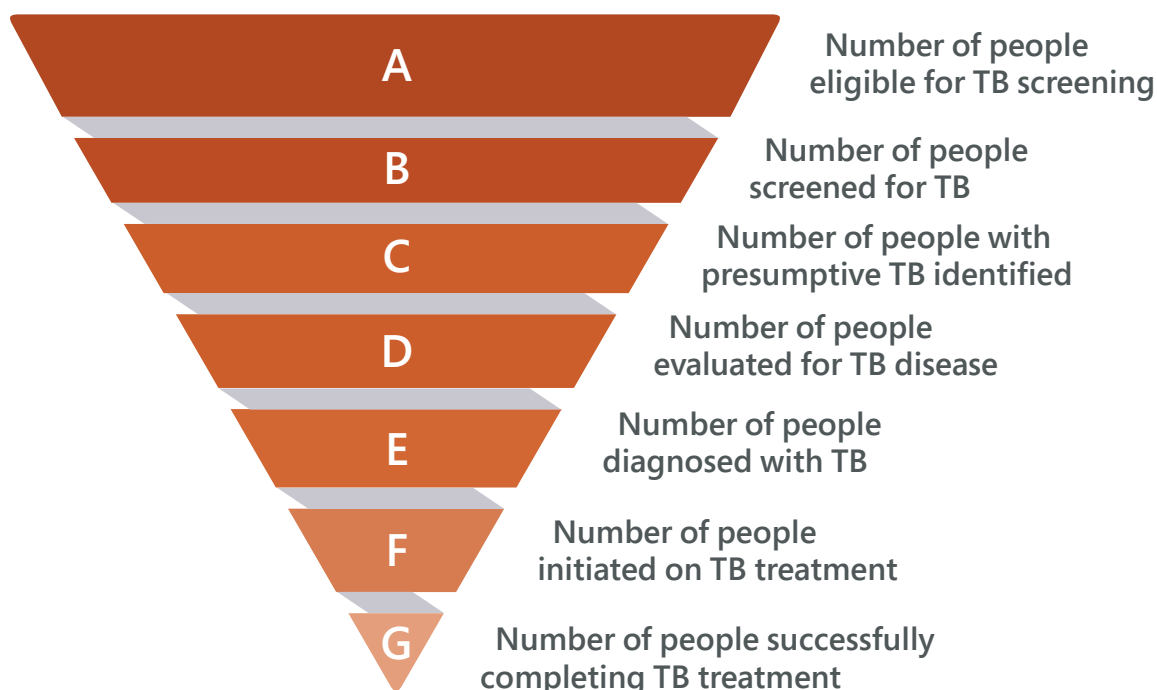
The data collected can be used to calculate the following basic indicators for each risk group:

- *acceptability:* the proportion of people screened for TB among those eligible (B/A);
- *screened positive:* the proportion of people presumed to have TB among those screened (C/B);
- *testing retention:* the proportion of people tested or evaluated for TB with a confirmatory diagnostic test among patients presumed to have TB (D/C);
- *NNS and number necessary to treat:* the proportion of people diagnosed with TB among those screened (E/B) and tested (E/D);
- *linkage to care:* the proportion initiating TB treatment among those diagnosed (F/E); and
- *treatment success:* the proportion of people who successfully complete TB treatment among those who initiated treatment (G/F).

It is critical to monitor the yield of bacteriologically confirmed and unconfirmed TB patients. A high proportion of unconfirmed TB patients referred from screening programmes might indicate over-diagnosis and should lead to closer evaluation of screening and diagnostic routines, considering the limitations of the diagnostic tests and the need for empirical or clinical diagnosis for certain populations, such as people living with HIV and children. In the case of late-stage detection of TB patients, the proportion of people with presumptive TB among those screened (C/B) and the proportion of those diagnosed among those screened (E/B) would be high. This finding would suggest a need for wider active TB case finding in a risk group. Low values for indicators such as the proportion of eligible people screened (B/A), the proportion of those tested who receive diagnostic confirmation (D/C) and the proportion of people diagnosed who start treatment (G/F) may reveal weaknesses in capacity at critical points in the TB care pathway, which should be addressed.

Data should be disaggregated by variables such as age group and sex. This requires collection of some personal data on each individual screened, which should be within the means of most programmes; the necessary software and hardware requirements are relatively modest.

Additional indicators of process (such as the number of people reached and screened per day, the time required for each step of screening and diagnosis and the number of people who require referral) should be collected during the pilot phase of a screening programme to ensure that it operates as designed and to inform logistics and capacity (e.g. number of tests needed). These data are easier to collect precisely than estimates of eligible populations and may indicate problems and can help to plan operational capacity (e.g. screening activities via mobile-vans over time). Once the programme has been established, however, these additional indicators should be discarded and the focus be shifted to streamlining the programme and scaling it up.

The uptake of screening in a risk group (that is, 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 usually possible to obtain the relevant information for screening conducted in health facilities, closed settings (such as prisons) and through contact investigations; however, it is often difficult to obtain such information in outreach screening programmes, such as when screening is done in the community, although the estimated population of a targeted community provides a rough estimate of the eligible population.

Whenever screening is done, a baseline TB notification rate should be set from historical data, if available (29). These data are usually available to most programmes from notification records. If they are stored in case-based format (or individual patient data), they will permit more extensive disaggregation by the risk groups of interest. Historical data may have to be adjusted for time trends. Screening may generate a substantial yield but with no real change in TB notifications. This could indicate badly located screening points, but may also be the product of better case finding in populations that were previously neglected and a decrease in false-positive cases that previously inflated notification numbers. If this is the case, the proportion of notified TB patients with bacteriologically confirmed disease would be expected to increase over time even if the numbers remain stable.

2.7.3 Routines for recording and reporting

To obtain the information required for the indicators described above, a recording and reporting system for TB screening should include the following elements.

- A log of the number of people screened in each risk group. A special database with information for each person screened may be used to obtain more refined data on subcategories of people within a risk group. Collection of these data is resource-intensive, but it may be relevant when a screening programme is started as part of an operational research project. Electronic data collection facilitates the process and permits easy transfer of information. It may be feasible to collect this type of data continually for certain risk groups, such as people seeking care in medical facilities.
- A database of all individuals presumed to have TB who underwent further diagnostic evaluation. If a database is used to collect individual-level information for all people who are screened, this information can be included by adding a variable.
- Additional variables in the digital laboratory register to indicate whether the tested patient was identified through screening, which screening methods were used to identify the patient and to which risk group the patient belongs.
- Additional variables in the treatment register to indicate whether the patient was identified through screening and to which risk group the patient belongs.
- Other forms or databases may be necessary, depending on the approach used and the existing databases or registers. For example, if contact investigation is implemented, there should be specific data-capture tools to track this activity properly. Such tools can be used on smartphones or other mobile devices at the site of investigation.

2.7.4 Programmatic evaluations

Depending on the objectives of the screening programme and the results of monitoring the indicators discussed above, a special assessment may be necessary to determine, for example, the reasons for low uptake of screening, an unexpectedly low proportion of people presumed to have TB identified by screening, a low proportion of those presumed to have TB who were further evaluated for TB, a higher-than-expected NNS or a high proportion of cases that are not bacteriologically confirmed. Programmes are unlikely to be able to replicate the performance observed in trials and other studies conducted under controlled conditions, in which study subjects may even have been pre-screened.

Additional quantitative and qualitative analyses may be necessary to determine whether there are barriers to screening, to identify opportunities to improve the screening approach and whether there have been any social or financial consequences of screening (e.g. costs of CXR and travel shifted to patients). It is also prudent to evaluate the effects of screening on overall operations at health clinics, especially the impact of an increased burden of laboratory testing.

2.7.5 Monitoring time trends for re-screening and re-prioritization

A successful screening programme may lead to a diminishing yield over time, at least if the risk group is a fixed population. Over time, changes in the background burden of TB and changes in the profile of TB patients in the community (for example, a trend towards fewer patients with symptomatic TB, fewer cases of sputum smear-positive TB and decreasing TB mortality) 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 harm. Successful programmes that facilitate access to care may also lead to diagnosis of more people with TB through screening than via the patient-initiated pathway. Trends in all these indicators should be monitored, and the priority of risk groups, the choice of screening approach and the screening interval should be reassessed regularly. Criteria for stopping screening should be established before a screening initiative is implemented.

Chapter 3. Screening tools and algorithms

The algorithms for screening in the general population and in high-risk groups (not including people living with HIV) are presented in Fig. A1.1 - A.1.10 in Annex 1.

3.1 Screening tools

Screening tests should distinguish between people with a high likelihood of having TB disease from those who are unlikely to have TB. A screening test is not intended to be diagnostic but rather to identify the subgroup of people with the highest likelihood of disease. Screening must always be conducted with a screening and diagnostic algorithm; thus, if people screen positive, they are referred to the next step in the algorithm, which could be a subsequent screening tool or diagnostic evaluation with bacteriological testing to confirm or rule out TB disease.

In general, high sensitivity is important for screening tests, as the goal is to detect TB disease early, although, if specificity is low at the screening stage, a significant proportion of people being screened who do not have TB disease will be referred for additional screening or diagnostic evaluation, with additional costs. Thus, the objectives of the screening programme must be considered when selecting a screening and diagnostic algorithm, including maximizing case detection (and thus prioritizing sensitivity) or maximizing efficiency (and thus prioritizing specificity). See 3.2 for further discussion of screening and diagnostic algorithms.

The tools for initial screening of the general population and high-risk groups (not including people living with HIV) include symptom screening for clinical features associated with pulmonary TB (including cough, haemoptysis, weight loss, fever or night sweats) and screening with CXR or an mWRD. Table 3.1 presents the accuracy of these tools observed in studies of populations without HIV, from a systematic review presented in 2020 as part of the update of the TB screening guidelines, with bacteriologically confirmed TB as the reference standard *(30)* (see Annex 2 for more details). It should be noted that most data on the accuracy of screening tools derives from TB prevalence surveys, in which screening for TB is conducted in the general population in high-burden settings. Thus, their performance in other populations and settings may differ; particularly in clinical settings, generally with a sicker population, the tools may not perform as well.

Screening tools and algorithms for people living with HIV are discussed in Chapter 5, and those for children in whom TB screening is recommended in Chapter 6.

Table 3.1 Diagnostic accuracy of symptoms, CXR and mWRDs for screening for TB disease among HIV-negative individuals *

Screening test	Sensitivity (%)	Specificity (%)
Prolonged cough (≥ 2 weeks)	42	94
Any cough	51	88
Any TB symptom (cough, haemoptysis, fever, night sweats, weight loss)	71	64
CXR (any abnormality)	94	89
CXR (abnormality suggestive of TB)	85	96
MWRDs (adults at high risk)	69	99

* For people living with HIV, see Chapter 5. For more detail on the systematic review and data presented here, see **Web Annex B** of the guidelines)

3.1.1 Symptom screening

Symptom screening is feasible, easy to implement and low-cost. It is also highly acceptable, because it is non-invasive and is a usual part of the clinical assessment of people under care. Symptom screening, particularly for cough, has the added advantage that it usually detects people with TB who are most likely to transmit the disease. Symptom screening has, however, low and variable sensitivity especially for detecting TB early. The positivity rate for screening with symptoms differs from setting to setting, depending on the prevalence of other, non-TB conditions and the quality of screening. In particular, the occurrence of cough may vary with the frequency of other lung conditions, smoking and levels of air pollution. Symptom screening is also subjective and depends on the interpretation of the provider conducting the screen and the person being screened. For example, definitions of cough may differ (e.g. any cough, current cough, "long-standing" or prolonged cough, cough lasting ≥ 2 weeks).

Cough
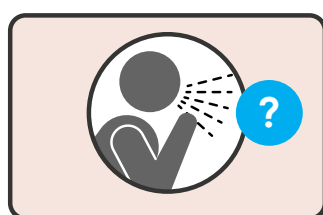
The review performed for the 2021 guidelines update estimates the sensitivity of screening for *any* cough for detection of TB disease is 51%, which implies that, in many settings, about half of people with TB do not cough; therefore, screening for this clinical feature alone would detect only about half of people with TB disease. In contrast, it has a fairly high specificity (88%), suggesting that, in many settings included in the reviews, most people without TB disease did not cough. This is likely to depend on the prevalence of non-TB diseases and other conditions in the population being screened.

Screening for prolonged cough – defined as lasting ≥ 2 weeks – is estimated to be even less sensitive (42%) but highly specific (94%) (Table 3.1). It can be a helpful screening tool for programmes that wish to be efficient and reduce the number of people without TB referred unnecessarily for diagnostic testing, but it will not detect the majority of people with prevalent TB, which is unacceptable for most screening interventions.

Any TB symptom
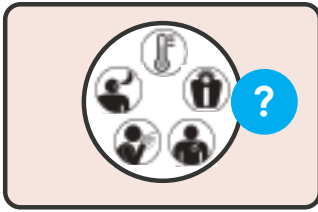
An alternative is to screen for *any symptom* that commonly occurs in TB, including cough of any duration, sputum, haemoptysis, fever, night sweats and weight loss. In studies reviewed for the latest revision of the screening guidelines, the estimated sensitivity of screening for any TB symptom is 71% – higher than for cough alone but with lower estimated specificity (64%) (Table 3.1). The positivity rate can be quite high in certain populations, as the same symptoms may be caused by other conditions. In contrast to cough alone, the lower specificity of *any symptom* would imply that more people without TB would be sent for diagnostic evaluation and more tests would have to be done to confirm one TB case.

3.1.2 CXR screening
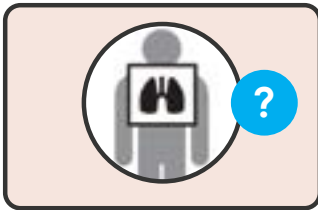
CXR is a rapid imaging technique for identifying lung abnormalities. It is used in clinical evaluation for conditions of the thoracic cavity, including the airways, ribs, lungs, heart and diaphragm. CXR is a good screening tool for pulmonary TB because of its high estimated accuracy for detecting TB disease, especially before the onset of symptoms. From the perspective of the person being screened, CXR is valuable because it can also detect medical conditions other than TB, including other pulmonary and thoracic conditions.

The sensitivity of CXR for the threshold of any abnormality is estimated to be 94%, and its specificity is estimated to be 89% (Table 3.1). For a threshold of an abnormality suggestive of TB, the estimated sensitivity is lower (85%) but the specificity is higher (96%). Thus, either "any abnormality" or "abnormality suggestive of TB" detected by CXR can be used, depending on the context, radiological expertise, the availability of other resources, including diagnostic testing, and a preference for higher sensitivity or for higher specificity of the screening algorithm.

Although CXR is the preferred screening tool from the viewpoint of test accuracy, it can be expensive and logistically challenging to use, especially during active case finding, when screening is done as an outreach activity outside the health services. It is important to keep in mind that people may have to travel away from their usual facility for a CXR and to pay for it out of pocket. CXR is a good choice in most screening scenarios, particularly those based in a healthcare setting or where mobile X-ray technology can be used, but it is not feasible in some scenarios.

Implementation considerations for CXR as a screening tool

Equipment and resources

- Implementation of CXR requires equipment. Consider the resources required (budget, health workforce, personal protective equipment, imaging equipment).
- Ensure the functioning of radiography equipment and establish a mechanism for regular maintenance for optimal functioning of the equipment.
- Portable chest radiography equipment can increase access to TB screening for eligible populations outside the health centre *(31)*.

Digital technology

- Favour digital radiography equipment to increase access to CXR screening, as the throughput can be higher and the time for processing shorter and it will reduce the environmental impact of used films and printing. Newer radiography technology emits lower doses of radiation and may be much more portable *(31)*.

- Comparison of multiple CXR images for the same individual over time can aid diagnosis. If appropriate technology and processes are available, archiving and retrieval of digital images may be more convenient than for physical films.
- Consider the transfer of images for remote reporting (teleradiology) and CAD of TB on digital radiographs as necessary to broaden implementation of CXR for screening (e.g. in settings where radiologists are not available for on-site reporting, or their availability is scarce).

Skilled CXR reading and interpretation and appropriate follow-up

- Provide appropriate training of radiologists and technologists to maximize the accuracy of reading of images by accepted local protocols.
- Develop standard operating procedures for use of CXR and for appropriate follow-up, including for abnormalities associated with diseases other than TB.
- Develop job aids to assist providers in informing the test recipient and to respond to frequently asked questions about the utility and procedure of CXR.
- Strengthen mechanisms for supportive supervision and monitoring of accurate implementation.
- Develop tools for systematic recording and reporting of CXR findings and linkage to confirmatory diagnostic testing.

Access

- Consider providing funding for people to travel for CXR screening or using mobile screening to improve access to CXR screening (32).
- Patients should not have to make out-of-pocket payments for CXRs performed as part of TB screening. Consider removing patient costs for CXR entirely or using vouchers to further reduce barriers to accessing this critical tool for TB control.

Safety of radiation

- Radiography involves exposure to some ionizing radiation, which may increase the long-term risk for cancer. Recent innovations in radiography have substantially reduced exposure to radiation. CXR is largely considered safe at 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). Manufacturers provide information on doses in technical specifications of the machine being used.
- When performing CXR, minimize the radiation dose while maintaining diagnostic image quality (e.g. low-dose scanning protocols); use digital imaging rather than film-screen equipment.
- Lead shields can be used to reduce exposure to ionizing radiation of other parts of the body. While lead shields are preferred, they are not a requirement for conducting CXR as part of TB screening, and exposure to ionizing radiation can be minimized in other ways.
- Pregnant women are especially vulnerable to ionizing radiation from radiography. CXR does not pose any significant risk for pregnant women or the fetus, provided that good practices are observed, with the primary beam targeted away from the pelvis. Children have a longer life expectancy and therefore more time to develop radiation-induced health effects within their lifetime.
- Inform the person who is screened about the safety provisions for radiation protection.

For more resources on use of CXR for TB screening

- WHO Chest radiography in TB detection: https://apps.who.int/iris/handle/10665/252424 (33)
- TB prevalence surveys: a handbook: https://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/resources_documents/thelimebook/en/ (35)

3.1.3 CAD technologies for screening and triage
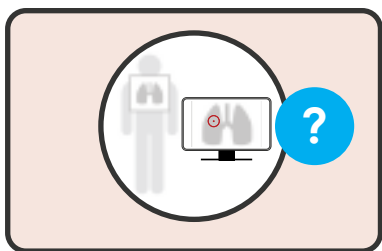
CAD software packages have been introduced to automate interpretation of digital CXR images for pulmonary TB disease-related abnormalities. CAD products analyse digital CXR images and generate a continuous numerical score that corresponds to an increasing likelihood of TB as the score increases. It should be noted that the scores are usually between 0 and 1 or 1 and 100 but are not percentages, and they should not be interpreted as directly reflecting the risk of TB.

CAD can resolve numerous difficulties in human interpretation of CXR. These include the lack or scarcity of trained health personnel to interpret radiographic images for TB screening and substantial intra- and inter-reader variation in correct detection of abnormalities associated with TB. CAD could thus allow significant scale-up of TB screening and increase access to CXR screening. The score given by CAD when reading a chest film relates solely to the likelihood of TB; in contrast a human reader can identify between multiple pathologies simultaneously when interpreting a CXR.

The performance of three CAD software programmes – all of which were on the market by January 2020 and had received a CE mark[1] – were evaluated for the update of the TB screening guidelines. The performance of the class of software was assessed in multiple external evaluations against a library of digital radiographs and associated clinical data, independently of validation studies conducted by the product manufacturers themselves. These evaluations indicated that CAD software programmes are accurate and their performance compares well with human interpretation of CXR for detection of pulmonary TB disease.

The recommendation that CAD software programmes be used in place of human readers for interpretation of digital CXR in screening and triage for TB disease applies to software brands that are found by external evaluation to have a performance that is not inferior to that of the products reviewed by the Guidelines Development Group in 2020. It should also be noted that the recommendation is specific to adults and adolescents aged 15 years and older and applies only to interpretation of antero-posterior or postero-anterior views of digital plain CXR for pulmonary TB.

If a programme includes use of CAD for automated interpretation of CXRs as part of screening or triage, it is essential that calibration be conducted to determine the appropriate threshold score for any given setting and programme according to the spectrum of radiographic findings in members of the target population with and without TB disease. Section 4 describes a toolkit for implementation and calibration of CAD technology for screening and triage, including a protocol and guidance for conducting a CAD calibration study and a web-based tool to facilitate analysis of data, calculation of receiver operator characteristics (ROC) curves, the accuracy of different thresholds and interpretation of findings.

Considerations for implementing CAD technology for screening or triage

- Implementation of CAD will require thorough consideration of the infrastructure requirements, including digital radiography equipment, electricity, computer availability, Internet access, and the fees for use and the cost of the licence for the CAD products. The resources required and cost–effectiveness will depend on the setting, including the current availability and salaries of human readers.
- Although CAD technologies can reduce the burden on human readers, maintenance of human reader capacity for TB screening radiography is essential, for example for children aged < 15 years for whom CAD is not currently recommended or for interpretation of abnormal images when a disease other than TB is suspected.

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[1]   CAD4TB v6, from Delft Imaging; Lunit Insight CXR, from Lunit Insight; and qXR v2, from Qure.ai

- The abnormality score thresholds recommended by the manufacturer, when available, do not perform uniformly in different contexts. Users may also differ in their preferences for higher sensitivity or specificity, depending on their circumstances or objectives of screening (e.g. desire to maximize case detection rather than reduce false-positive screening test results). CAD software should thus be calibrated for each setting or population in which it will be used for screening.
- After initial calibration, monitoring and analysis of CAD performance should continue. This may include assessment of consistency with human reader interpretation, proportion of images read as abnormal and requiring further investigation and the proportion of patients with images read as abnormal who have bacteriologically confirmed TB.

3.1.4 Molecular WHO-recommended rapid diagnostics for screening
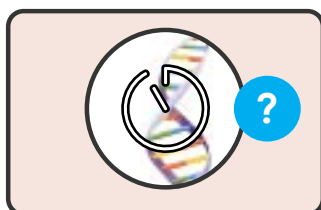
mWRD are rapid, sensitive molecular tests for detecting TB. In the 2021 update of the screening guidelines, mWRDs are also recommended for screening for TB disease.[2] For the purposes of this handbook, the mWRDs that can be used for screening are Xpert® MTB/RIF and Xpert MTB/RIF Ultra (Cepheid, USA), loop-mediated isothermal amplification (LAMP, Eiken Chemical, Japan) and Truenat™ MTB and MTB Plus tests (Molbio Diagnostics, India).

Several considerations apply to use of mWRDs as a screening tool. mWRDs perform differently when used for screening than when used for diagnosis. The sensitivity of mWRDs for screening high-risk populations (non-HIV-infected) is estimated to be 69% and the specificity 99% (see WHO consolidated guidelines on TB diagnosis for estimates of mWRDs used for diagnosis (12)). Because of the differences in accuracy and the lower TB prevalence typically found in a population undergoing screening rather than diagnostic evaluation, the positive and negative predictive values of mWRD also differ. For example, despite a quite high estimated specificity of 99%, over one half of positive screening tests will be false-positive when mWRDs are used to screen a population with a 1% prevalence of TB. Thus, the different implications for clinical interpretation and programmatic use of mWRDS for screening and for diagnosis must be understood.

People who screen positive for TB with an mWRD should always be followed up with a thorough clinical evaluation, including symptom screening and further tests, such as CXR or repeat mWRDs on additional sputum samples, to establish a definitive diagnosis of TB. For patients with a history of TB in the previous 5 years, a positive result may be due to the detection of DNA persisting from the earlier TB episode. Therefore, a positive test in such cases should be investigated with phenotypic methods to exclude a false-positive result (12). A negative mWRD for a single sputum sample does not exclude TB, as patients with TB may test mWRD-negative because they cannot produce sputum or an adequate quantity of sputum, have a very low bacillary burden in the sample or have extrapulmonary disease.

Considerations for using mWRDs for screening

With use of mWRDS for screening, test results are in theory available within a few hours; however, because of laboratory batching and burden, they are usually available within 1-2 days. Inefficient reporting (on paper forms) and transport of samples introduce additional delays. A delay of more than a few hours could adversely impact the retention of patients in the screening pathway and should be considered before use of mWRDs for screening.

Implementation of mWRD as a screening tool will require significant resources, including increased capacity and expansion of diagnostic and sample transport networks. There has been limited experience in widescale use of mWRDs for screening under programmatic conditions. Priority should be given to ensuring universal access to mWRDs as a diagnostic test for TB and drug-resistant TB before extending its use to screening. If use of mWRDs for screening requires decentralization of the

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[2] In the reviews conducted to update the TB screening guidelines, the only data for evaluation of mWRDs for screening pertained to Xpert MTB/RIF

technology, there may be significant implications in terms of the purchase of machines, cartridges and other consumables, an uninterrupted supply of electric power and maintenance. If mWRD does not reach most health centres, samples will have to be transferred; in this situation, shifting from mWRDs for diagnosis to screening would substantially increase the workload for sample transport. Diagnostic connectivity platforms that automate the transmission, storage and retrieval of test results will improve the utility of mWRDs for decision-making.

3.1.5 Tests of TB infection

The tuberculin skin test, like the Mantoux test and interferon-g release assays **should not be used in screening of TB disease** *(13, 34)*. These tests cannot distinguish TB infection from TB disease and cannot predict who will progress to TB disease. The role of these tests in decision-making for TPT is discussed elsewhere *(4)*.

3.2 Algorithms for screening

3.2.1 Basic features of TB screening and diagnostic algorithms

An algorithm for systematic TB screening should combine one or several screening tests and a separate diagnostic evaluation for TB disease, as recommended by WHO *(12)*. A negative diagnostic test result may be followed up by further clinical evaluation if clinical suspicion of TB is still high. This could include re-testing with the same or another diagnostic method and/or close follow-up of clinical symptoms with or without chest imaging. A positive diagnostic test result might have to be re-confirmed with further testing and clinical evaluation if the positive predictive value of the test result is low.

Different configurations of screening tests have different implications for the sensitivity, specificity and costs of the algorithm. Single screening algorithms comprise one screening test; people who screen positive require diagnostic evaluation for TB. Examples of single screening algorithms are screening all clinic attendees for any cough or a mobile van screening campaign in which everyone in the community is screened by CXR.

Parallel screening algorithms comprise an initial screening step with two screening tests (e.g. screening for symptoms and CXR simultaneously). A positive or abnormal result in either (or both) screening test is an indication for referral onwards towards a diagnostic evaluation. Parallel screening algorithms are more sensitive, as they capture a broader population of people to be evaluated for TB with a diagnostic test. This approach is ideal if the goals of screening are to maximize case detection or to measure the prevalence of TB in the population being screened. (A parallel screening approach is used in prevalence surveys, in which screening for symptoms is combined with CXR) *(15)*. Parallel screening algorithms are, however, typically less specific and therefore have higher cost implications because of the larger number of people referred for diagnostic evaluation and a higher risk of false-positive screening results.

Serial screening algorithms comprise two screening tests conducted successively, with referral for a second screening test according to the results of the first test. A **sequential positive serial screening algorithm** is one in which a positive or abnormal result on the first test requires referral to a second screening test, followed by diagnostic evaluation of those who screen positive on both screening tests. An example of this approach is screening for any TB symptom, followed by screening by CXR for those with symptoms. This screening approach increases the pre-test probability of TB in the population being screened before referral for diagnostic evaluation, thereby increasing the efficiency of the screening programme and reducing the risk of false-positive diagnoses. This approach is, however, less sensitive.

A **sequential negative serial screening algorithm** is one in which a positive or abnormal result on the first screening test results in referral to diagnostic evaluation, while a negative or normal result on the first screening test results in referral for a second screening test and then subsequent referral for diagnostic evaluation for those who screen positive or abnormal in the second screening test. A sequential negative serial screening algorithm has the same sensitivity and specificity as a parallel screening algorithm with the same tests (the same number of people will be referred for diagnostic evaluation) but reduces the cost, because the second screening test is limited to individuals who test negative in the first. For example, an algorithm that begins with screening for symptoms and then CXR for those who do not present with symptoms will result in fewer CXRs being conducted with the same case detection as CXR plus symptom screening for all. This may, however, introduce delays, given that the tests are not run simultaneously. The specificity of a negative sequential screening approach will be lower than that of a positive sequential algorithm because of the larger number of people referred for diagnostic evaluation and the higher risk of false-positive screening results.

3.2.2 Screening and diagnostic algorithm options

This operational handbook includes 10 screening algorithm options for screening the general population and groups at higher risk (not including people living with HIV or children), consisting of a combination of one or two screening tests and a diagnostic evaluation (Annex 1). Algorithms for screening people living with HIV are discussed in Chapter 5 and algorithms for screening children in Chapter 6.

The algorithms differ in sensitivity and specificity and, therefore, have different yields of detection of prevalent TB, predictive values and associated costs. The performance of the algorithms also depends on the prevalence of TB in the population being screened. Tables A2.1-A2.3 in Annex 2 contain modelled estimates of the performance of the algorithms described below, including the results of true- and false-positive diagnoses for the entire algorithm, consisting of the screening test(s) followed by diagnostic evaluation with an mWRD.

For all algorithms, the risk of a false-positive diagnosis increases as the prevalence declines; therefore, special attention must be paid to diagnostic accuracy of the screening algorithm, particularly when the prevalence of TB in the screened population is < 1%. At a TB prevalence of 0.5% in the screened population, all the algorithms have a positive predictive value of < 75% (i.e. 25% give a false-positive diagnosis). Efforts must therefore be made to ensure high-quality diagnostic procedures and clinical assessment, especially when the TB prevalence in the screened population is moderate to low.

In each given screening situation, it is critical to consider the proportions of false-positive and false-negative results that are unacceptable. Ethical considerations such as unnecessary anxiety and inappropriate TB treatment due to a false-positive diagnosis and the adverse consequences of missing or delaying a TB diagnosis should guide the acceptable sensitivity and specificity of the algorithm. Considerations will depend on risk groups. For groups of individuals who are at high risk of dying or of other severe negative effects of a missed or delayed diagnosis and treatment, however, the algorithm used should have very high sensitivity, even at the expense of lower specificity.

The algorithms have different costs and requirements in terms of human resources and health systems. The choice of algorithm depends on the risk group, the prevalence of TB, the availability of resources and the feasibility of implementation.

Algorithms that begin with screening for cough

Fig. A.1.1 – Screening with cough (page 60)

Fig. A.1.2 – Parallel screening with cough and CXR (page 61)

Fig. A.1.3 – Sequential positive serial screening with cough and CXR (page 62)

Fig. A.1.4 – Sequential negative serial screening with cough and CXR (page 63)

Algorithms that begin with screening for any symptom compatible with TB

Fig. A.1.5 – Screening with any TB symptom (page 64)

Fig. A.1.6 – Parallel screening with any TB symptom and CXR (page 65)

Fig. A.1.7 – Sequential positive serial screening with any TB symptom and CXR (page 66)

Fig. A.1.8 – Sequential negative serial screening with any TB symptom and CXR (page 67)

Algorithm that begins with screening with CXR (page 68)

In addition to the parallel and sequential algorithms that include CXR above, the algorithm in Fig A.1.9 presents an option to screen only with CXR, followed by referral for diagnostic evaluation for people with an abnormal CXR.

Algorithm that begins with screening with mWRD (page 69)

The algorithm in Fig A.1.10 presents a screening approach that begins with an mWRD, followed by a thorough clinical evaluation (including physician assessment and further tests such as CXR or repeat mWRDs on additional sputum samples) for those with a positive test result.

3.2.3 Choosing an algorithm for a screening programme

The choice of screening and diagnostic algorithms should be based on:

- the specific objectives of screening;
- the accuracy and yield of the screening and diagnostic tests (see table of modelled performance in Annex 2);
- the profile of the prioritized risk groups;
- the TB prevalence in the risk groups;
- the costs, availability and feasibility of different tests; and
- the ability to engage the population to be screened.

The specific objectives of screening partly determine the relative importance of the sensitivity of the algorithm as compared with its specificity, as well as the trade-off between cost and yield or potential epidemiological impact. For example, if one objective is to determine eligibility for TPT (for example, as part of an investigation of contacts, people living with HIV or other populations or individuals who may benefit from TPT), it is critical to have very high sensitivity (and thus very high negative predictive value of a test result), even if the specificity is suboptimal (which in this case might lead to referral of additional people for diagnostic evaluation and possibly unnecessary treatment for TB disease). In other situations, it may be critical to avoid false-positive diagnoses and maximize efficient use of limited resources for diagnostic evaluation, and a less sensitive but highly specific algorithm might be preferable, such as a clinic-based screening programme in a densely populated urban area, in which laboratory capacity and the supply of cartridges for diagnostic testing would be rapidly depleted if a screening and diagnostic algorithm with low specificity was used.

The profile of the risk group can influence the choice of algorithm because the accuracy of certain tools is affected by underlying biological factors associated with certain risk factors (for example, CXR screening is less sensitive in people living with HIV). Certain considerations for the best algorithms for specific risk groups are based on their risk for TB and for unfavourable outcomes if TB is not detected early and logistical considerations in screening specific to the risk group and the location in which screening is conducted (see further discussion below).

The prevalence of TB in a risk group directly affects the predictive values of all tests and therefore the occurrence of true or false results. The lower the prevalence, the more important it is that the algorithm has very high specificity, in order to avoid a high proportion of false-positive diagnoses.

The total cost of an algorithm depends on the unit cost of each test (including start-up and running costs), the total number of tests required and the overhead costs for delivering the services.

Different algorithms require different numbers of tests for any given population with any given TB prevalence. The tables in Annex 2 provide the estimated numbers of tests required for different algorithms in relation to case-detection yield. The tool described in 3.3 can be used to generate cost estimates for each algorithm and risk group according to local cost assumptions. This information can be used to conduct a simple cost–effectiveness analysis of the cost per true case detected. The **availability, cost and feasibility** of tests may, however, differ considerably in different parts of the health-care system. Outreach screening requires consideration of mobility and field conditions. For example, digital CXR technology offers lower running costs and greater mobility than conventional CXR but requires a high initial investment. Symptom screening may be relatively low cost, especially in integrated services, but it is also relatively insensitive. Diagnostic evaluation may become more feasible under outreach conditions if proper sputum collection and transport can be organized. The additional resources required to implement TB screening should not discourage managers from investing in this intervention but should stimulate mobilization of the necessary funds.

Consideration must be given to the **ability to engage with the population** to be screened. Although the algorithm used will have significant implications for the budget and logistics, so too will the approach used to conduct screening. Contact investigation might require home visits, or individuals with TB can be requested to bring their contacts to a health facility to be tested. Although the latter option may be far cheaper, far fewer people may actually be screened. Similarly, community outreach may involve setting up mobile treatment teams and laboratories, home visits or simply using loudspeakers to announce the availability of testing services. Different approaches work differently in different settings, and their impact will depend on the number of people reached and tested and on the yield. The acceptability of a given test and the beliefs of people who are screened and health-care workers may have to be considered. Out-of-pocket expenditure required to complete screening should also be considered.

Considerations for algorithms for risk groups

The prevalence of TB and risks of poor health outcomes or mortality, logistical factors associated with the likely location of screening and considerations for initiating TPT for certain risk groups all influence the choice of screening algorithm. Certain algorithms inevitably require more resources, and therefore resource availability will likely determine which algorithm is feasible.

Contacts

As close contacts of individuals with TB have a high prevalence of TB, their high risk of TB and their eligibility for TPT indicate urgent screening of this risk group. As the goal of screening in this group is to identify TB disease early and to rule out TB accurately, a highly sensitive algorithm is preferred – if possible one that begins with CXR because of its high sensitivity and specificity. Screening of contacts should ideally begin in the patient's household to ensure high coverage of this risk group. Thus, either transport of the patient to a nearby health facility or mobile CXR will be required to implement CXR-based algorithms in this risk group. The cost of such screening will be substantial, but this risk group is smaller than other groups. Although a CXR-based algorithm is preferred for this group, a more feasible algorithm must be selected when CXR services are not yet available for the screening programme.

Miners

A CXR-based screening approach, together with screening for symptoms of TB and lung disease, is also preferred for miners exposed to silica, given their high risk of lung disease (including TB) and lung damage from silicosis. Large mines often have facilities on site to conduct CXR screening for employees; smaller, informal mines may have limited capacity and may have to use other providers while increasing capacity.

Prisoners

Given the high risk of transmission in this group, a highly sensitive algorithm beginning with CXR is preferred. Larger prisons and penitentiary institutions may have radiography capacity on site or can bring mobile vans for screening campaigns. In smaller institutions or locations where CXR capacity is not available, screening algorithms based on symptoms or mWRD may be acceptable until CXR services are available.

People with clinical risk factors

In settings where the general TB prevalence is > 100/100 000, TB screening may be conducted among people with TB risk factors who are seeking health care for any medical reason or among those who are in health care. Access to radiography is more likely in a health facility. This can maximize screening sensitivity. Symptom screening is also valuable for immediate decisions on triage and infection control.

General population and communities with structural risk factors

For screening in the community, in populations with structural risk factors for TB and/or in the general population when the TB prevalence is ≥ 0.5%, a highly sensitive screening algorithm will provide the highest yield in terms of maximizing case detection, as substantial work is usually required to take intervention activities into the field. Such an algorithm, however, requires substantial resources for implementation. Screening for symptoms is much easier but is less sensitive and specific, depending on the symptom approach, and has a smaller potential impact on population prevalence or transmission. Screening with mWRDs is highly accurate (particularly specific) but has substantial resource implications.

3.3 *ScreenTB* tool

The most desirable screening strategy is one with high total yield of true-positive TB cases, few false-positives, low NNS, low cost, a rapid and simple algorithm and high client acceptability. In practice, many of these factors can run in opposite directions, and multifactorial analysis is required. The *ScreenTB* online tool has been developed to assist in prioritizing risk groups for screening and choosing appropriate screening and diagnostic algorithms. The tool allows users to select one or several risk groups and to estimate the yield and costs of screening for each with different screening algorithms. The tool must not be used as the only source for prioritization, planning and budgeting but rather as a starting point.

The tool can be found at https://www.who.int/activities/screening-for-tb.

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Chapter 4. Implementation of CAD technologies in a new setting

4.1 Considerations in selecting and using CAD for screening in TB programmes

CAD technologies for automated reading of digital CXR for TB detection offer a promising solution for high-TB burden countries; however, selecting the appropriate CAD product for a particular setting can be complex. When selecting a CAD product, TB programmes and implementers should consider multiple aspects of the technology and its interface with existing infrastructure, including:

- national and international regulatory approval of the products;
- the accuracy of the product for detecting abnormalities consistent with TB;
- the requirements for running the CAD programme, including:
  - the requisite software and hardware. Most CAD products can be run on any digital radiography platform, but not all. This consideration should include options for integration with existing and legacy systems.
  - the Internet connectivity required to run the programme. Although online deployment is the most common method of implementation, access to a stable Internet connection may be difficult. "Cloud-based" CAD programmes require stable Internet to function, and most CAD developers offer offline solutions that can be operated independently of Internet connection, although the cost may vary.
- the cost of running CAD. Pricing schemes for CAD programmes vary widely according to factors such as: bundled costs (whether hardware will be purchased with software), the costs of installation and set-up and the costs of reading. Each automated reading may be priced per CXR (usually volume) or structured as a set price for unlimited use for a certain time. Maintenance costs should also be considered.
- data security and privacy. Commercial cloud servers are used for online deployment by default. Countries are, however, increasingly concerned about privacy and request that servers be set up within their borders. Local or in-country servers could be set up, although at additional cost. When CXRs are analysed via commercial cloud servers, images will have to be anonymized before uploading. Most CAD solutions include an anonymization tool.

The market of CAD products for TB detection is constantly changing and expanding, with new versions of products and new companies coming online almost every day. FIND and the Stop TB Partnership have jointly created an online data repository of the CAD products currently available on the market and their key characteristics as described above, based on results of surveys with developers, which can be found at https://www.ai4hlth.org/. The goal of this publicly accessible, regularly updated, living database is to enable implementers to keep abreast of the rapidly changing artificial intelligence landscape.

Effective integration of CAD products into routine TB screening or triage requires determination of an appropriate CAD threshold that will be used to signal a positive screen and trigger further TB diagnostic evaluation. As threshold values for CAD products are not static or consistent across software or even versions of the same software, the user must determine the most appropriate abnormality or threshold score for their setting and use case, above which a confirmatory diagnostic test would be conducted. Identifying the ideal threshold for each use of CAD requires decisions on the goals and acceptable costs of screening. As with other screening tools, there is an inherent trade-off in the selection of the threshold score; lower scores will maximize the sensitivity of the tool to detect true TB patients in the population being screened but will incur additional costs for diagnostic testing because of reduced specificity. Higher scores will reduce the volume, and thus costs, of diagnostic testing and will probably focus case detection on more severe cases, but the reduced sensitivity will result in missed cases (Fig. 4.1).

Fig. 4.1 Sensitivity vs specificity over the CAD threshold spectrum
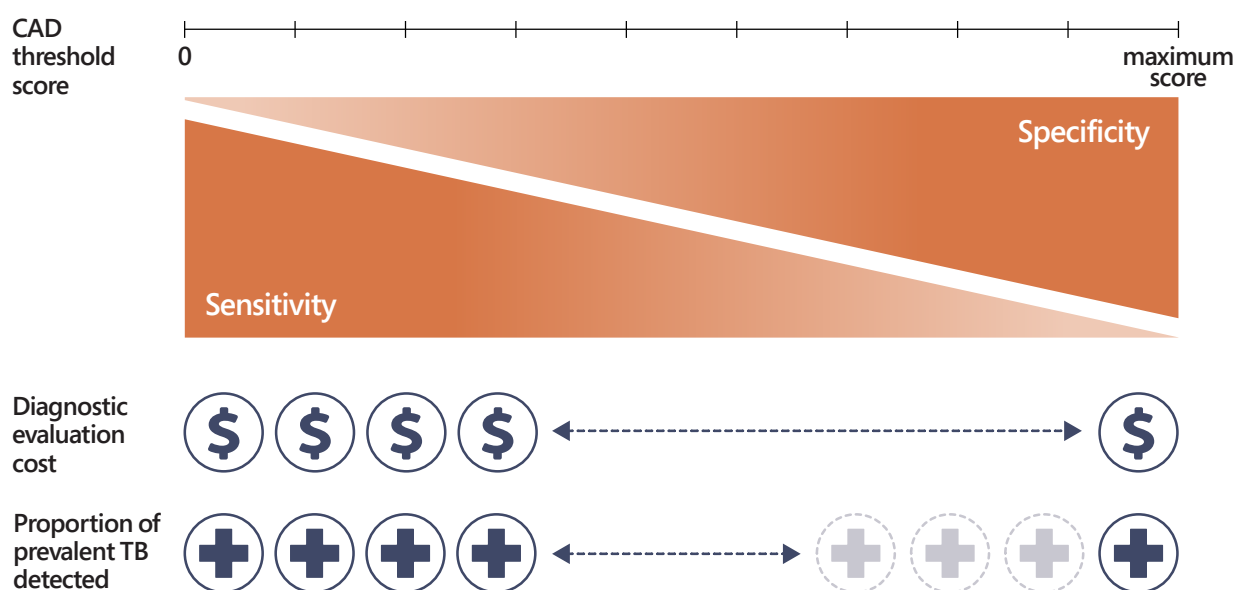
CAD can be integrated into TB screening or triage when human interpretation is not available, or it can be used with trained readers to reduce the workload.

- CAD can be used for initial screening, with any abnormal result referred to a human reader for final reading.
- CAD can be used for initial screening, with a portion of all results verified by a human reader (e.g. all abnormal and 10% of normal CAD results).
- CAD can entirely replace a human reader, with all abnormal results referred for diagnostic evaluation.
- CAD and human reading can be done in parallel, with an abnormal reading from either reading referred for diagnostic evaluation.

The performance of CAD in terms of the sensitivity and specificity of a particular threshold score are likely to depend on TB epidemiology and subgroups, such as people living with HIV and older people. Threshold scores also differ substantially by CAD product and even among versions of the same software. Determination of appropriate threshold scores based on local realities is therefore an integral part of the set-up and use of CAD and requires that TB programmes consider the overall aim of CAD in TB screening and diagnostic algorithms.

4.2 Toolkit for CAD calibration to enable implementation

A toolkit has been developed jointly by the WHO Global Tuberculosis Programme and the Special Programme for Research and Training in Tropical Diseases for conducting a CAD calibration study in a new setting. The toolkit consists of three parts.

- Part A introduces CAD calibration studies, including their designs, outcomes of interest and guidance for interpreting study findings and their application in a TB programme.
- Part B is a generic study protocol, with the proposed research method, data collection and analysis. The protocol can be adapted by users to seek ethics approval. Detailed information assists users in conducting operational research, including study procedures and sample size estimates for various study designs and sampling options, a generic study protocol, data collection tools and an online tool for data analysis.
- Part C is a guide to use of an online tool, "CAD for TB detection", to support data analysis, to determine appropriate thresholds by demonstrating the practical implications of various CAD thresholds, including for true- and false-positive CAD readings and the costs incurred for follow up confirmatory testing. Part C also includes case studies and guidance to help users interpret the results generated by the online tool and their practical application to local contexts.

The full toolkit can be found online at https://tdr.who.int/activities/calibrating-computer-aided-detection-for-tb.

In general, a CAD calibration study requires identification of the population in which CAD is to be used, sampling of the population to obtain CAD scores and the TB status of a subset of the population, and use of that data to calculate the sensitivity and specificity of CAD at different potential thresholds. The implications of the thresholds in terms of yield of true- and false-positive cases detected and the cost of diagnostic evaluation can then be used to guide the choice of a CAD threshold for a given implementation according to the goals of the screening or triage programme.

4.3 Online tool for calibration of CAD in a new setting

The CAD for TB detection calibration tool has been developed for analysis of the data collected in the CAD calibration protocol described above. The tool estimates the primary outcomes of yield and cost at every possible CAD threshold, including yields of true-positive, true-negative, false-positive and false-negative results; sensitivity and specificity; negative and positive predictive values; proportions of prevalent TB cases diagnosed and missed; and cost implications, including total costs for diagnostic evaluation and cost per true case detected. These values are then used to construct a ROC curve to illustrate the sensitivity and specificity of CAD at a range of possible thresholds. These outputs allow users to visualize potential scenarios and to select a threshold score for a given CAD implementation according to the objectives of the screening programme, the desired accuracy and yield, and the cost implications. The tool also allows users to conduct sub-population analyses for specific patient characteristics, such as separate ROC curves and threshold calculations for individuals who are HIV-positive or who are over 55 years of age. The tool can be found online at https://tdr.who.int/activities/calibrating-computer-aided-detection-for-tb.

Chapter 5. Screening for tuberculosis disease among adults and adolescents living with HIV

The algorithms for screening adults and adolescents ≥ 10 years of age living with HIV are presented in Fig. A.3.1-A.3.11 in Annex 3.

5.1 Introduction

Since 2011, WHO has recommended that people living with HIV be systematically screened for TB disease at each visit to a health facility. The recommendation is based on the high risk of this group for TB and mortality and a lingering gap in case detection in this population. In 2019, people with HIV were at 18 times greater risk for incident TB than people without HIV and close to one third of deaths from AIDS were due to TB *(2)*. Only 56% of the total estimated number of HIV-positive incident TB cases were detected in 2019 *(2)*. Early detection and timely treatment of TB among people living with HIV is critical for reducing mortality.

To date, the recommendation has been to screen for four primary symptoms of TB among people living with HIV: cough, fever, weight loss or night sweats. Screening with the WHO four-symptom screen (W4SS) is recommended for all people living with HIV at every encounter with a health-care worker, both to detect prevalent TB disease and to rule it out before initiation of TPT. Recent evidence indicates, however, that the accuracy of W4SS may be suboptimal for all subpopulations living with HIV *(35)*. Therefore, for the 2021 update to the TB screening guidelines, a systematic review and a meta-analysis of individual patient data were commissioned to evaluate the performance of W4SS and alternative screening tools among subpopulations of people living with HIV, each with distinct clinical characteristics and implications for implementation:

- **Outpatient people living with HIV not receiving ART:** This population may include people with newly diagnosed HIV, those who discontinued ART and are re-engaging in care and those who experience ART failure. This subpopulation is at a high risk of TB disease or reactivation because of their probably weakened immune system. They are also at greater risk of death, and therefore a highly sensitive and specific screening strategy is required to ensure rapid initiation of treatment for TB disease or infection, as appropriate. Ideally, TB screening in this population will be accompanied by prompt enrolment in HIV/AIDS care and initiation of ART. Staging of HIV disease and testing to exclude TB with LF-LAM or mWRD is recommended in people with advanced HIV disease (i.e. ≤ 200 CD4 cells/µL or in clinical stage 3 or 4) *(12)*.
- **Outpatient people living with HIV on regular ART:** Once in regular ART care, this population is likely to have suppressed viral replication of HIV and therefore a reduced viral load and significant immune recovery. This decreases the chances of TB reactivation and incident disease. Thus, this population is at lower risk of TB and has a physiological presentation similar to that of

non-HIV-infected screening participants. People living with HIV who are currently in care should be screened for TB at every regular contact with the health services as part of integrated HIV care.

- **Medical inpatients living with HIV:** This population is usually at an acute state of illness and requires immediate care, including screening, diagnostic evaluation and treatment, to decrease the risk of death. Regardless of their ART status, people living with HIV should be screened for TB at any episode of hospitalization.
- **Pregnant women living with HIV:** This is a key population, given the suppressed immune status of the mother and the importance of protecting the health of the fetus. TB screening for this population should be integrated with prevention of mother-to-child transmission and antenatal care.
- **Children < 10 years living with HIV:** This subpopulation is addressed in 6.3.

Health-care workers should suspect TB in any person living with HIV. People with HIV who screen negative for TB and show no evidence of TB disease should be offered TPT if they are eligible.

5.2 Screening tools

5.2.1 WHO-recommended four-symptom screen
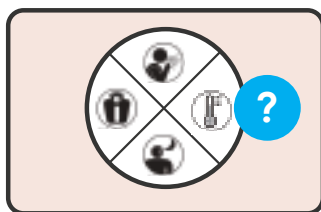
W4SS was first recommended in 2011, with an initial recommendation for systematic screening of all people living with HIV at every visit to a health-care facility. W4SS is a simple screening approach that is non-invasive, does not require infrastructure (technology, electricity, Internet) and is feasible to implement in any setting. The results of a symptom screen are, however, subjective and depend on the patient's level of understanding and their willingness to share their physical experience of symptoms and on the provider's interpretation of the patient's self-reported symptoms. Thus, the quality and consistency of the W4SS is likely to vary among clinical settings.

Table 5.1 shows the accuracy of W4SS in different sub-populations of adults and adolescents living with HIV. The latest evidence review for the 2021 guidelines showed that W4SS has relatively high sensitivity in adults and adolescents living with HIV, 83%, but low specificity, 38%. The sensitivity of W4SS among outpatients on ART is relatively low, 53%, indicating that W4SS alone would not be sufficient to detect TB among people in regular ART care. W4SS also has low sensitivity in pregnant women living with HIV. It is relatively sensitive in outpatients not on ART (84%), indicating that W4SS is useful in finding people with TB among people who are starting HIV care, but the lack of specificity has implications for resources and rational use of diagnostic testing.

Table 5.1 Diagnostic accuracy of W4SS in different subpopulations of adults and adolescents with HIV

| Population	Sensitivity (%)	Specificity (%)
All people living with HIV	83	38
Inpatients	96	11
Outpatients on ART	53	70
Outpatients not on ART	84	37
≤ 200 CD4 cells/μL[a]	86	30
Pregnant women living with HIV	61	58

For more detail, see **Web Annex B** of the screening guidelines.

[a] Indicator of advanced HIV disease

In view of its exceptionally low specificity among medical inpatients, W4SS is not a suitable tool for screening in this population, as the resulting high positivity rate renders it clinically useless for indicating further care. Given the severity of the disease and the need for rapid action in this acutely ill population, other tools may be necessary.

Nonetheless, W4SS is an essential part of the clinical examination of most subpopulations and is the most accessible screening tool at all levels of the health system. It can be repeated as often as necessary, while more intense screening strategies might be used less frequently, such as at annual intervals check-ups. Familiarity with W4SS is already widespread in many HIV services as a result of capacity-building and supervision. It also has an important role in ruling out TB disease due to its high negative predictive value in most settings. This is important in the preventive TB care pathway of people with HIV who would benefit from TPT in the absence of TB disease.

5.2.2 C-reactive protein (CRP)
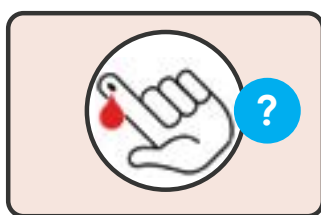
C-reactive protein (CRP) is an indicator of systemic inflammation that can be measured with a blood test. A point-of-care test is available that is performed on capillary blood collected from a finger-prick, making it simple, affordable and feasible in primary care. The turnaround time from testing to result with many CRP test kits is 3–5 min, allowing a quick clinical decision to refer a patient for diagnostic evaluation for TB disease or initiation of TPT. An additional potential benefit of CRP is that it can alert clinicians to the presence of other diseases, such as bacterial pneumonia, bronchitis or other infectious or non-infectious conditions (e.g. lymphoma). Health staff and patients may be more confident in the results of a biochemical test than of a more subjective symptom screen.

The threshold for considering a result as abnormal may differ by setting. Evidence for the use of a cut-off value of > 5 mg/L or > 10 mg/L was reviewed for the screening guideline; both were found to have the necessary accuracy for detecting TB disease. Currently, the cut-off value of > 5 mg/L is recommended, as it is the lowest threshold indicating abnormality in many clinical settings and because it is the most sensitive. At this cut-off, CRP has a similar sensitivity and higher or similar specificity to symptom screening in all subpopulations of adults and adolescents living with HIV tested (Table 5.2, and see **Web Annex B** of the screening guidelines). CRP shows clinically significantly greater sensitivity and specificity than W4SS among outpatients living with HIV who are not on ART (CRP, sensitivity 89% and specificity 54%; W4SS, sensitivity 84% and specificity 37%). CRP can also be used in combination with W4SS. While a parallel approach will have resource implications because

of the higher sensitivity and lower specificity, data reviewed for the 2021 guideline revision support sequential combination of a positive W4SS followed by CRP with a cut-off of > 5 mg/L, particularly for people not on ART (see 5.4, and **Web Annex B** of the screening guidelines).

CRP can play an important role in ruling out TB disease before initiation of TPT, which is essential in this population, and requires a test with the highest possible negative predictive value. CRP with a cut-off of > 5 mg/L had a negative predictive value of 99.8% among outpatients not on ART in a setting with a 1% prevalence of TB.

Table 5.2 Accuracy of CRP with cut-off values of > 5 mg/L and > 10 mg/L compared with a culture reference standard

Population	Cut-off > 5 mg/L		Cut-off > 10 mg/L	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
All people living with HIV	90	50	83	65
Inpatients	98	12	97	21
Outpatients on ART	40	80	20	90
Outpatients not on ART	89	54	82	67
≤ 200 CD4 cells/μL[a]	93	40	90	54
Pregnant women living with HIV	70	41	70	54

For more detail, see **Web Annex B** of the screening guidelines.

[a] Indicator of advanced HIV disease

5.2.3 Chest X-ray
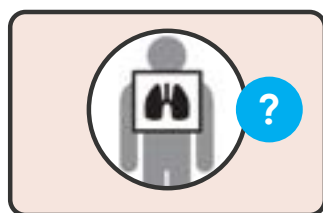
CXR is useful for screening people living with HIV for TB. It is currently recommended by WHO for use in parallel with W4SS for ruling out TB disease before initiating TPT. Similarly, CXR can be used in parallel with W4SS to screen for TB disease, a positive or abnormal result on either screen indicating referral for diagnostic evaluation. CXR can be used to either add to the sensitivity of W4SS (in a sequential negative algorithm) or to improve the pre-test probability of TB among those who screen positive for symptoms (in a sequential positive algorithm) (see 3.2). Reading modalities of "any abnormality" or "abnormality suggestive of TB" can be used, depending on the context, the availability of radiological expertise, resources and a preference for higher sensitivity or higher specificity.

Table 5.3 shows the diagnostic accuracy of CXR combined with W4SS in different sub-populations of people living with HIV. A combined screening strategy of W4SS and CXR offers a significant improvement in sensitivity, particularly for screening outpatients enrolled in ART care, over W4SS alone, although with lower specificity (W4SS: sensitivity 53%, specificity 70%). However, in some subgroups like inpatients and people with advanced HIV disease the specificity is very low.

Table 5.3 Diagnostic accuracy of W4SS combined with CXR (any abnormality) in different subpopulations of people living with HIV as compared with a culture reference standard, with a positive or abnormal result on either or both screens

Population	Sensitivity (%)	Specificity (%)
All people living with HIV	93	20
Inpatients	90	7
Outpatients on ART	85	33
Outpatients not on ART	94	19
≤ 200 CD4 cells/μL[a]	94	14
Pregnant women living with HIV	75	56

For more detail, see **Web Annex B** of the screening guidelines.

[a] Indicator of advanced HIV disease

5.2.4 WHO-recommended rapid molecular diagnostic tests
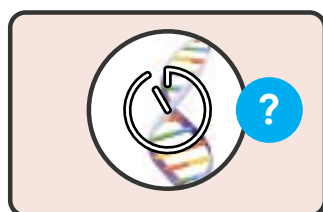
mWRDs are now also recommended for screening people living with HIV. (See 3.1.4 for a full description of their use in screening). A positive mWRD screen result in a person with HIV must be followed by further diagnostic evaluation to confirm or rule out TB.

Among medical inpatients in settings where the prevalence of TB is ≥ 10%, mWRDs are strongly recommended for screening for TB disease because of the severity of illness in this population. As rapid diagnosis and care are required, a positive mWRD result in this population can be considered an indication for treatment and need not be followed by a separate diagnostic evaluation, while ensuring proper monitoring of treatment response and evaluation for alternative diagnoses, particularly if the patient had TB in the previous 5 years.

Table 5.4 shows the accuracy of mWRD screening in different sub-populations of adults and adolescents living with HIV. The overall sensitivity of mWRD in all people living with HIV is estimated to be 69% and the specificity 98%, while W4SS followed by a mWRD is estimated to have a sensitivity of 62% and a specificity of 99% (see **Web Annex B** of the guidelines). The accuracy of mWRD in most sub-populations is not significantly different from that of W4SS followed by mWRD.

Table 5.4 Diagnostic accuracy of mWRD for screening for TB in different subpopulations of people living with HIV as compared with a culture reference standard

Population	Sensitivity (%)	Specificity (%)
All people living with HIV	69	98
Inpatients	77	93
Outpatients on ART	54	99
Outpatients not on ART	72	98
≤ 200 CD4 cells/μL[a]	76	97
Pregnant women living with HIV	55	99

For more detail, see **Web Annex B** of the screening guidelines.

[a] Indicator of advanced HIV disease

5.3 Considerations for use of all screening tools

All the screening tests described above, when positive or abnormal, identify adults and adolescents living with HIV who have a higher probability of TB disease and who are then to be referred for diagnostic evaluation. TB diagnosis among people living with HIV should include use of an mWRD as a diagnostic test *(12)*, LF-LAM where indicated *(12)*, and other clinical, radiological or laboratory procedures as necessary.

When a screening test or algorithm is used and the results are normal or negative, if the algorithm has sufficient negative predictive value in the setting, patients should be referred for evaluation for TPT. TPT is strongly recommended for people living with HIV in whom TB disease has been ruled out *(4)*.

Before use, all the screening tools described here should be included in the guidelines of national and local TB and HIV programmes and in national and local algorithms for screening and diagnostic care for people living with HIV (see 5.4 and Annex 3 for further discussion of screening algorithms for people living with HIV). Health staff will require adequate training in use of each tool, and the results of each screening test conducted should be recorded in patient clinical records.

New screening tools should not replace W4SS, which should continue to be conducted at every encounter with a health-care worker or peer supporter, regardless of the inclusion of new screening tools in the algorithm. The W4SS strengthens interpretation of the results obtained with other screening tests and is also valuable for immediate infection control measures. W4SS is also critical for indicating eligibility for an LF-LAM test if a CD4 cell count is not available *(12)*.

Countries should include new tools for screening people living with HIV in national TB screening algorithms according to feasibility, level of health facility and available resources. Lack of access to any of the tools described in this section should not be a barrier to TB screening or ruling out TB in order to allow initiation of TPT or ART.

Implementation considerations for CXR

Interpretation of CXR images for people living with HIV

CXR requires interpretation by a radiologist, other trained health personnel or CAD software. CXR findings may differ widely in people with HIV-associated TB, from a completely normal picture to multiple radiological abnormalities typically associated with advanced TB disease *(36)*.

Periodicity of CXR screening

Although no data are available on the optimal periodicity of CXR screening, a pragmatic approach would be to perform CXR annually among outpatients living with HIV at the time of viral load testing or other investigations, in addition to W4SS at every encounter with a health worker between annual screens. The frequency might be determined according to the regularity of ART, use of TPT and TB transmission setting. A baseline CXR and access to films taken previously are useful for comparing subsequent radiological changes. (See 3.1.2 for further considerations for screening with CXR).

Service delivery

HIV services should be integrated with TB and radiography services to maintain a "one-stop shop". It is essential to engage with local civil society organizations, given that this screening approach is most relevant for people living with HIV who are stable, in care, immunocompetent and likely to be supported in the community. The risks of exposure to ionizing radiation, especially from non-compliant equipment, might be a greater concern for this group, who undergo CXR regularly and may also receive radiography to evaluate health problems between screenings.

Implementation considerations for CRP

Choice of cut-off value

CRP at cut-off values of either > 5 mg/L or > 10 mg/L is similarly or more accurate than W4SS. The cut-off of > 5 mg/L is recommended because it is the lowest threshold that indicates abnormality in many clinical settings and is more sensitive. The choice of cut-off value will, however, depend on the availability of CRP technology, the prevalence of other conditions that may increase CRP values and a preference for increased sensitivity or increased specificity.

Requirements and service delivery

Currently, many analysers are available for measuring CRP at points of care, with different levels of detection, although all can be used for TB screening with a CRP cut-off between 5 and 10 mg/L. The results obtained with most quantitative point-of-care analysers are strongly correlated with those of laboratory analysers.

Like finger-stick measurement of glucose with a glucometer, point-of-care CRP tests provide rapid (≤ 5 min) quantitative results from capillary blood (obviating the need for phlebotomy) and are simple enough to be performed by front-line health-care workers after minimal training. Containers for safe disposal of needles and other sharp tools for pricking the finger must be available, and other infection control measures in the collection of blood must be followed.

The overall laboratory requirements are minimal; however, most analysers require a continuous electricity source, and most CRP assays require cold storage and refrigeration (+2 to +8 °C). Some semi-quantitative test strips are available with operational characteristics ideal for use in remote settings (inexpensive, no analyser required); however, the agreement of results with those of laboratory analysers is moderate and may decrease further if time-to-test strip interpretation exceeds 5 min.

If point-of-care testing for CRP is not available, blood samples will have to be sent to the nearest laboratory, which will significantly undermine the utility of the test for on-the-spot decision-making and render it less useful for screening in outpatient settings.

Implementation considerations for mWRD

Resource requirements

Use of mWRDs for screening in addition to diagnostic testing represents a significant shift and requires significant resources. (See Annex 3 on modelled algorithms.) Providers and health staff require training in the proper use and interpretation of mWRDs when used for screening.

Service delivery

Depending on feasibility and available resources, countries may choose to prioritize TB screening with mWRDs in certain subpopulations other than those for whom it is generally recommended, such as medical inpatients in settings where the TB prevalence is < 10% or pregnant women living with HIV.

Use of mWRDs for screening among outpatients with HIV in regular ART care should be aligned with regular HIV services (e.g. viral load monitoring). Similarly, for pregnant women with HIV, it should be aligned with antenatal services.

To use of mWRDs to screen medical inpatients with HIV, the TB prevalence in medical wards may be calculated as the percentage of admissions that are diagnosed with TB during a recent 6–12-month period. Prevalence is calculated for all inpatients, not just those with HIV, to reflect the risk of transmission and the burden of disease in the community.

See 3.1.4 for further considerations on screening with mWRDs.

5.4 Algorithms for screening

Eleven algorithm options are proposed for screening of people living with HIV for TB that include the new and existing screening tools presented in this section (see Annex 3). (See 3.3 for an introduction and discussion of screening algorithms in general, including the definitions and implications of single, parallel, sequential positive and sequential negative screening algorithms.)

The algorithms focus on screening and referral to a diagnostic evaluation, including an mWRD test, although LF-LAM should be used where indicated to enhance early detection of TB *(12)*. Each algorithm has a different sensitivity and specificity and therefore different potential for true-positive, true-negative, false-positive and false-negative results. The yields of TB patients and predictive values also depend on the prevalence of TB in the population being screened. For all algorithms, the risk of a false-positive diagnosis increases as the prevalence decreases; therefore, attention must be paid to diagnostic accuracy, particularly when the prevalence of TB in the screened population is low.

The algorithms, when combined with mWRD for diagnosis, have different costs and requirements in terms of human resources and health systems. Which algorithm is chosen for screening and diagnosis depends on the risk group, the prevalence of TB, the availability of resources and the feasibility of implementing the algorithm. The tables in Annex 4 show modelled estimates of the performance and outcomes of the screening algorithms described below, including the results of true- and false-positive diagnosis for the entire algorithm, consisting of the screening test(s), followed by diagnostic evaluation with an mWRD.

Algorithm options

Fig. A.3.1 W4SS single screening algorithm (page 76)

Fig. A.3.2 CRP single screening algorithm (page 77)

Fig. A.3.3 CXR single screening algorithm (page 78)

Fig. A.3.4 Parallel screening algorithm with W4SS and CRP (page 79)

Fig. A.3.5 Sequential positive screening algorithm with W4SS and CRP (page 80)

Fig. A.3.6 Sequential negative screening algorithm with W4SS and CRP (page 81)

Fig. A.3.7 Parallel screening algorithm with W4SS and CXR (page 82)

Fig. A.3.8 Sequential positive screening algorithm with W4SS and CXR (page 83)

Fig. A.3.9 Sequential negative screening algorithm with W4SS and CXR (page 84)

Fig. A.3.10 mWRD single screening algorithm for medical inpatients in settings with TB prevalence > 10% (page 85)

Fig. A.3.11 mWRD single screening algorithm for people living with HIV (page 86)

Chapter 6. Screening for tuberculosis disease in children

The algorithms for screening children are listed in Fig. A.5.1-A.5.6 in Annex 5.

6.1 Introduction

It is estimated that, in 2019, approximately 1.2 million children under 15 years of age fell ill with TB, and 230 000 died of TB *(2)*. In about 56% of the 1.2 million patients, TB was not diagnosed or reported, the proportion being highest in children < 5 years of age (65%). The symptoms of TB are under-recognized in children because they are less specific and overlap with those of common childhood diseases, often leading to delayed diagnosis. Children are more prone to extrapulmonary forms of TB, which may challenge timely detection. Certain forms, especially TB of the central nervous system, carry a high risk of death or permanent disability when detected late, even if treated. Screening children for TB disease is imperative to detect TB earlier, start treatment earlier and increase the likelihood of better treatment outcomes. As children frequently have extrapulmonary TB disease with or without pulmonary involvement, health-care workers must be aware of symptoms that indicate TB at other sites (such as lymphatic, abdominal, meningeal and osteoarticular TB). TB meningitis, disseminated TB and spinal TB are medical emergencies that must be recognized quickly and immediately referred to the appropriate level of care. The risks of severe disease and death from TB can be reduced by BCG vaccination *(37, 38)*; however, the considerations for screening discussed in this section apply regardless of immunization status.

The children who should be targeted for screening are those who are at particularly high risk of TB disease, especially those in close contact with someone with TB and children aged 0–10 years who are living with HIV. Screening of adolescents (10–19 years) living with HIV is discussed in Chapter 5 of this handbook.

Countries are encouraged to monitor and evaluate the yield of TB screening approaches among children to be screened, including child close contacts and children living with HIV, disaggregated by screening tool and algorithm, to broaden the evidence base of the yield, costs, safety and clinical outcomes of different strategies.

6.2 Screening child contacts of patients with TB

Child contacts are at high risk of TB disease, and the risk varies substantially by age. Newborn infants are at particularly high risk of infection with TB if the mother had untreated TB disease when they were born. Apart from the risk of exposure because of close proximity to adults in a household with TB, children < 5 years who are infected with TB have a 19% chance of progression to TB disease within 2 years *(39)*. Most paediatric mortality occurs in this age group, with 80% of paediatric deaths from TB occurring in children < 5 years *(40)*. An infant infected with TB has a very high risk of rapidly developing TB disease and dying. Among infants (< 1 year) infected with *M. tuberculosis*, 20–50% will develop TB disease, almost all of them within 1 year of infection *(39-41)*. The risk of progression to TB disease among older children and adolescents (5–14 years) in the 2 years after TB infection is

somewhat lower but still consequential, at 9% *(39)*. The high risk of progression to TB disease and the associated high mortality rates underline the importance of screening children exposed to close contacts with TB.
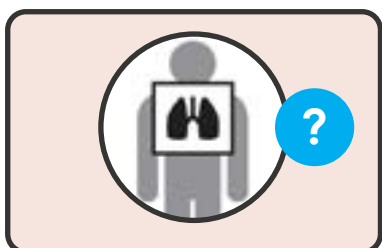
6.2.1 Symptom screening

Any child < 15 years who has had close contact with someone with TB disease should be screened for TB with a symptom screen and/or CXR as part of active contact-tracing (see Algorithm A.5.1 in Annex 5). Symptoms that should be used to screen for TB are cough, fever and poor weight gain (or weight loss). In young children, reduced playfulness or lethargy should also be included in symptom screening; cough may be absent. It is useful to examine growth charts regularly to determine whether a child has been losing weight or their weight has plateaued. A plateau in weight gain should be a warning sign for possible TB. In the latest review, a symptom screen in which a child has any of the symptoms of cough, fever or poor weight gain has a sensitivity of 89% and a specificity of 69% for TB disease (against a composite reference standard) (see **Web Annex B** of the screening guidelines).

The low specificity of a symptom screen alone means that about 30% of children may undergo unnecessary diagnostic tests or even treatment for TB. The risk of a false-positive diagnosis of TB after a false-positive symptom screen among children may be higher than for adults because such a diagnosis is frequently made solely on clinical grounds. Because of the high rates of mortality and morbidity among children with TB, however, the risk of a missed diagnosis is generally judged to outweigh the risk of a false diagnosis and unnecessary TB treatment, especially because children generally tolerate TB treatment and TB preventive treatment well. Health-care workers should nonetheless remain vigilant to possible false-positive TB diagnoses among children, monitor their response to treatment carefully and consider alternative causes, especially if a child is not improving on treatment. If a plausible alternative diagnosis is confirmed, providers may consider stopping TB treatment while remaining mindful that TB may co-exist with other diseases.

6.2.2 CXR

The sensitivity for TB of "any abnormality" as reported on CXR in children is 84%, and the specificity is 91%. It is thus more specific than symptom screening alone. The estimates of the accuracy of CXR are not, however, disaggregated by age group, and significant differences in CXR findings between younger and older children may lead to important differences in sensitivity and specificity by age group.

Abnormalities caused by TB seen on CXR in children may differ widely from those in adults. While older children may have "adult type" disease presentation, such as cavitary disease, the changes on CXR associated with TB disease in younger children may be subtle and hard to see if the quality is not optimal. When using CXR for TB screening in children, both posteroanterior and lateral views should be done. Besides cavitary disease, the other most common abnormalities are enlarged hilar lymph nodes, enlarged hilar and paratracheal lymph nodes, enlarged lymph glands compressing the airways, pneumonic consolidation with lymph node enlargement, miliary TB and pleural effusions. It may sometimes be difficult to distinguish abnormally enlarged paratracheal and hilar lymph nodes from the normal vascular structures. These subtle findings on CXR in younger children may affect the sensitivity and specificity of CXR. The help of a practitioner experienced in interpreting paediatric chest radiography may be sought to resolve questions about interpretation. CAD software for interpreting plain CXR for TB is now recommended by WHO as an alternative to human reading (Chapter 4); however, this recommendation is limited to people aged ≥ 15 years, and more data should be collected to validate the performance of CAD for TB in children.

CXR can be used in combination with symptom screening (see 6.4 for algorithm options for screening child contacts). CXR is not, however, readily available in many locations, and travel to another location for a CXR may not be feasible for a caregiver, who may be unable to make time or to afford direct or indirect costs for travel, time, support or the radiography service. Mobile CXR units may be used to reach populations that otherwise would be unable to access a health centre with a radiography machine. These, however, require financial and logistical support, and, to be clinically useful, a mobile unit would have to have a regular schedule.

CXR emits a small amount of radiation; however, the radiation risk is very low. Chapter 3 outlines additional considerations for implementing CXR, including the benefits and drawbacks of serial and parallel screening when CXR is combined with symptom screening.

6.2.3 WHO-recommended rapid molecular diagnostic tests

mWRDs are not currently recommended for screening for TB disease in children < 15 years.

6.2.4 Tests of TB infection

As for adults, tuberculin skin tests and interferon-g release assays should not be used to screen for TB disease in children *(12, 34)*, as these tests cannot distinguish TB infection from TB disease and cannot predict who will progress to TB disease. Both tests may be influenced by mechanisms unrelated to TB infection and give false-negative or false-positive results. The role of these tests in decision-making for TPT is discussed elsewhere *(4, 5)*.

6.2.5 Considerations for implementation

Contact screening can be difficult. Once the contacts of a TB patient have been identified, they should be screened for TB symptoms and/or undergo CXR, followed by appropriate diagnostic evaluation *(4, 5)*. Tracing of household contacts usually identifies many close contacts who are eligible for screening and TPT; however, it is expensive and time-consuming for health-care workers to identify the contacts of all known TB patients. Additionally, TB is still a highly stigmatized disease in many countries and contexts, and the visit of a health worker to a patient's home may draw attention to a diagnosis, risking violation of a patient's right to medical privacy and discrimination against the household. Alternatively, health-care workers can ask patients to bring their contacts, including children, to a health centre for TB screening, although caretakers or parents may not be able to bring children in for evaluation, for a variety of reasons, such as financial or time constraints, lack of appreciation of the importance of screening or distrust of health-care services *(42)*. Health-care providers, health-care managers and health programmes should therefore consider the potential preferences and concerns of parents and caregivers and manage them with sensitivity and tact.

Like contacts of any age, children and adolescents who are exposed to someone with TB and who are found not to have TB disease should be assessed for TPT as per national guidelines *(4, 5)*. Inability to conduct CXR should not prevent a child from receiving TPT. Health managers should plan for the resources and logistics necessary to deliver screening tests according to the chosen algorithm, to register data on contact-tracing, including the results of screening tests (preferably electronically) and to integrate screening and TPT services.

Routine screening of children who access health care is currently not recommended. Children and adolescents < 15 years who access health care represent a much larger population for potential screening than contacts of TB patients, which has important resource implications for scaling up screening, particularly with more expensive screening and diagnostic tools. In addition, the generally low pre-test probability of TB disease in children and the diagnostic pathway that children typically follow when they screen positive, could lead to false-positive diagnoses and inappropriate treatment of large numbers of children.

6.3 Screening children living with HIV

Children living with HIV have a high risk of rapid progress to severe disease and death if a diagnosis of TB is missed. A child with HIV infection is 3.5 times more likely to progress to TB disease than a child who is HIV-negative *(39)*. An estimated 16% of paediatric deaths from TB are among HIV-positive children, resulting in 36 000 deaths annually *(2)*. It is for this reason that WHO strongly recommends that children with HIV be screened for TB.

6.3.1 Screening for symptoms and contact
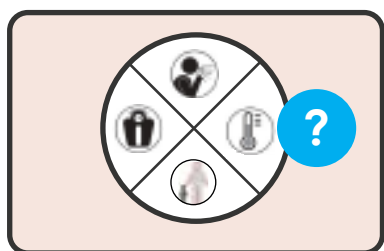
Children with HIV who are < 10 years should be screened for TB at every encounter with a health-care worker, with the following screen: cough, fever, poor weight gain or close contact with someone who has TB. The systematic review conducted for the 2021 screening guidelines showed that presence of any one of these conditions has a sensitivity of 61% and a specificity of 94%, and children who are positive on this screen should undergo further diagnostic evaluation for TB disease.

Screening for TB can be difficult in a child living with HIV. Even older children, who may otherwise be expected to have more typical "adult-type" TB disease if they are HIV-infected, frequently have extrapulmonary disease and atypical symptoms *(43)*. Health-care workers should maintain strong clinical suspicion of TB in any child with HIV, even in the absence of classical symptoms of TB, especially in areas with a high TB burden.

6.3.2 Other screening tests

There are currently inadequate data to extrapolate use of CXR, CRP or mWRDs as screening tests in adults to children < 10 years living with HIV. Tests for TB infection are not useful for TB screening (see also 6.2.4).

6.3.3 Considerations for implementation

Children living with HIV should be followed up closely in the health-care system and should be screened for TB at every routine contact with an HIV care provider, at a health facility or in the community. Given the high risk of progression to TB disease and the high mortality rate, combined symptom screening should also be done at every contact with the health-care system, including events such as vaccination days, maternal health appointments, at nutritional screening and at food support programmes. The combined symptom screen has low specificity, which may lead to a large number of false-positive screens and unnecessary diagnostic tests or treatment for TB. Nevertheless, given the high mortality due to untreated TB among children living with HIV, the risk of overtreatment is often outweighed by the benefit of TB treatment. Health-care workers should closely monitor therapy and remain vigilant to the possibility of a false-positive TB diagnosis when the symptoms are due to another disease, such as pneumonia.

It may be difficult to determine whether a child has close contact with a person with TB, and it is important to take a careful history of the known exposures of the caretaker and the child. Household contacts are often considered, but, particularly in areas with a high TB prevalence, close contact can occur in a variety of community settings, including school, day care and religious gatherings. A study in South Africa indicated that only half of children with TB had a known household contact with TB *(44)*, and even young children had a high risk of being infected in the community, not just from household members with TB. Therefore, a high index of suspicion of TB in young children should be maintained, especially for children with HIV or of unknown HIV status in settings with a high TB prevalence.

Children living with HIV who are found not to have TB disease should receive TPT as per WHO guidelines *(4, 5)*.

6.4 Algorithms for screening

Screening algorithms for children are listed in Annex 5.

Children 0 to < 15 years with a close contact with TB

Any of the following screening algorithms can be used:

Fig. A.5.1 Screening with symptoms (page 90)

Fig. A.5.2 Screening with CXR (page 91)

Fig. A.5.3 Parallel screening with symptoms and CXR (page 92)

Fig. A.5.4 Sequential positive serial screening with symptoms and CXR (page 93)

Fig. A.5.5 Sequential negative serial screening with symptoms and CXR (page 94)

Children 0 to < 10 years living with HIV

Fig. A.5.6 Screening with symptoms (page 95)

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Annex 1 Screening algorithms for the general population and high-risk groups (not including people living with HIV)

Illustrations of 10 possible algorithms for screening individuals aged 15 years and older among the general population and high-risk groups where screening is recommended.

Fig. A.1.1 – Screening with cough

Population

Prolonged Cough

➕

➖

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Negative Screen

Evaluate for TPT per
eligiblity
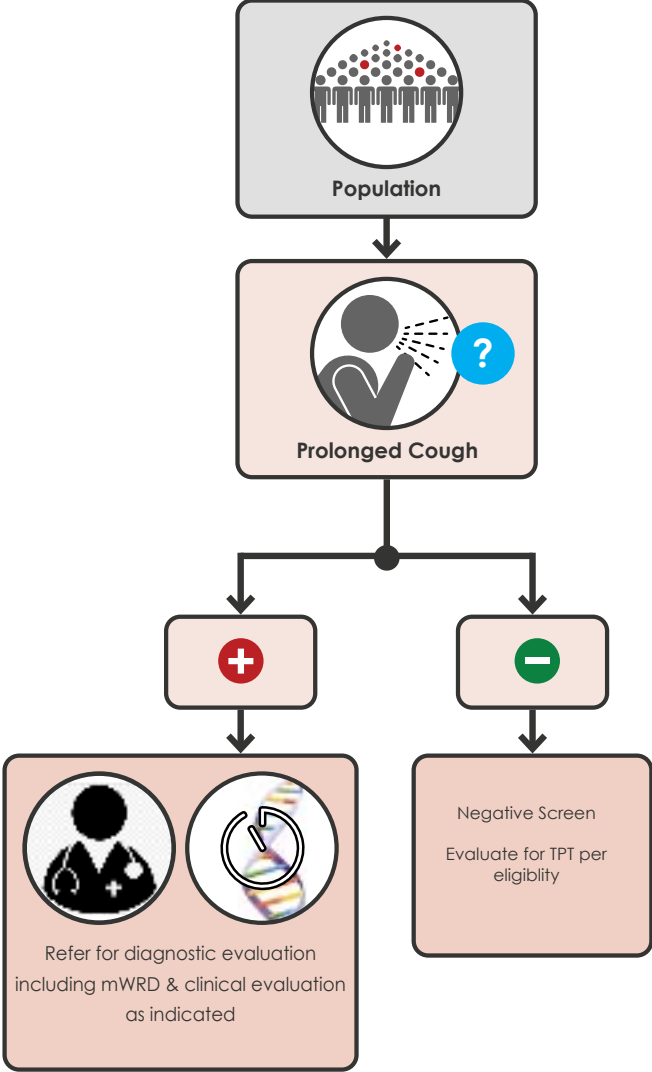
Fig. A.1.2 – Parallel screening with cough and CXR
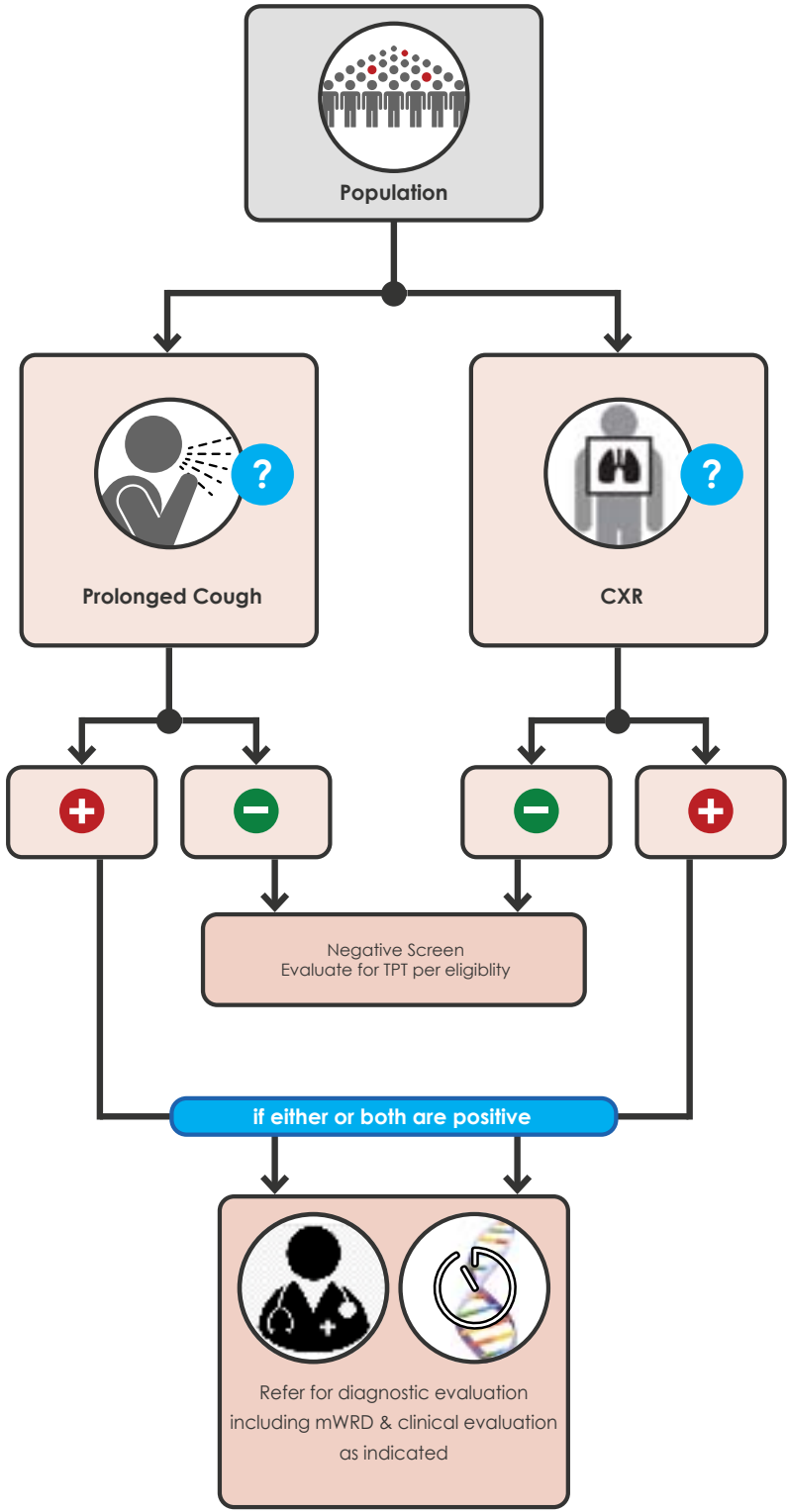
Fig. A.1.3 – Sequential positive serial screening with cough and CXR
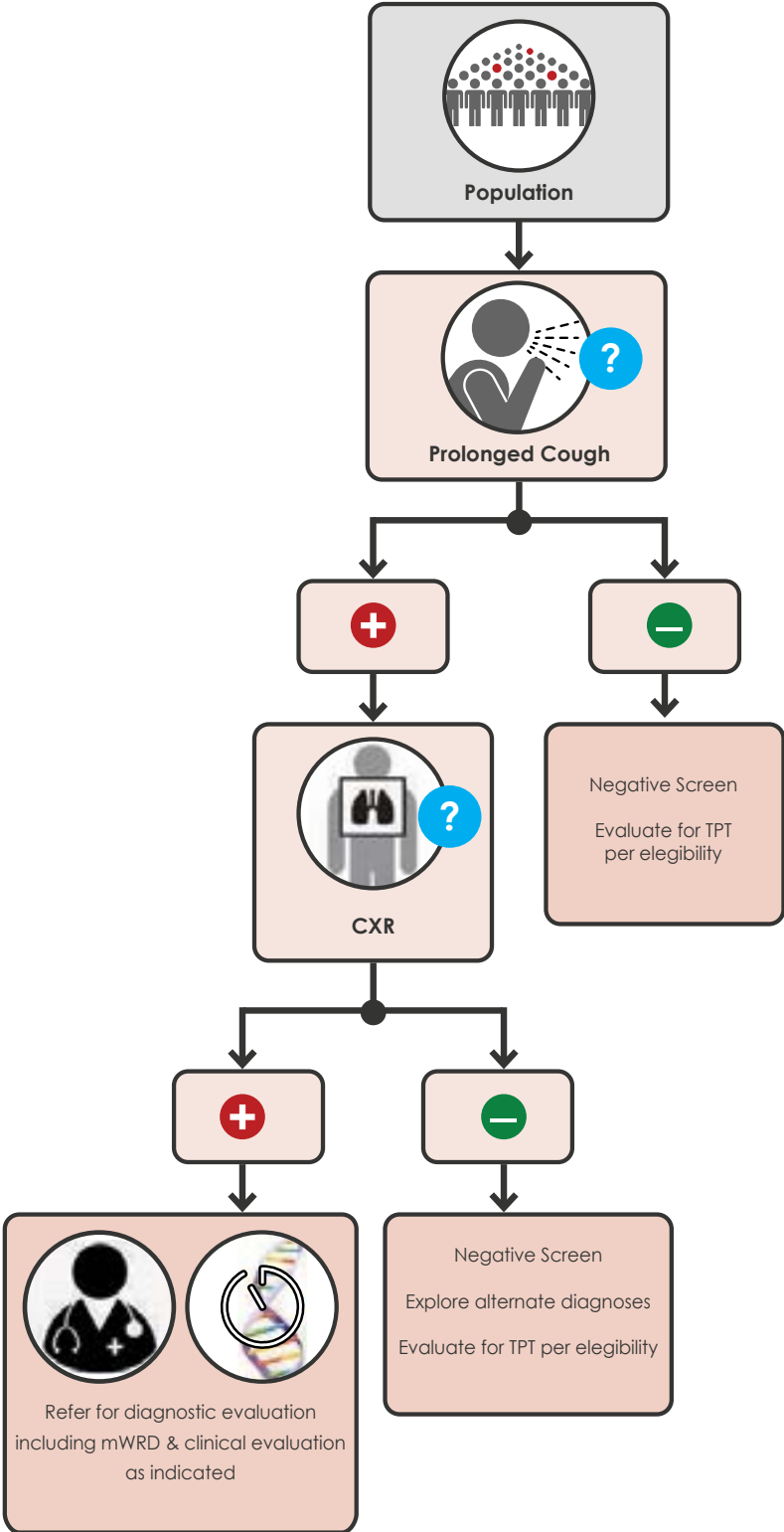
Fig. A.1.4 – Sequential negative serial screening with cough and CXR

Population

Prolonged Cough ?

➕ ➖

CXR ?

➕ ➖

Refer for diagnostic evaluation including mWRD & clinical evaluation as indicated

Negative Screen

Evaluate for TPT per elegibility
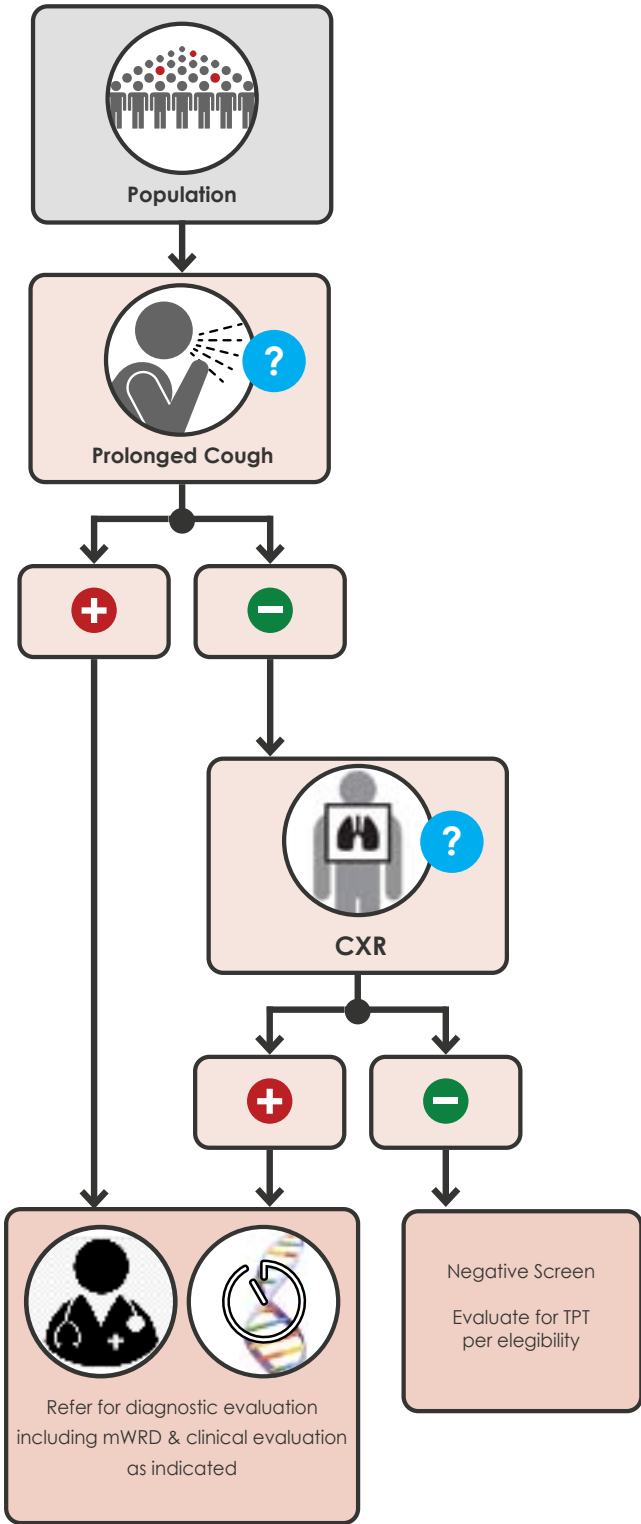
Fig. A.1.5 – Screening with any TB symptom

Fig. A.1.6 – Parallel screening with any TB symptom and CXR

Fig. A.1.7 – Sequential positive serial screening with any TB symptom and CXR

Population

TB Symptoms

+ / −

CXR

Negative Screen

Evaluate for TPT per elegibility

+ / −

Refer for diagnostic evaluation including mWRD & clinical evaluation as indicated

Negative Screen

Explore alternate diagnoses

Evaluate for TPT per elegibility

Fig. A.1.8 – Sequential negative serial screening with any TB symptom and CXR

Fig. A.1.9 – Screening with CXR

Fig. A.1.10 – Screening with mWRD

Population

mWRD

?

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Refer for diagnostic evaluation to assess for clinical manifestations of TB disease.

Explore alternate diagnoses if patient has been treated for TB in past 5 years.

Negative Screen

Evaluate for TPT per eligiblity
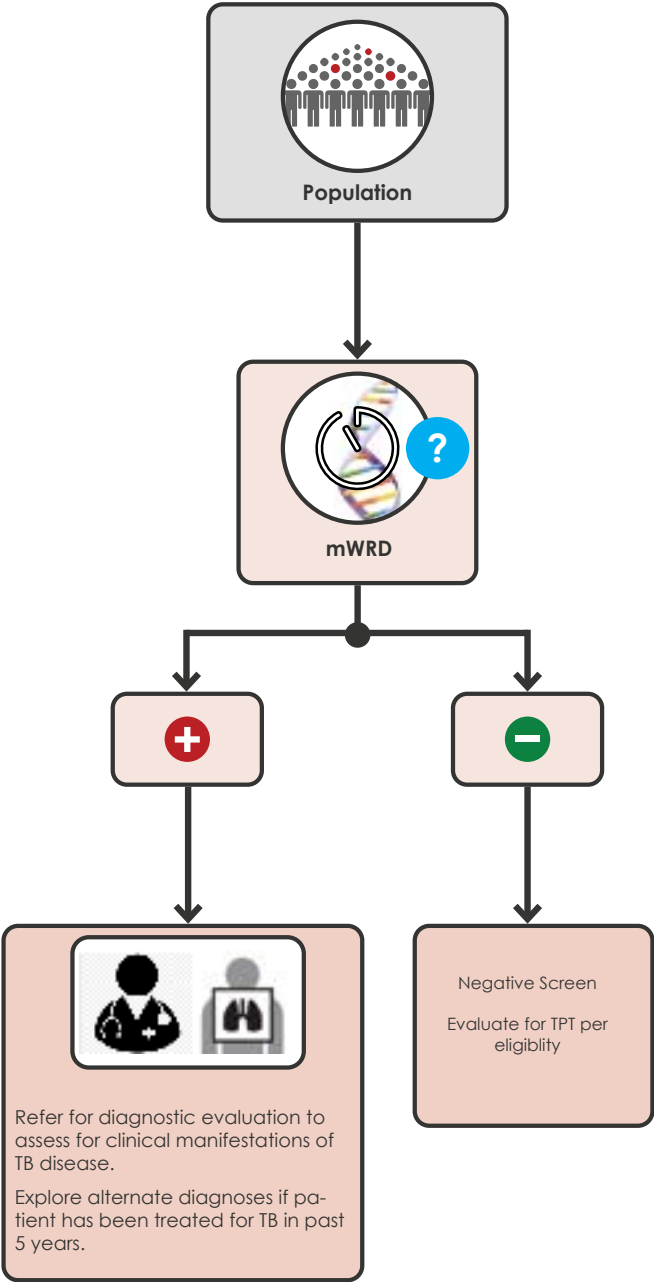
Annex 2 Comparative performance of algorithms for the general population and high-risk groups (not including people living with HIV)

The tables below contain modelled estimates of the performance and outcomes of the 10 screening algorithms described above, when applied to a population of 100,000 people being screened, across three different TB prevalence settings: 0.5%, 1% and 2%.

1 – Screening with cough

2 – Parallel screening with cough and CXR

3 – Sequential positive serial screening with cough and CXR

4 – Sequential negative serial screening with cough and CXR
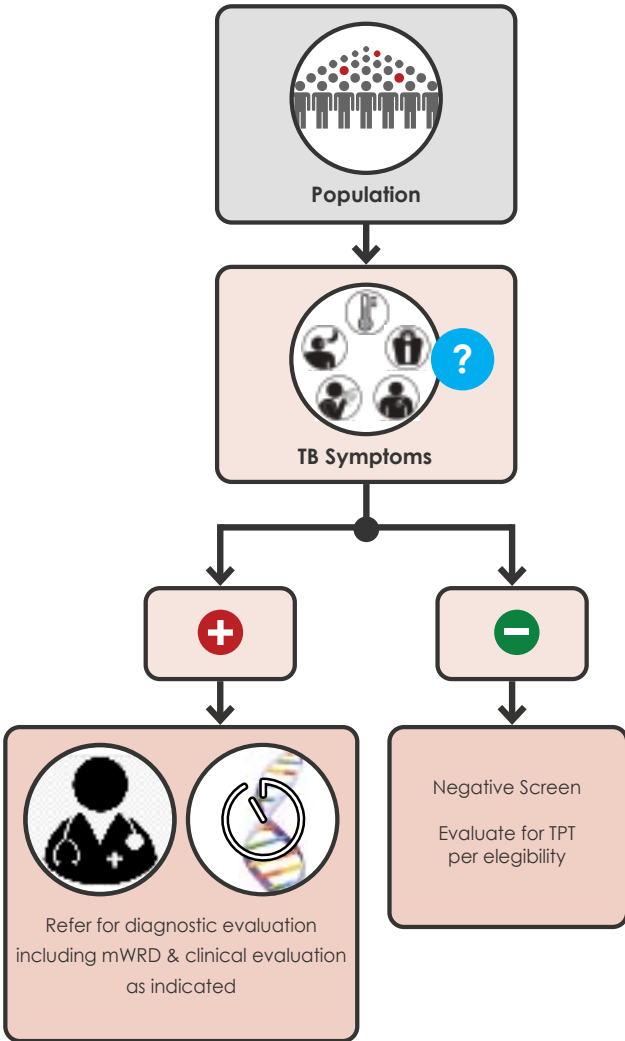
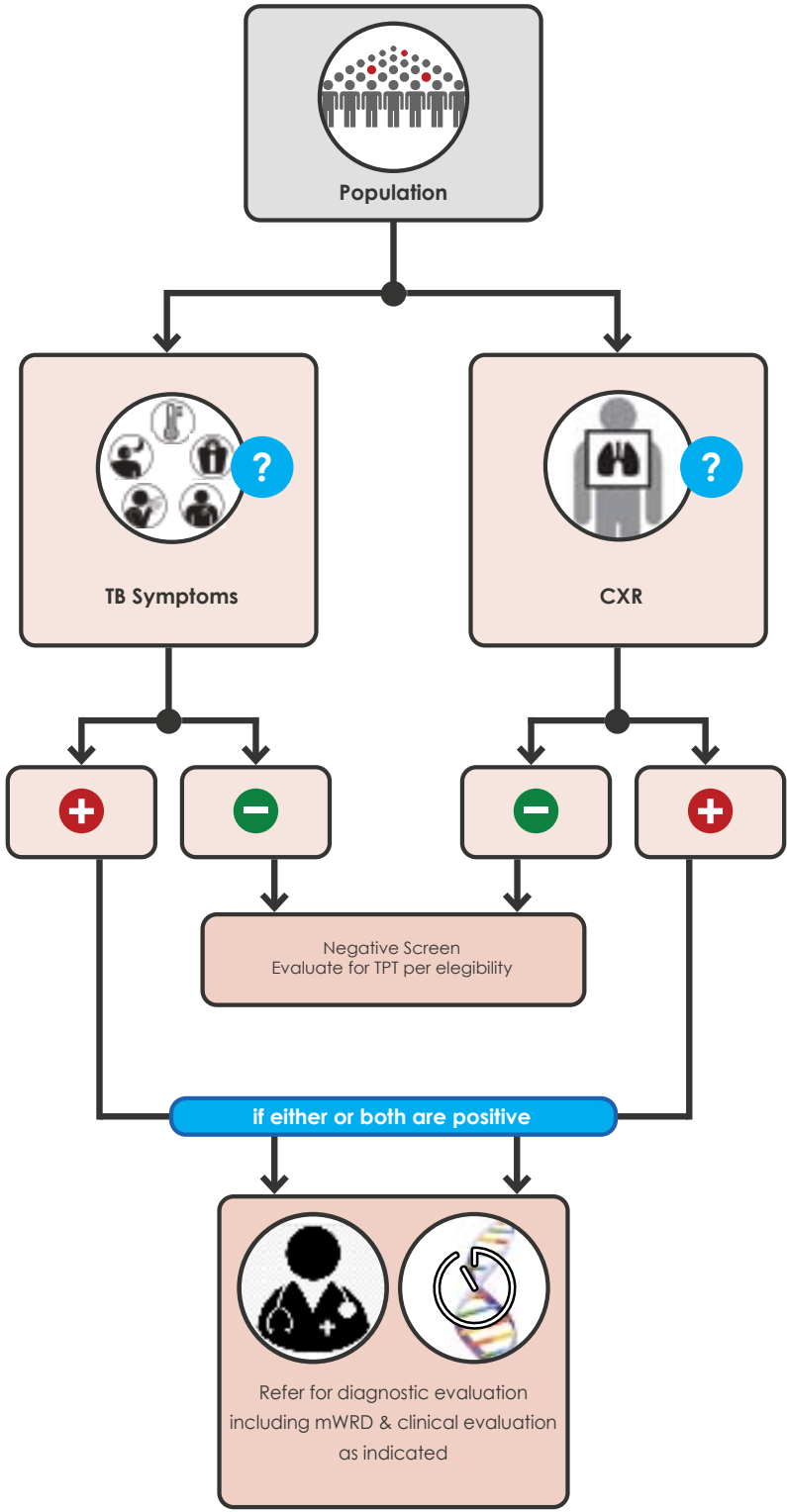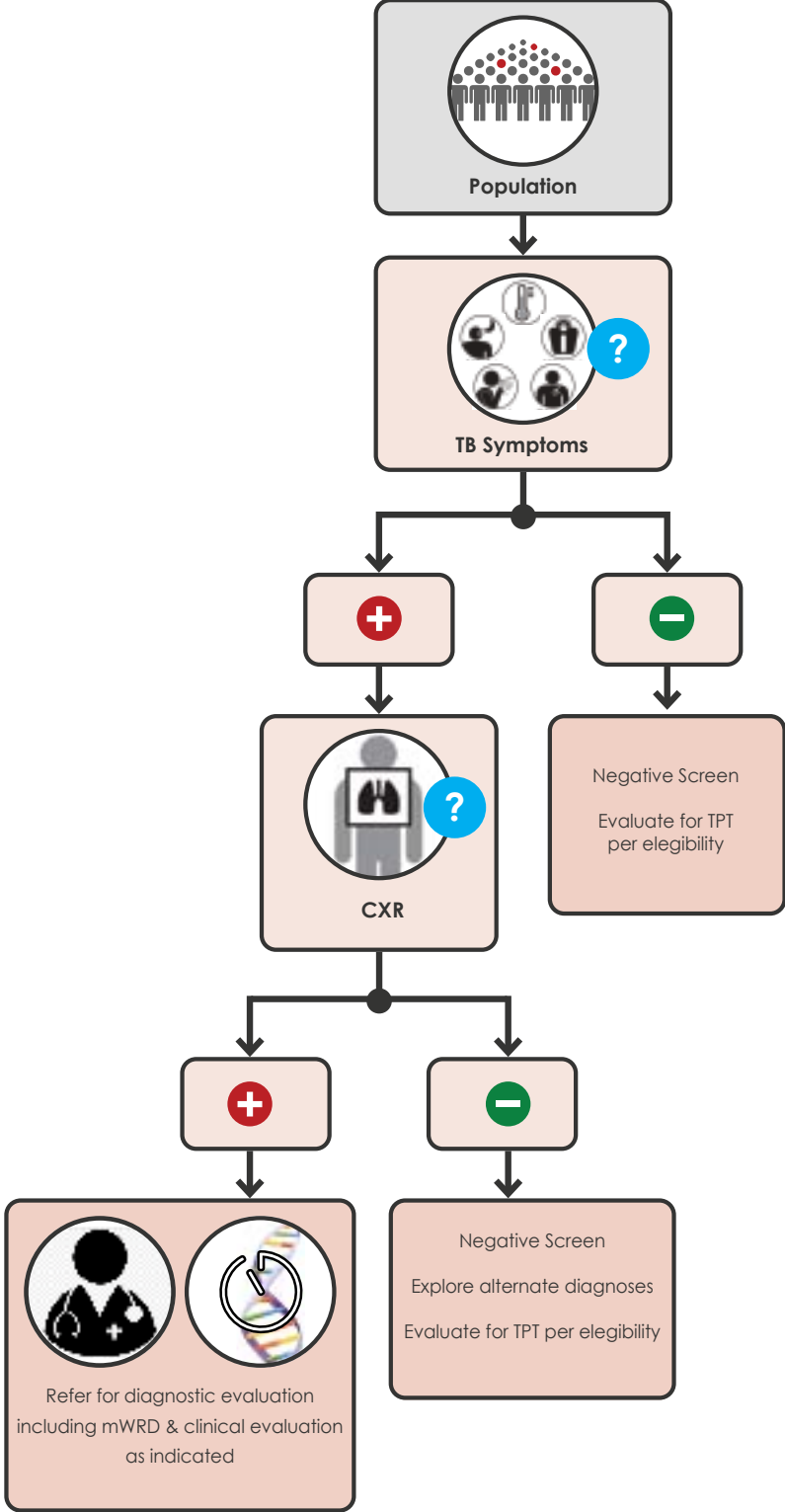5 – Screening with any TB symptom

6 – Parallel screening with any TB symptom and CXR

7 – Sequential positive serial screening with any TB symptom and CXR

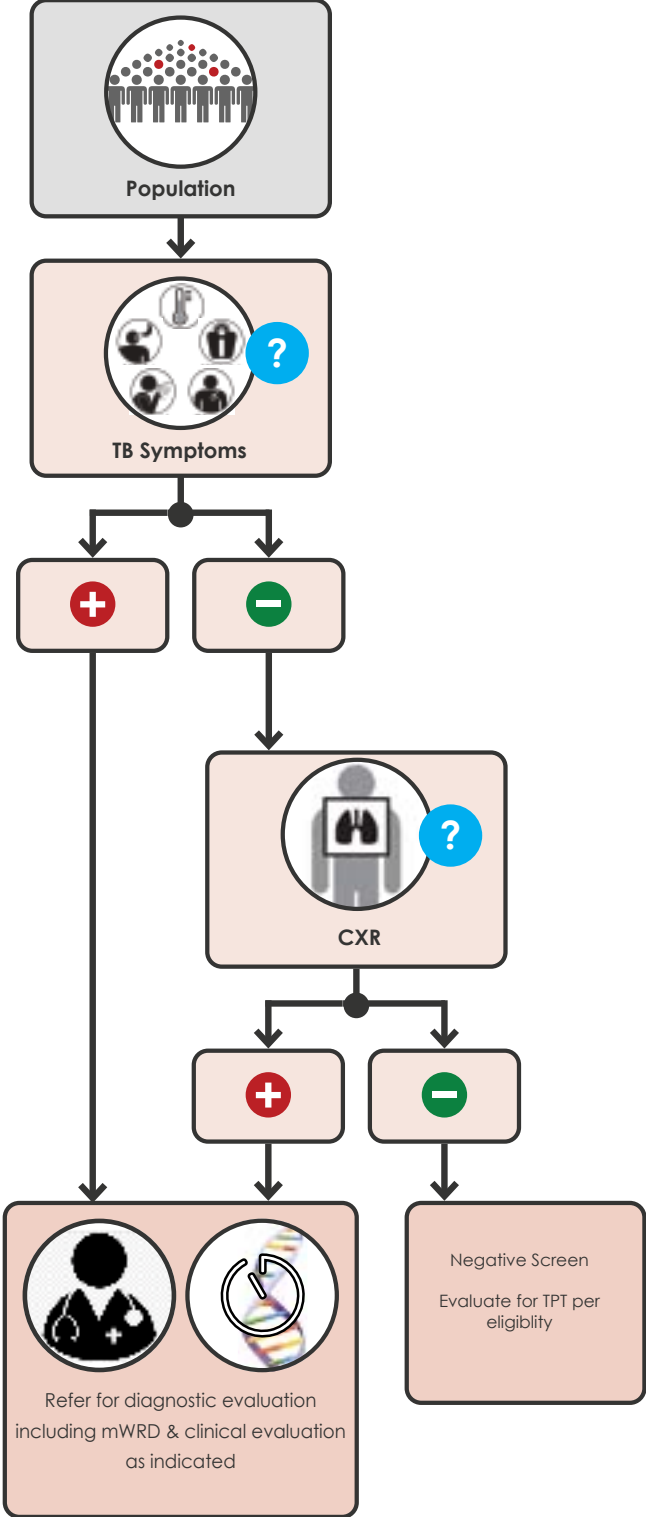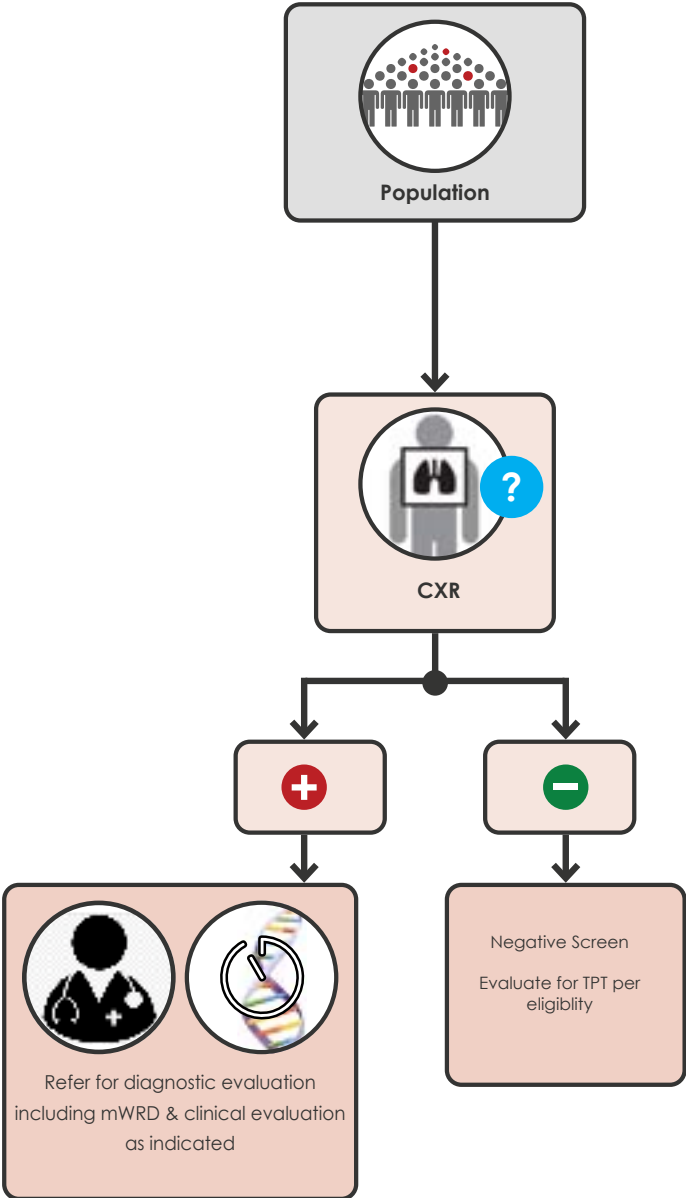8 – Sequential negative serial screening with any TB symptom and CXR

9 – Screening with CXR followed by mWRD

10 – Screening with mWRD followed by diagnostic exam (consisting of repeated mWRD, CXR, other clinical tests and procedures as indicated)

Table A.2.1 100 000 people screened with 0.5% TB prevalence (with 500 prevalent TB cases)

Algorithm	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV
1	179	113	321	99 387	36%	61.1%	99.7%
2	422	313	78	99 187	84%	57.4%	99.9%
3	170	62	330	99 438	34%	73.4%	99.7%
4	422	313	78	99 187	84%	57.4%	99.9%
5	301	722	199	98 788	60%	29.4%	99.8%
6	424	324	76	99 176	85%	56.7%	99.9%
7	286	392	214	99 108	57%	42.2%	99.8%
8	424	324	76	99 176	85%	56.7%	99.9%
9	402	222	98	99 278	80%	64.4%	99.9%
10	345	527	155	98 973	69%	39.5%	99.8%

Table A.2.2 100 000 people screened with 1% TB prevalence (with 1000 prevalent TB cases)

Algorithm	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV
1	357	113	643	98 887	36%	76.0%	99.4%
2	843	312	157	98 688	84%	73.0%	99.8%
3	339	61	661	98 939	34%	84.7%	99.3%
4	843	312	157	98 688	84%	73.0%	99.8%
5	602	718	398	98 282	60%	45.6%	99.6%
6	848	322	152	98 678	85%	72.5%	99.8%
7	572	390	428	98 610	57%	59.5%	99.6%
8	848	322	152	98 678	85%	72.5%	99.8%
9	803	221	197	98 779	80%	78.5%	99.8%
10	690	525	310	98 475	69%	56.8%	99.7%

Table A.2.3 100 000 people screened with 2% TB prevalence (with 2000 prevalent TB cases)

Algorithm	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV
1	714	112	1286	97 888	36%	86.5%	98.7%
2	1687	308	313	97 692	84%	84.5%	99.7%
3	678	61	1322	97 939	34%	91.8%	98.7%
4	1687	308	313	97 692	84%	84.5%	99.7%
5	1204	711	796	97 289	60%	62.9%	99.2%
6	1696	319	304	97 681	85%	84.2%	99.7%
7	1143	386	857	97 614	57%	74.8%	99.1%
8	1696	319	304	97 681	85%	84.2%	99.7%
9	1607	218	394	97 782	80%	88.0%	99.6%
10	1380	519	620	97 481	69%	72.7%	99.4%

TP – True positive diagnosis

FP – False positive diagnosis

FN – False negative diagnosis

TN – True negative diagnosis

PPV – Positive predictive value

NPV – Negative predictive value

Annex 3 Screening algorithms for adults and adolescents living with HIV

Illustrations of 11 possible screening algorithms for people living with HIV.

Fig. A.3.1 – W4SS single screening algorithm
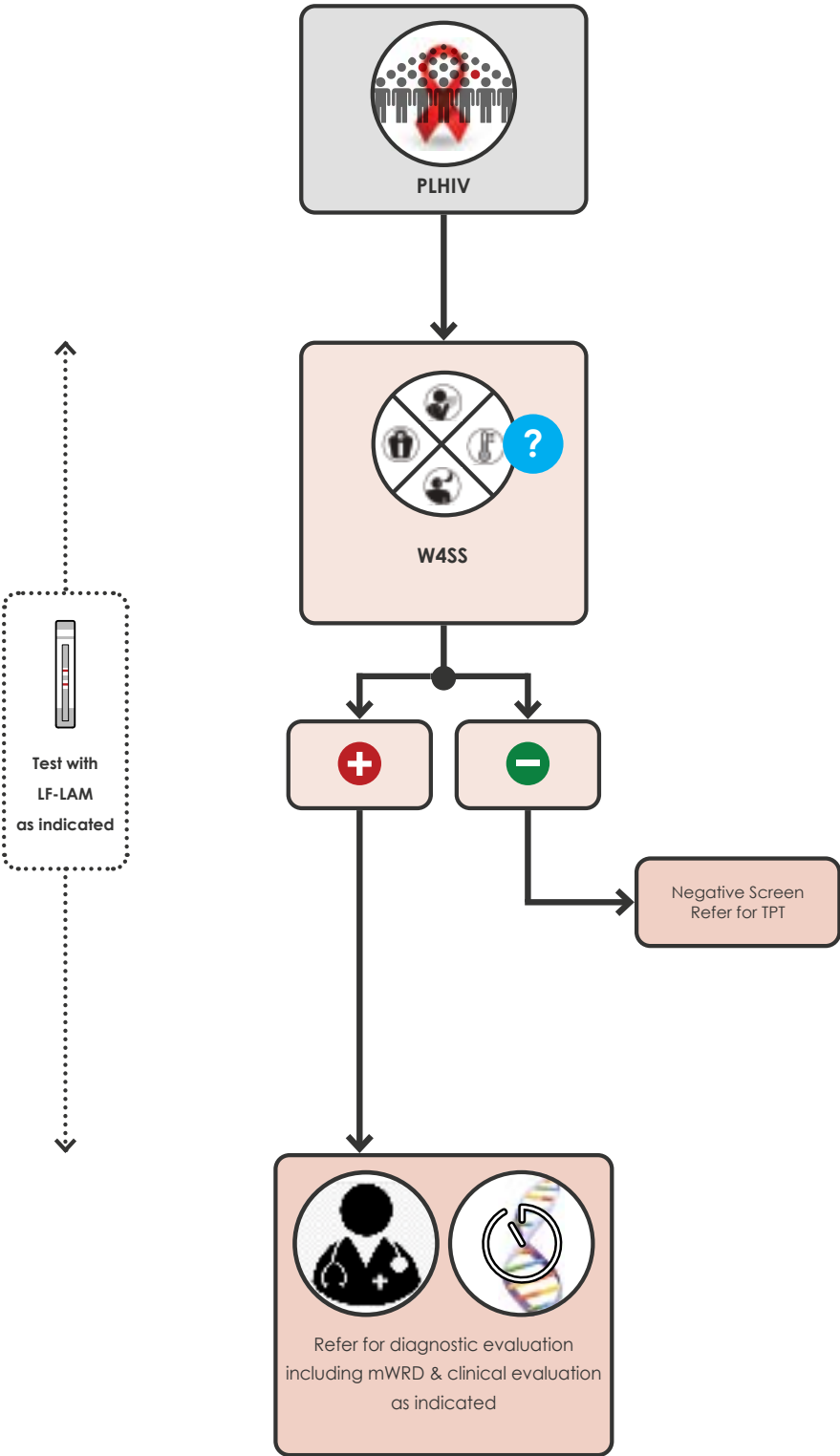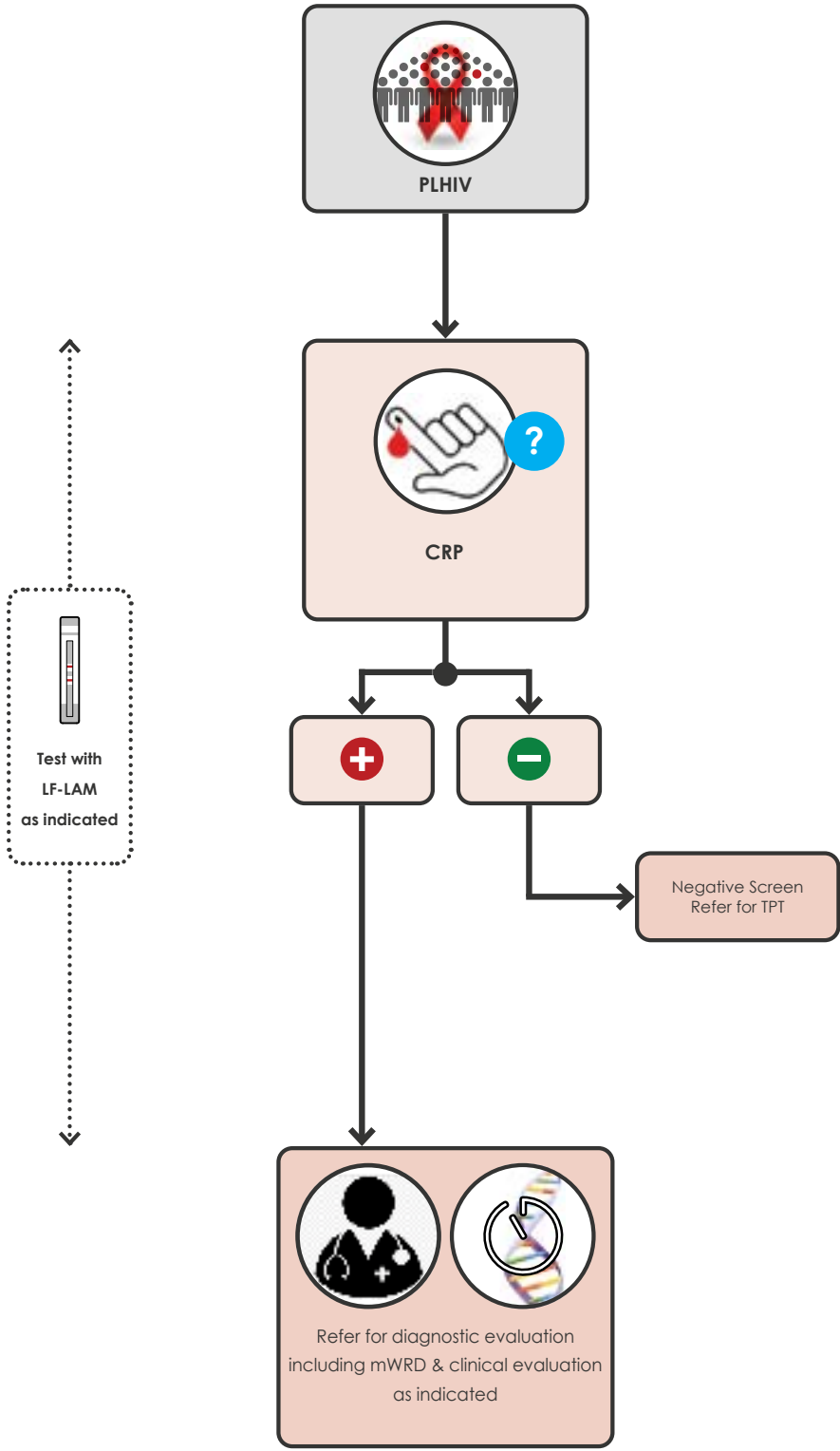
PLHIV

W4SS

Test with
LF-LAM
as indicated

➕

➖

Negative Screen
Refer for TPT

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Fig. A.3.2 – CRP single screening algorithm

PLHIV

CRP

Test with
LF-LAM
as indicated

+

−

Negative Screen
Refer for TPT

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Fig. A.3.3 – CXR single screening algorithm

PLHIV

CXR

?

Test with
LF-LAM
as indicated

+

−

Negative Screen
Refer for TPT

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

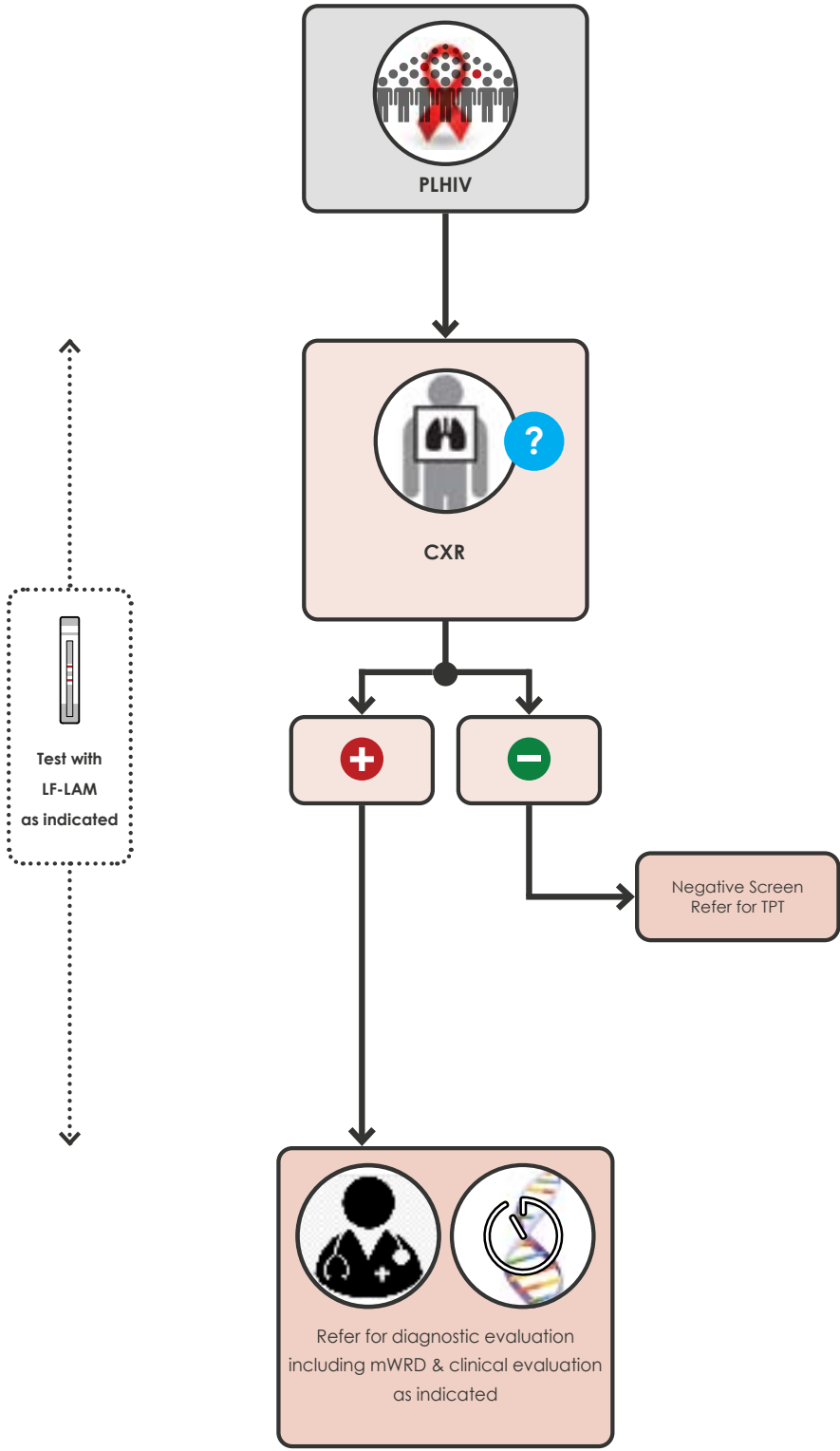# Fig. A.3.4 – Parallel screening algorithm with W4SS and CRP

Fig. A.3.5 – Sequential positive screening algorithm with W4SS and CRP

PLHIV

W4SS

? **+** **−**

Negative Screen
Refer for TPT

Test with
LF-LAM
as indicated

CRP

? **+** **−**

Negative Screen
Explore alternate diagnoses
Refer for TPT

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

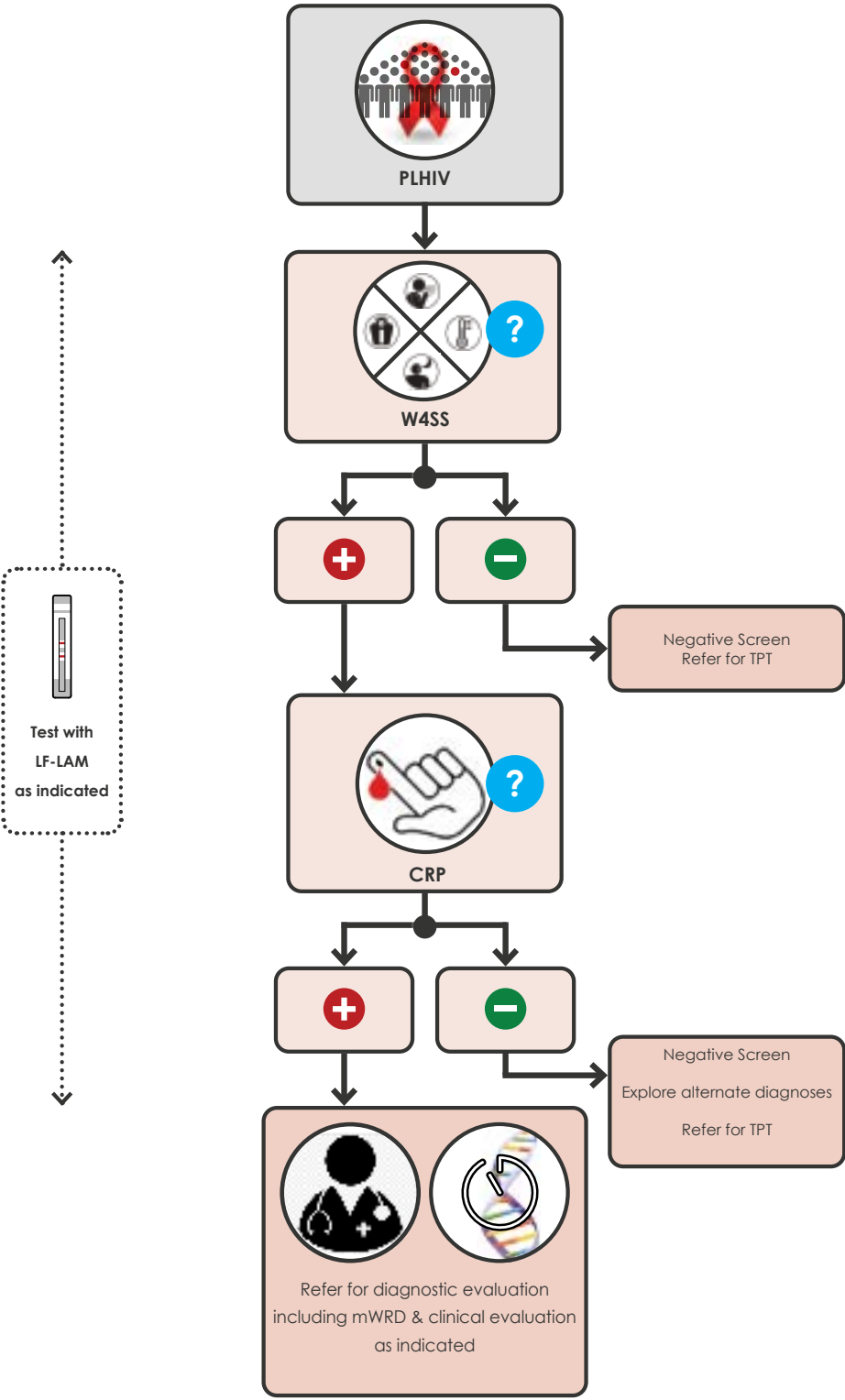# Fig. A.3.6 – Sequential negative screening algorithm with W4SS and CRP

Fig. A.3.7 – Parallel screening algorithm with W4SS and CXR

PLHIV

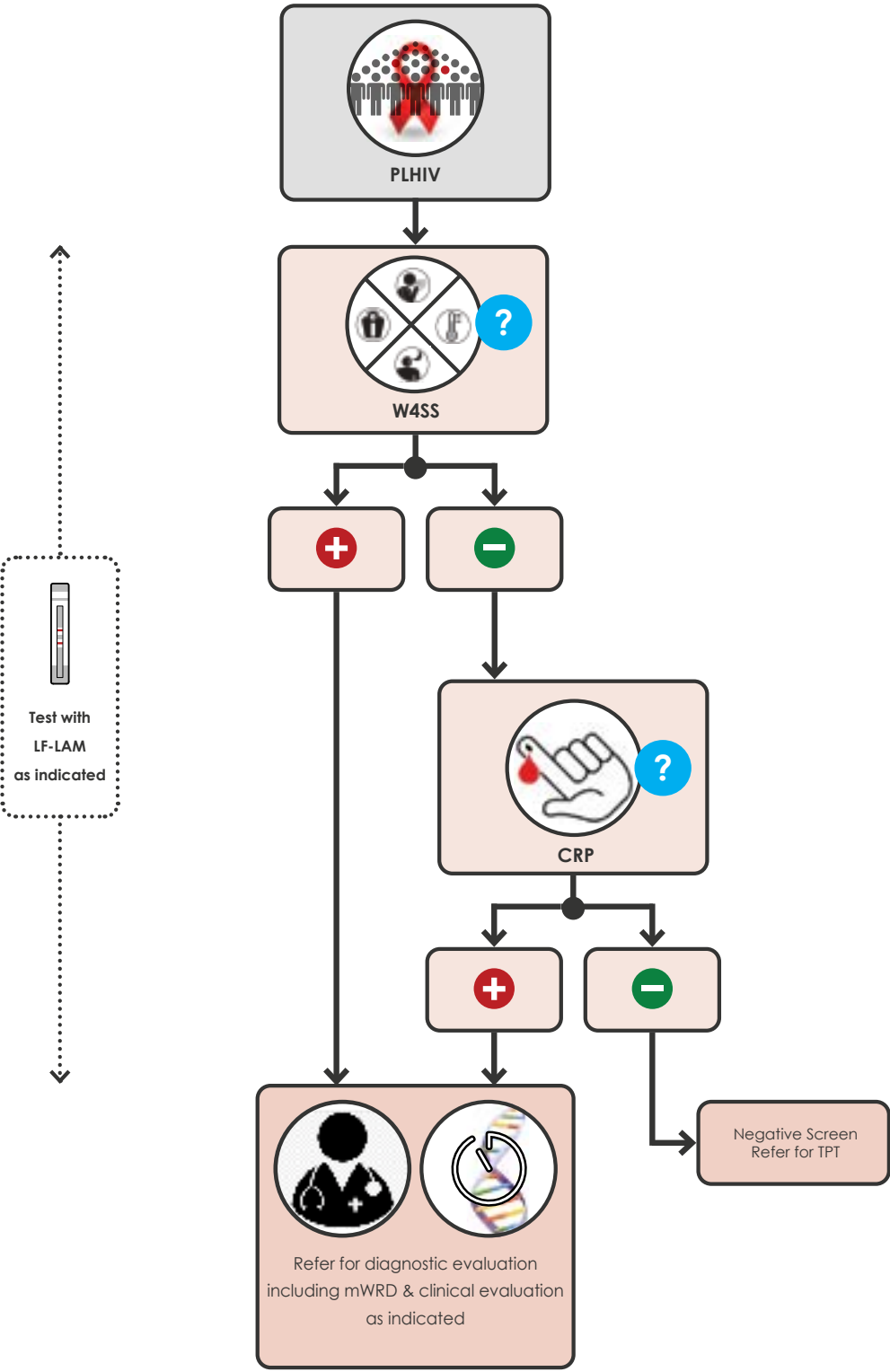Test with LF-LAM as indicated

CXR

W4SS

Negative Screen
Refer for TPT

if either or both are positive

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Fig. A.3.8 – Sequential positive screening algorithm with W4SS and CXR

PLHIV

W4SS ?

+ −

Negative Screen
Refer for TPT

CXR ?

+ −

Negative Screen
Explore alternate diagnoses
Refer for TPT

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Test with
LF-LAM
as indicated

Fig. A.3.9 – Sequential negative screening algorithm with W4SS and CXR

Test with
LF-LAM
as indicated

PLHIV

W4SS

CXR

Refer for diagnostic evaluation
including mWRD & clinical evaluation
as indicated

Negative Screen
Refer for TPT

Fig. A.3.10 – mWRD single screening algorithm for medical inpatients in settings with TB prevalence > 10%

PLHIV

mWRD ?

⊕

⊖

Assess for clinical manifestations of TB disease.

Explore alternate diagnoses if patient has been treated for TB in past 5 years.

Test with LF-LAM if indicated

Explore alternate diagnoses

Refer for TPT if TB disease ruled out

Fig. A.3.11 – mWRD single screening algorithm for people living with HIV

PLHIV

mWRD

?

Test with
LF-LAM
as indicated

➕

➖

Refer for diagnostic evaluation to assess for clinical manifestations of TB disease.

Explore alternate diagnoses if patient has been treated for TB in past 5 years.

Negative Screen
Refer for TPT

Annex 4 Comparative performance of algorithms for adults and adolescents living with HIV

The tables below contain modelled estimates of the performance and outcomes of the screening algorithms described in Annex 3, when applied to different subpopulations of people living with HIV: outpatients not on ART, outpatients on ART, and inpatients. For each subpopulation, a model is presented of 1,000 persons being screened with a representative TB prevalence. The models were informed by the results of the IPD analysis that was commissioned to evaluate the performance of the W4SS and alternative screening tools in people living with HIV.

Table A.4.1 Screening 1000 outpatients living with HIV not enrolled on antiretroviral treatment (ART) with a TB prevalence of 5%

Algorithm	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV
1	32	12	19	938	63%	72%	98%
2	33	9	17	941	67%	79%	98%
3	26	7	24	943	53%	78%	98%
4	36	16	14	934	72%	70%	99%
5	29	5	21	945	59%	85%	98%
6	36	16	14	934	72%	70%	99%
7	35	15	15	935	71%	70%	98%
8	24	6	26	944	48%	81%	97%
9	35	15	15	935	71%	70%	98%
11	36	19	14	931	72%	65%	99%

Table A.4.2 Screening 1000 outpatients living with HIV on antiretroviral treatment (ART) with a TB prevalence of 1%

#	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV
1	4	12	6	978	41%	26%	99%
2	3	8	7	982	31%	28%	99%
3	5	15	5	975	54%	27%	100%
4	2	8	8	982	15%	16%	99%
5	1	0	9	990	6%	61%	99%
6	2	8	8	982	15%	16%	99%
7	7	27	3	963	65%	20%	100%
8	4	7	6	983	38%	35%	99%
9	7	27	3	963	65%	20%	100%
11	4	0	6	990	42%	91%	99%

Table A.4.3 Screening 1000 inpatients living with HIV with a TB prevalence of 10%

Algorithm	TP	FP	FN	TN	% of prevalent cases detected	PPV	NPV	NNS
W4SS followed by mWRD (1)	74	56	26	844	74%	57%	97%	14
mWRD (10)	77	63	23	837	77%	55%	97%	13

WHO operational handbook on tuberculosis: systematic screening for tuberculosis disease

Annex 5 Screening algorithms for children

Illustrations of 6 possible screening algorithms for children (Fig A.5.1 - A.5.5 for child contacts and Fig. A.5.6 for children <10 years living with HIV).

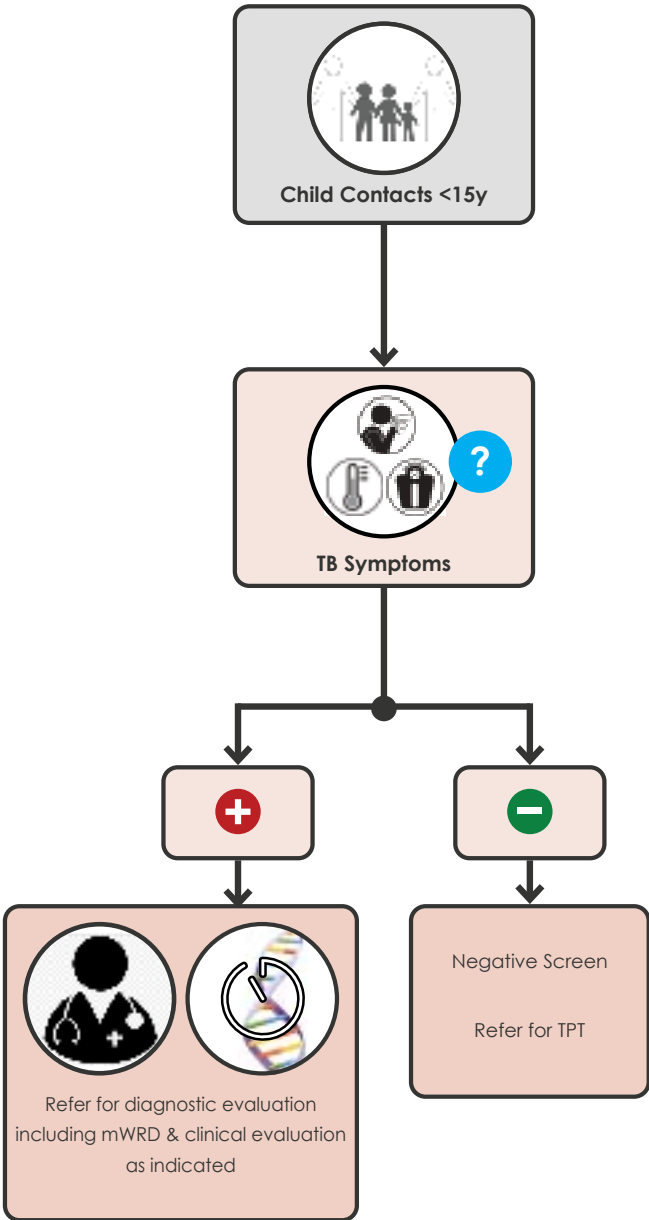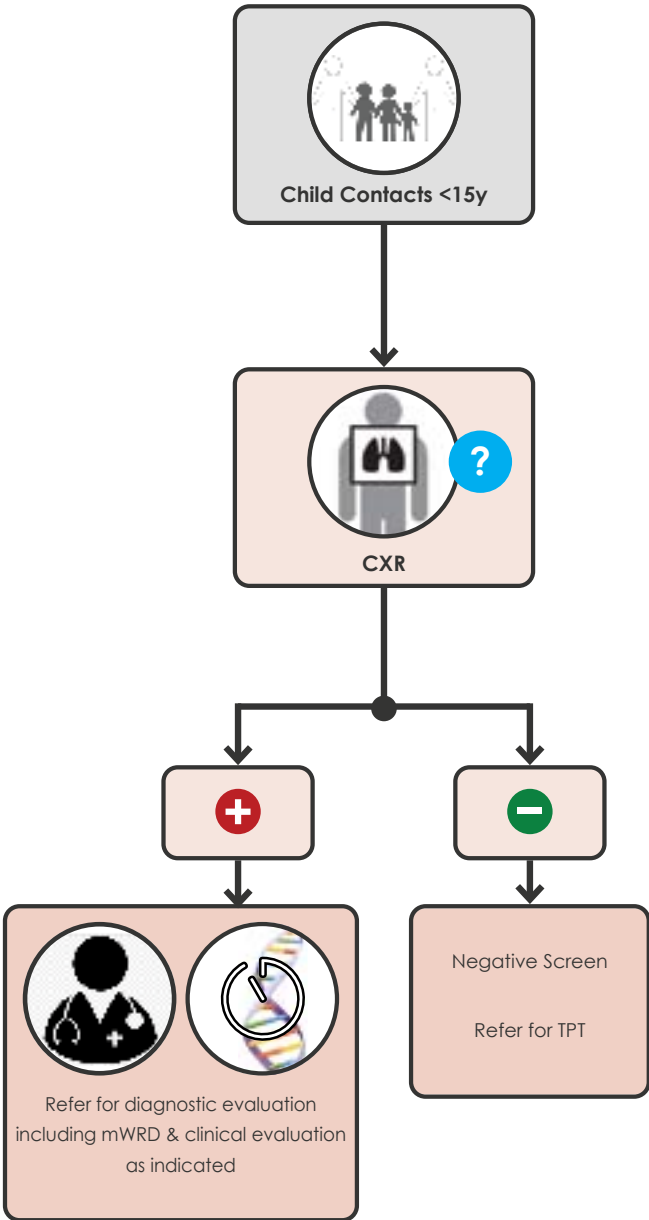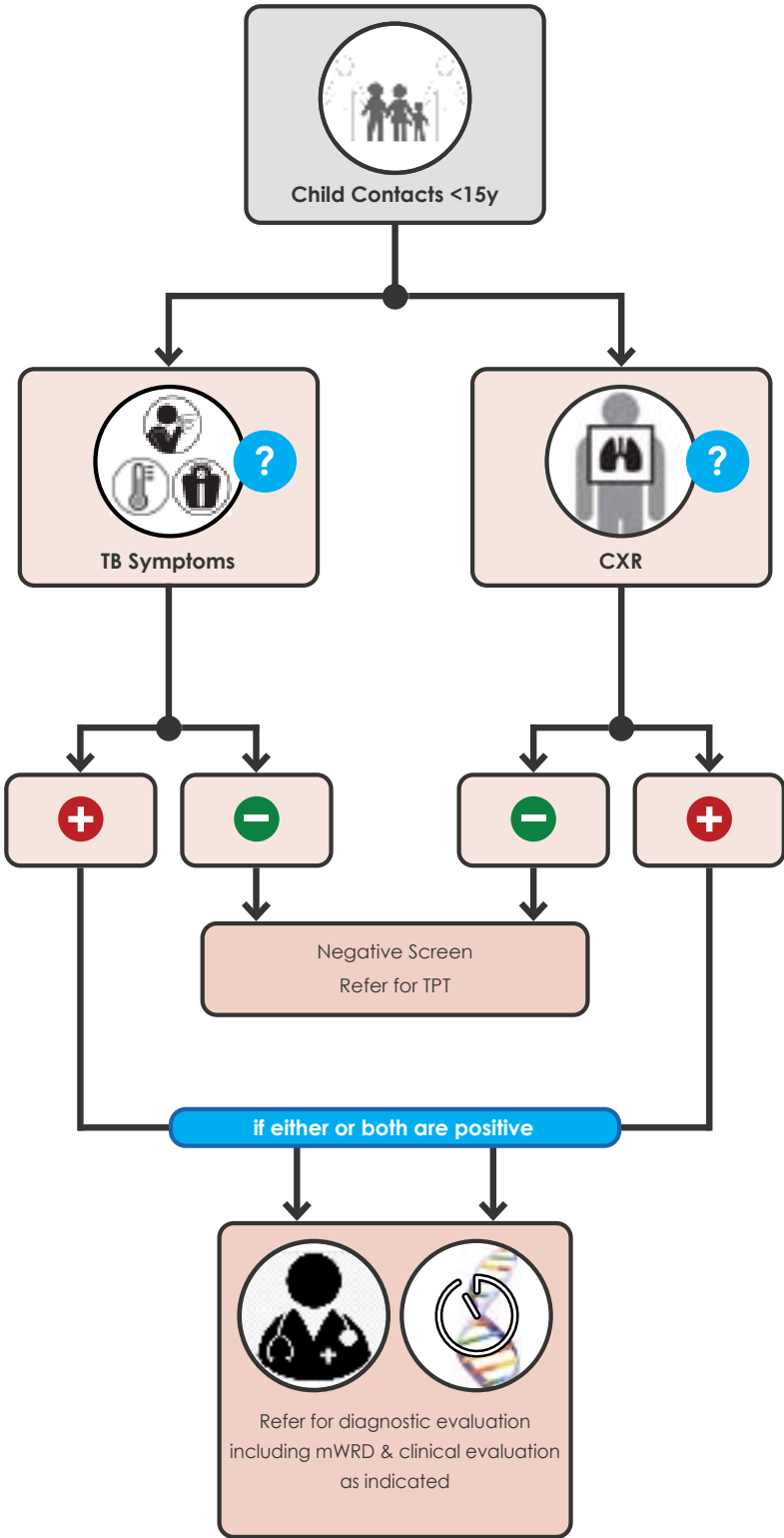# Fig. A.5.1 – Screening with symptoms

Fig A.5.2 – Screening with CXR

Fig. A.5.3 – Parallel screening with symptoms and CXR

Fig. A.5.4 – Sequential positive serial screening with symptoms and CXR

Child Contacts <15y

TB Symptoms

+ → CXR

− → Negative Screen
Refer for TPT

+ → Refer for diagnostic evaluation including mWRD & clinical evaluation as indicated

− → Negative Screen
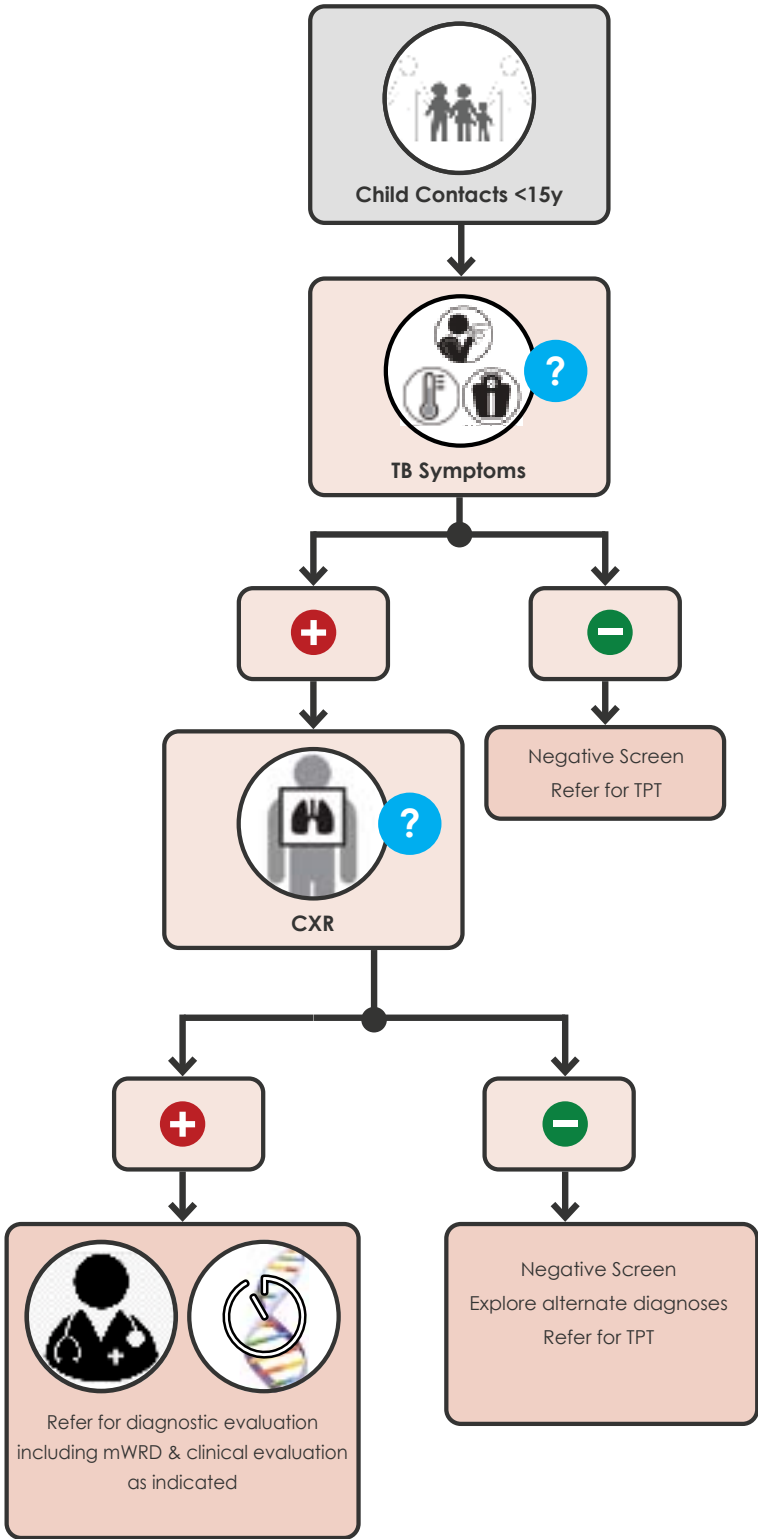Explore alternate diagnoses
Refer for TPT

Fig. A.5.5 – Sequential negative serial screening with symptoms and CXR
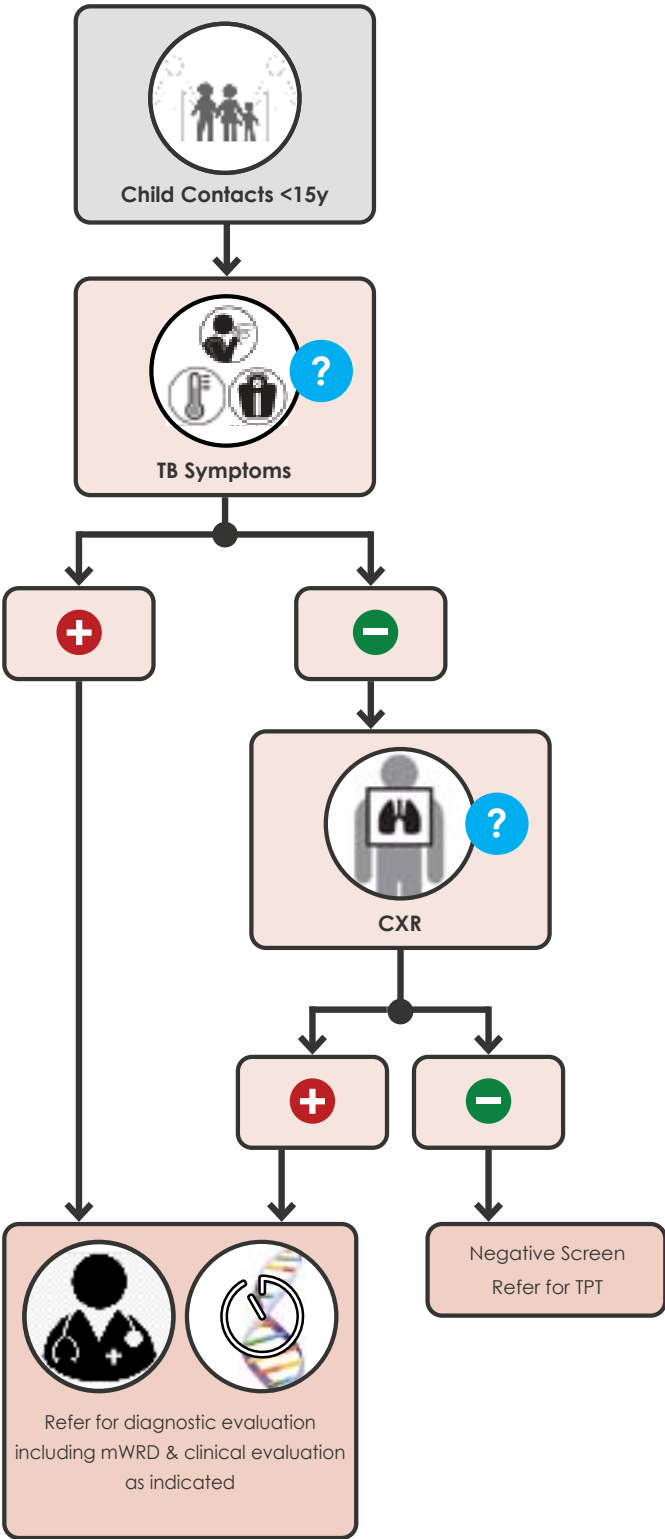
Fig. A.5.6 – Screening with symptoms (for children living with HIV < 10 years)

Children Living with HIV <10y

TB Symptoms

➕ ➖

Refer for diagnostic evaluation including mWRD & clinical evaluation as indicated

Negative Screen Refer for TPT
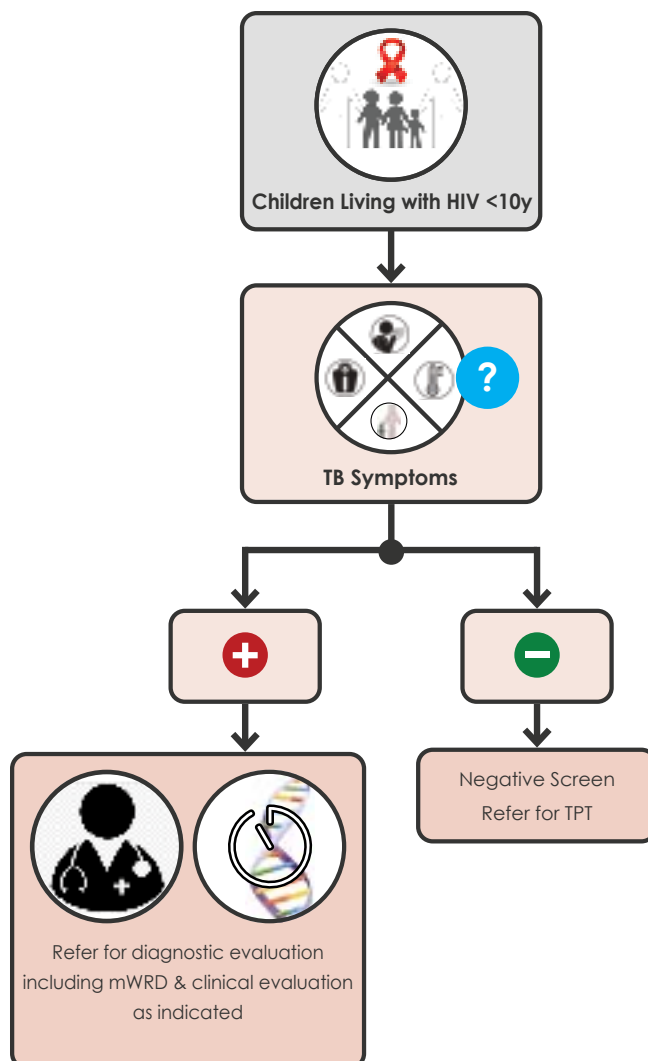
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Web site: www.who.int/tb

World Health Organization

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