



Systematic screening for active tuberculosis: *an operational guide*



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Additional information available online: <http://who.int/tb/tbscreening/en/>

- Tool to assist with prioritization of risk groups for screening and choice of algorithm
- Systematic screening for active tuberculosis: principles and recommendations
- Checklists for screening in specific risk groups
- Systematic reviews:
 - The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review
 - A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status
 - A systematic review of number needed to screen to detect a case of active tuberculosis in different risk groups
 - Acceptability of TB screening among at-risk and vulnerable groups
 - Acceptability of household and community-based TB screening in high burden communities

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Definitions

Active tuberculosis

Active tuberculosis (TB) refers to disease that occurs in someone infected with *Mycobacterium tuberculosis*. It is characterized by signs or symptoms of active disease, or both, and is distinct from latent TB infection, which occurs without signs or symptoms of active disease.

Active tuberculosis case-finding

Active case-finding is synonymous with systematic screening for active TB, although it normally implies screening that is implemented outside of health facilities.

Number needed to screen

The number needed to screen (or NNS) is the number of people that need to undergo screening to diagnose one person with active TB.

Passive tuberculosis case-finding

This is a patient-initiated pathway to TB diagnosis involving: (1) a person with active TB experiencing 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 suspected TB; and (4) the successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB. Passive case-finding may involve an element of systematic screening if the identification of people with suspected TB is done systematically for all people seeking care in a health facility or clinic.

Risk groups

A risk group is 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 active tuberculosis

A test, examination or other procedure for active tuberculosis distinguishing people with a high likelihood of having active TB from people who are highly unlikely to have active TB. A screening test is not intended to be diagnostic. People with positive results on a screening test should undergo diagnostic evaluation.

Second screening

A second screening test, examination or other procedure applied to persons whose results were positive during the initial screening.

Systematic screening for active TB

Systematic screening for active TB is the systematic identification of people with suspected (presumptive) active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly. Among those screened positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.

Abbreviations

CXR	chest X-ray
HIV	human immunodeficiency virus
NNS	number needed to screen (to detect one true case of active tuberculosis)
PPV	positive predictive value
TB	tuberculosis
WHO	World Health Organization

Executive summary

More than one third of the 9 million people who fall ill with tuberculosis (TB) each year are not diagnosed, not notified, or do not start treatment. Many of those who do start treatment have a delayed start due to a range of challenges.^{1,2} Such obstacles to receive care can result in poor health outcomes for the affected individuals, catastrophic costs for their families and continued transmission of TB to others in their communities. In addition, the individuals and communities at highest risk of falling ill with TB are often those with the least access to health care and treatment for the disease, further compounding the negative effects of the disease.

These barriers to care, coupled with the magnitude and persistence of the global TB burden, argue for a redoubling of efforts to ensure early identification of and treatment for all people with TB.³ To this end, the systematic screening of those at high risk for TB is a key component of the World Health Organization's (WHO) *End TB strategy, 2016 to 2035*.^{4,5}

Like all case-finding strategies, systematic screening for TB has three primary goals:

1. to ensure the early detection and initiation of appropriate treatment for those with active TB;
2. to reduce the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB; and
3. to reduce transmission of TB, with the ultimate goal of reducing future incidence.

The WHO has published guidelines that set out the principles for screening for active TB and provide recommendations on prioritizing of risk groups and choosing a screening approach.⁶ Screening should not be done on a mass, indiscriminate scale because this is expensive, of relatively low benefit and can result in many false positive results. One of the key principles set out in the guidelines is that screening for TB needs to be properly targeted to high-risk groups and tailored to each specific situation, depending on the epidemiological, social and health-systems contexts.

This document provides practical guidance on translating WHO's principles and recommendations into a national or local screening strategy by:

1. assessing the situation;
2. defining the objectives of screening;
3. prioritizing risk groups for screening;
4. choosing screening tools, algorithms and approaches for each risk group;
5. planning and budgeting for, and implementing the strategy;
6. monitoring and evaluating the strategy.

The guide includes a description of a web-based tool that can be used to help identify and prioritize risk groups and chose appropriate screening and diagnostic algorithms. The tool is designed to assist with the initial planning stages of creating a targeted screening strategy, but several other factors than those covered by the tool need to be considered in the planning process. This guide also includes additional online material, including other tools and references to assist with planning and implementing screening programmes.

1. Introduction

1.1 Rationale for systematic screening for active TB

Concerted efforts during the past two decades – first under the DOTS strategy and later the Stop TB Strategy – have made remarkable worldwide progress in controlling tuberculosis (TB) and caring for patients with TB.³ However, millions of patients ill with TB are still not notified to public health authorities, and the declines in TB deaths and incidence are still too slow. These call for a redoubling of efforts for early identification and treatment of all cases of TB, as envisioned in WHO’s End TB Strategy approved by the World Health Assembly in 2014.^{4,5}

Of the estimated 9 million persons who fall ill with TB each year, about 3 million are not diagnosed and registered for quality-assured TB treatment.¹ Additionally, many persons are delayed in seeking care for their illness before they are eventually diagnosed and treated,² and this can lead to worse health outcomes, higher costs for patients and their families, and more transmission of the disease. Therefore, intensifying efforts to increase early case detection is a key component of improving TB care and preventing the disease.

Detecting TB cases only from among persons presenting themselves to health facilities with suggestive symptoms has until recently been the principal approach to case-finding.^{7,8} But the remaining case-detection gap, particularly in certain vulnerable populations, along with the persistence of delays in diagnosis and the accompanying continued transmission in the community, highlight the need for a more active approach to detect TB early, hence the need to consider systematic screening for active TB in selected risk groups.⁹⁻¹⁴

WHO’s End TB Strategy includes systematic screening for active TB in high-risk groups within the first component of Pillar 1, which highlights the need for early diagnosis of TB.^{4,5} The World Health Organization (WHO) has published guidelines that set out the principles for screening for TB and provide recommendations on prioritizing risk groups and choosing screening approaches.⁶ The principles and recommendations are summarized in *Box 1*.

1.2 Pitfalls of screening

One of the key principles set out in the guidelines is that TB screening needs to be tailored to each specific epidemiological, social and health-system situation, and planning for screening must be based on an assessment of these contexts. Pursuing systematic screening without planning properly to target the specific characteristics and needs of certain populations, without assessing system capacity to deliver screening interventions, and without first addressing the known constraints to case detection and treatment, may waste resources without achieving clear individual and public-health benefits.

The cost of screening, especially as an outreach activity, can be high. The opportunity cost must be considered and compared with other efforts to improve early TB detection, such as improving access to diagnostic services. However, well-planned and well-targeted

systematic screening has the potential to minimize avoidable delays in diagnosis and the initiation of treatment. It thereby can contribute to improving the health of individuals as well as reducing TB transmission.

Indiscriminate, mass screening is expensive and has uncertain benefits. Therefore, it should be avoided. Screening low-risk groups can cause more harm than benefit – for example, by detecting more false-positive cases than true-positive cases. After identifying relevant risk groups that potentially may benefit from screening, it is necessary to prioritize those groups with the highest risk. It is also necessary to choose the appropriate screening and diagnostic tests and algorithms for each risk group and for each epidemiological situation.

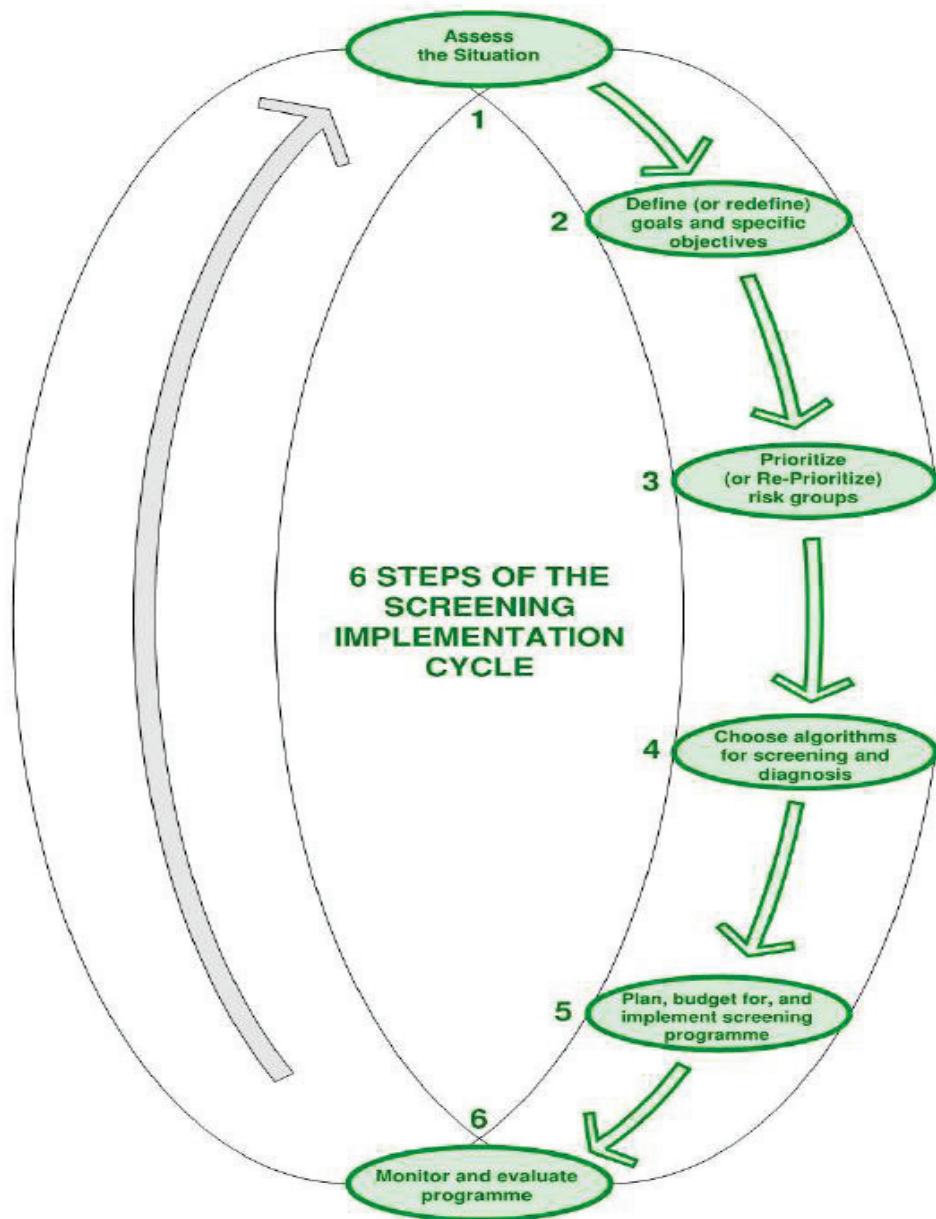
1.5 Objectives of the operational guide

This document provides practical guidance on translating WHO's principles and recommendations for screening into a national or local strategy that sets out clear objectives for screening, prioritizes risk groups, and defines the most appropriate screening approaches. The following essential steps should be pursued:

1. the situation must be assessed;
2. the objectives of screening must be defined;
3. risk groups must be prioritized for screening;
4. screening algorithms and implementation approaches for each risk group must be chosen;
5. a budgeted implementation plan must be developed;
6. the strategy must be monitored and evaluated.

These six steps form a cycle of assessing, planning, implementing, monitoring and evaluating the programme, which then leads to revising the strategy and updating the implementation as necessary. Thus, these six steps are an iterative process that should be continually followed throughout screening and integrated with overall national TB and health systems activities (*Figure 1*).

Figure 1. The six essential steps in the cycle of designing and implementing a tuberculosis screening programme



Key principles of systematic screening for active TB

The following key principles should be considered when planning a TB-screening strategy.

1. Before screening is initiated, high-quality TB diagnosis, treatment, care, management and support for patients should be in place, and there should be the capacity to scale these up further to match the anticipated rise in case detection that may occur as a result of screening. In addition, a baseline analysis should be completed in order to demonstrate that the potential benefits of screening clearly outweigh the risks of doing harm, and that the required investments in screening are reasonable in relation to the expected benefits.
2. Indiscriminate mass screening should be avoided. The prioritization of risk groups for screening should be based on assessments made for each risk group of the potential benefits and harms, the feasibility of the initiative, the acceptability of the approach, the number needed to screen, and the cost effectiveness of screening.
3. The choice of algorithm for screening and diagnosis should be based on an assessment of the accuracy of the algorithm for each risk group considered, as well as the availability, feasibility and cost of the tests.
4. TB screening should follow established ethical principles for screening for infectious diseases, observe human rights, and be designed to minimize the risk of discomfort, pain, stigma and discrimination.
5. The TB screening approach should be developed and implemented in a way that optimizes synergies with the delivery of other health services and social services.
6. A screening strategy should be monitored and reassessed continually to inform re-prioritization of risk groups, re-adaptation of screening approaches when necessary and discontinuation of screening at an appropriate time.

Recommendations on risk groups to screen

Seven recommendations on prioritizing risk groups for screening have been developed. The recommendations are divided into strong recommendations and conditional recommendations.

A **strong recommendation** is one for which the desirable effects of adhering to the recommendation are judged to clearly outweigh the undesirable effects, and for which screening is judged to be feasible, acceptable and affordable in all settings.

A **conditional recommendation** is one for which the desirable effects of adhering to the recommendation probably outweigh the undesirable effects but the trade-offs, cost effectiveness, feasibility or affordability, or some combination of these, are uncertain. Reasons for uncertainty may include:

- a lack of high-quality evidence to support the recommendation;
- high costs or low feasibility or acceptability, or a combination of these.

Strong recommendations

Recommendation 1: Household contacts and other close contacts should be systematically screened for active TB.

Recommendation 2: People living with the human immunodeficiency virus (HIV) should be systematically screened for active TB at each visit to a health facility.

Recommendation 3: Current and former workers in workplaces with silica exposure should be systematically screened for active TB.

Conditional recommendations

Recommendation 4: Systematic screening for active TB should be considered in prisons and other penitentiary institutions.

Recommendation 5: Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion.

Recommendation 6: In settings where the TB prevalence in the general population is 100/100 000 population or higher, systematic screening for active TB should be considered among people who are seeking health care or who are in health care and who belong to selected risk groups.

Recommendation 7: (a) Systematic screening for active TB may be considered for geographically defined subpopulations with extremely high levels of undetected TB (1% prevalence or higher). (b) Systematic screening for active TB may be considered also for other subpopulations that have very poor access to health care, such as people living in urban slums, homeless people, people living in remote areas with poor access to health care, and other vulnerable or marginalized groups, including some indigenous populations, migrants and refugees.

2. The six steps of the planning and implementation cycle

2.1 Assessing the situation

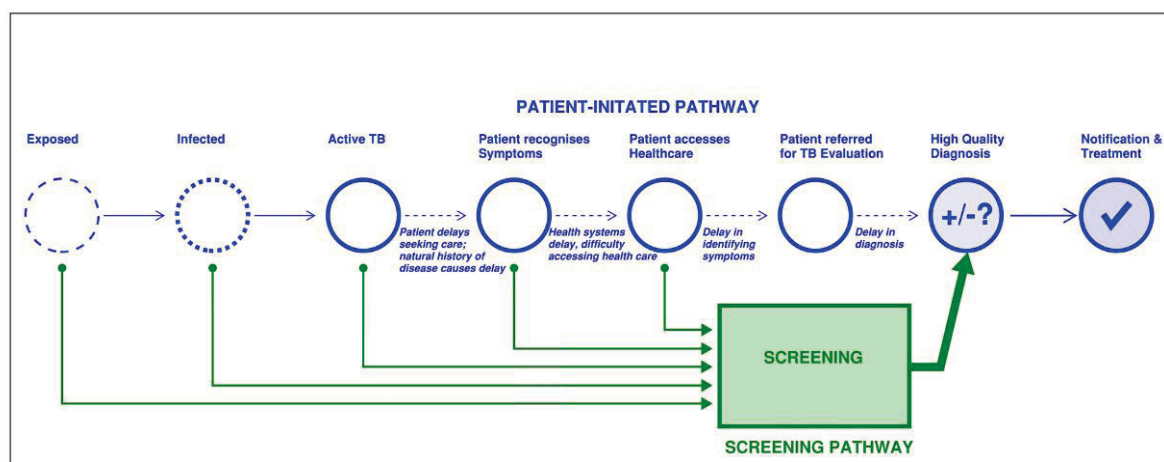
The specific epidemiology of TB in each setting as well as the social and the health-system contexts will inform decisions on a TB screening strategy, including how risk groups are prioritized, which screening approach is chosen, and whether screening in specific risk groups is feasible. Therefore, before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

- 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;
- the social setting – to assess if screening in specific communities or risk groups can be advised given acceptability, safety and stability of the community;
- the national TB programme and the general health-care system – to assess their preparedness for pursuing screening and health worker and facility capacity to manage a potential increase in evaluating, diagnosing, monitoring and treating patients with TB and referral of persons identified with symptoms of other respiratory ailments/health conditions identified during TB screening;
- the coverage and rights of those screened for and those ill with TB – to ensure that all people diagnosed with TB have access to high-quality care and to ensure that they are protected from undue harm as a result of their diagnosis or due to the screening process.

There are two complementary approaches for improving the early detection of TB (Figure 2):

1. enhancing the *patient-initiated pathway* to TB diagnosis; and
2. utilizing the *provider-initiated screening pathway* to TB diagnosis.¹⁶

Figure 2. Comparison of patient-initiated and provider-initiated screening pathways for the diagnosis and treatment of tuberculosis (TB)



2.1.1 Assessing the potential to enhance the patient-initiated pathway to TB diagnosis

The primary approach to enhancing case detection is to optimize the *patient-initiated pathway* to TB diagnosis and treatment. This foundational approach to providing health care may be supplemented in clearly identified settings by systematic screening as a secondary approach along a *provider-initiated pathway*. However, the potential for enhancing early case detection by improving the patient-initiated pathway should be assessed first, and this assessment should include the potential benefits of:

- improving access to care – including reducing the direct and indirect costs to patients associated with seeking care, as well as addressing the specific needs of vulnerable groups by strengthening primary health-care services, providing additional outreach services that cater to these populations, and providing social protection schemes where possible and needed;
- community engagement and demand generation – education and awareness campaigns in communities that are at a higher risk of TB can increase the likelihood that those with prevalent active disease will seek care for their illness at facilities with the capacity to diagnose and treat TB;
- health-system strengthening – providing additional training and equipping all health-care workers across the health system, including those working in the public and private sectors and lay community workers and volunteers,¹⁷ will increase the likelihood that patients with symptoms of TB who seek care are recognized and referred for appropriate evaluation and care;
- reassessing the definition of a person suspected of having TB – 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, can help ensure that the appropriate people are targeted for evaluation
- making any other changes to the current algorithm for passive case-finding – since such changes may result in a higher yield of patients identified in facilities. Greater use of chest radiography, Xpert MTB/Rif (see below), and other tools may increase the sensitivity of the algorithm while achieving acceptable specificity.

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

- scaling up the Practical Approach to Lung Health;¹⁸
- improving the quality of sputum-smear microscopy;
- improving the diagnosis of smear-negative TB, extrapulmonary TB and TB in children;¹⁹
- introducing and scaling up new WHO-approved diagnostics, such as the Xpert MTB/RIF assay²⁰ (Cepheid, Sunnyvale, CA);
- providing access to chest radiography services; and
- improving referrals and notifications among all care providers.¹⁷

2.1.2 Assessing the potential for screening for TB in high-risk groups

Screening for active TB is a relevant complement to improving early TB detection in specific groups that are at high risk of TB or have poor access to TB services, or both. The following risk groups should always be systematically screened for TB:

- **close contacts of people with TB;**
- **people living with HIV;** and
- **people exposed to silica** (mainly some types of miners).

When assessing the situations of the three risk groups highlighted above, the focus should be on *how* to screen, not *if* to screen. The assessment of these groups should include the size and distribution of the group, the TB burden within the group, the past and current screening experiences, and any remaining considerations and challenges that will need to be addressed to optimize the screening efforts.

For other risk groups (see *Table 1*) screening may or may not be appropriate. In most settings it is relevant to consider only a few additional risk groups than those listed above. In some settings, no additional risk groups should be considered. In order to develop a rational screening strategy, **there is a need to assess the relevance and potential cost and cost-effectiveness of systematic screening in each potential risk groups** (see section 2.3, Identifying and prioritizing risk groups).

Table 1. Possible risk groups to consider when screening for tuberculosis (TB) ⁶

Potential site of screening	Risk group
Community	Geographical areas with a high prevalence of TB
	Subpopulations with poor access to health care and with other associated risk factors (such as living in a poor or a remote area; being a member of an indigenous or tribal population; being a migrant, refugee, homeless, or nomadic)
Hospital outpatient and inpatient departments, and primary health-care centres	People previously treated for TB
	People with an untreated fibrotic chest radiography lesion
	People living with HIV / People attending for HIV testing
	People with diabetes mellitus
	People who smoke / People with chronic respiratory disease
	Undernourished people
	People who have had a gastrectomy or jejunioileal bypass
	People with an alcohol-use disorder / Injection drug users
	People with chronic renal failure
	People on treatments that compromise their immune system
	Elderly people
	People in mental health clinics or institutions
Residential institutions	General outpatients/inpatients
	Prisoners and prison staff
	People residing in shelters
Immigration and refugee services	Other congregate institutions (such as the military)
	Immigrants from settings with a high prevalence of TB
Workplaces	People in refugee camps
	Health-care workers
	Miners or others who are exposed to silica
	Other workplaces with a high prevalence of TB

2.1.3 Assessing gaps in TB case detection, challenges to screening, and entry points for interventions

The main purpose of conducting a situation assessment is to identify gaps in TB case detection and opportunities for addressing those gaps through screening. This assessment must consider the potential benefits, risks and costs of systematic screening, particularly in relation to other possible interventions.

The analysis needs to be disaggregated by age, sex and geographical location, and special attention should be paid to vulnerable groups that are at high risk of TB or likely to face barriers to accessing TB services, or both.

The specific questions that should be addressed in a situation assessment are shown in *Table 2*. The web-based tool described in section 3 further highlights what quantitative baseline information is required to estimate potential yield and cost of screening. It is therefore advisable to use the web-based tool as a starting point for the assessment, while obtaining the additional information that need to be imputed in the tool.

Potential data sources include:

- surveillance data;
- data from prevalence surveys;
- evaluations of previous or continuing activities to improve case-finding and screening;
- national health and demographic statistics;
- findings from research studies.

Useful information on collecting and interpreting data can be found in:

- WHO's *Tuberculosis prevalence surveys: a handbook*;²¹
- WHO's guidance on *Understanding and using tuberculosis data*;²²
- WHO's *Framework for conducting reviews of tuberculosis programmes*;²³
- WHO's *Public–private mix for TB care and control: a tool for national situation assessment*;²⁴
- WHO's *ENGAGE TB: integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Operational guidance*;²⁵
- *The tool to estimate patients' costs*;²⁶
- WHO's guidance on *Contributing to health system strengthening - Guiding principles for national tuberculosis programmes*.²⁷

Table 2. Questions to be addressed when conducting a situation assessment before implementing screening for tuberculosis (TB)

Area to be assessed	Questions to be explored
Distribution of TB burden; size and distribution of gaps in case detection	<ul style="list-style-type: none"> • What is the current distribution of the TB burden in this setting (in terms of notification, 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 delays in diagnosis for each subpopulation or risk group? • Which subpopulations or risk groups have the highest risk of TB remaining undetected? • Which types of TB are most likely not to be detected? (extrapulmonary, smear-negative TB, etc.) • What are the main reasons for gaps remaining in case detection?
Current case-detection activities	<ul style="list-style-type: none"> • What is the level of knowledge about TB among health-care staff and others who provide care? • What is the current definition of suspected TB, and to what extent is it applied in practice? • Which diagnostic tests and algorithms are used to screen for and diagnose different types of TB? • To what extent has Xpert MTB/RIF (or other rapid molecular tests) been scaled up, and which individuals are eligible? • Are chest X-rays available? Are they of good quality? Are the interpretations of the chest X-rays of good quality? How are chest X-rays used for TB screening and diagnosis? • 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?
Role of different providers	<ul style="list-style-type: none"> • What are the common health-seeking patterns? • From which providers do people usually seek care first? • What diagnosis and treatment services are offered by different providers (for example, in the public and private sectors; among formal or informal providers; by health-care or other providers; by community or civil society organizations)? • What are patients' previous experiences of engaging with different health-care providers, communities or civil society organizations?
TB awareness and health seeking	<ul style="list-style-type: none"> • What barriers prevent access to diagnostic and treatment services among the targeted community? • What is the level of knowledge about TB and TB care in the targeted community? • What are the main reasons for delays in seeking health care among the targeted community?
Risk group size, distribution, and special challenges	<ul style="list-style-type: none"> • What is the size and geographical distribution of the different TB risk groups (<i>Table 1</i>)? • 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 experiences in improving early TB detection	<ul style="list-style-type: none"> • What were the results of any previous efforts to improve the patient-initiated pathway to enable earlier detection of TB? • What were the outcomes and lessons learnt from previous systematic screening initiatives in different risk groups?

2.1.4 Assessing the national TB programme and the preparedness of the health-care system

High-quality services for TB diagnosis, treatment and management, as well as support services for patients, should be in place before systematic screening for active TB is pursued. This will minimize the risks of any negative effects from screening, including the risk of a false-positive diagnosis and the accompanying anxiety, unnecessary treatment and delay in receiving an appropriate diagnosis (especially if the quality of TB diagnostic services are suboptimal) or worsening of TB treatment outcomes (if treatment services are suboptimal and not properly tailored to specific vulnerable groups that may be targeted through screening). Moreover, implementing systematic screening in a context of poor-quality general services raises ethical concerns, and may lead to a loss of confidence in the services provided among the population served. In addition, the capacity of specific health institutions and health staff to take on additional functions related to TB screening needs to be carefully assessed, so as not to undermine the quality of TB and other services.

The critical conditions that must be met before systematic screening is implemented include ensuring that:

- quality-assured diagnostic services are available;
- regular and 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;
- there is a low rate of initial loss to follow-up;
- the success rate of treatment is adequate and the rate of overall loss-to-follow-up is low;
- there are sufficient mechanisms to provide support for diagnosed patients, and there is capacity to tailor treatment programmes to the specific needs of the population that will be screened;
- if the Xpert MTB/RIF assay or other tests are used to assess drug resistance, there is adequate capacity for culture testing and drug-susceptibility testing and for programmatic management of drug-resistant TB;
- adequate financial resources and human resources can be made available for screening without adversely affecting other key functions of the health-care system. Primary and auxiliary health staff may be the most affected if their duties are expanded to take on screening functions at health services or in community settings without planning to ensure that other work is not foregone or their workloads become unmanageable. Supervision of screening efforts also requires capacity-building and time.

For most risk groups, systematic screening for TB should involve collaboration with other health and social programmes, which may already be engaged in screening the targeted population for other conditions. Thus, outreach activities focusing on health promotion or providing social support for vulnerable and hard-to-reach populations may already be in place. These may serve as platforms for TB screening within a broader, more integrated approach to outreach. The analysis of the situation should include mapping the screening and outreach activities that may be relevant, and assessing other programmes' potential

and readiness for intersectoral collaboration; this assessment will be important for making judgements about feasibility, costs and cost effectiveness of screening.

Table 3 highlights the programmes, services and stakeholders that could collaborate on screening activities.

The following key questions must be answered when considering whether to develop an intersectoral collaborative screening programme with other providers of health-care or welfare.

- Which health conditions are already being screened for?
- What links exist among health-care services?
- Do any of the potential collaborating agencies have experience screening for TB?
- Is there capacity to include TB screening?

Table 3. Services, programmes and stakeholders that could collaborate with systematic screening programmes for tuberculosis (TB)

Services	Programmes and stakeholders
Health services	<ul style="list-style-type: none"> • HIV programmes, clinics offering voluntary counselling and testing for HIV, clinics delivering antiretroviral therapy, programmes aimed at preventing mother-to-child transmission of HIV • Diabetes or endocrinology clinic screening initiatives, undertaken within the broader platform of preventing noncommunicable diseases • Maternal and child health and antenatal care programmes • Alcohol and drug-abuse clinics and their outreach programmes
Social services	<ul style="list-style-type: none"> • Outreach and community support or development programmes in remote rural areas or urban slums; programmes targeting homeless people and other vulnerable populations • Programmes providing social support for sex workers • Programmes providing social services for immigrants and refugees • Social protection schemes for poor people • Food support programmes • Other partner agencies working with affected or vulnerable populations
Other government services	<ul style="list-style-type: none"> • Prison health services • Occupational health services (especially those targeting workers in mines, health-care workers and workers in other high-risk occupations) • Migration authorities
Civil society organizations	<ul style="list-style-type: none"> • Nongovernmental organizations or others providing social support for vulnerable groups
Private health-care providers	<ul style="list-style-type: none"> • Private providers • Informal providers

2.1.5 Assessing policies on health-care coverage and frameworks for legal and human rights

TB screening carries both opportunities and risks for the individual. Before screening is started, it is essential to ensure that people who are diagnosed with TB have the right to 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 need to be assessed.

Discrimination against key affected populations – such as sex workers; injection drug users; and some ethnic minorities – can severely hamper access to treatment, and this may be reinforced by a lack of a framework for 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.

The possible stigmatization of and discrimination against people screened for TB and people diagnosed with TB can create risks for people undergoing screening. For example, people who are diagnosed with TB may lose their jobs temporarily or permanently, or be expelled from school or forced to divorce. Migrants may face deportation. The risks of discrimination and stigmatization should be carefully assessed prior to initiating screening. In particular, the legal status of migrants needs to be fully understood and considered when designing the screening plan, both with regards to their access to health services and the risks of expatriation if they are diagnosed with TB. Similarly, when specific occupational groups are screened, the legal protections of rights to care and the right to maintain employment must be considered.

2.2 Setting goals and specific objectives

The goals and specific objectives of screening depend on what targets have been set and what gaps have been identified by the situation assessment. Generally, the **primary objective of screening is to detect active TB early** in order to contribute towards two ultimate goals:

1. reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB for individuals with the disease. This reduces suffering, the prevalence of TB and death from TB;
2. reducing TB transmission by shortening the duration of infectiousness. This reduces the incidence of TB infection and consequently contributes to a reduced incidence of TB disease.

When goals and targets are set, it is important to ensure that there is equitable access to diagnosis and treatment, which implies that the groups that are most difficult to reach should be prioritized in screening.

A second objective can be to rule out active disease to help identify people who are eligible for treatment of latent TB infection, such as people living with HIV and close

contacts of TB patients who are younger than 5 years. For further information on screening and managing latent TB infection, see WHO's *Guidelines on the management of latent tuberculosis infection*.²⁸

Furthermore, **screening can help identify people who are at particularly high risk of developing active disease and thus may require repeat screening**. For example, people with an abnormal chest X-ray that is compatible with TB but who were not diagnosed with active disease at the time of screening may benefit from repeat screening in the future.

Combining screening for TB with screening for TB risk factors (such as HIV, diabetes mellitus, chronic obstructive pulmonary disease, low body mass index or smoking) can also help map individual or community-level risk factors and socioeconomic determinants that need to be addressed to more effectively prevent the disease. This may be an additional objective in settings where information about the prevalence and distribution of TB risk factors is lacking.

2.3 Identifying and prioritizing risk groups

Indiscriminate mass screening should be avoided. Risk groups should be prioritized for screening based on assessments of the potential benefits and harms in relation to costs, which is a function of; total potential yield, the risk of a false positive diagnosis, the number needed to screen (NNS) to detect a true case of TB, the potential impact on transmission, the feasibility of the initiative and the acceptability of screening to the group. These assessments should be made for each risk group.

A tool has been developed to assist with the process of prioritizing risk groups for screening. The tool produces estimates of the potential yield of true and false positive TB and cost of screening, according to the risk group(s) being targeted and the screening algorithm(s) being used. See section 3 for a full description.

Three groups should always be systematically screened, namely:

- **contacts of people with TB;**
- **people living with HIV; and**
- **people working in places where they are exposed to high levels of silica (mainly some types of miners).**

Other risk groups (*Table 1*) should be prioritized for screening based on the assessment of the situation and on the goals and objectives of screening. When prioritizing groups to screen, the factors described in sections 2.3.1–2.3.8 should be considered for each risk group and in relation to the specific objectives of screening.

Prioritization may vary depending on which stakeholder is responsible for the screening initiative. 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.

Systematically screening for active TB in children is problematic since both the screening and diagnostic tools are less accurate in children than in adults and, therefore, there is a higher risk of large number of diagnostic tests being required as well as a high risk of large numbers of false-positive cases unnecessarily starting TB treatment. In principle, **only children who are close contacts of someone with TB and HIV-positive children should be systematically screened for TB**. Other children should be assessed according to diagnostic algorithms for paediatric TB as part of standard clinical management practices.

2.3.1 Potential benefits for the individual

These 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 the highest risk of delayed diagnosis** because there are barriers to them obtaining health care (for example, people in poor communities, people living in remote areas) and especially **those who have the highest risk of poor treatment outcomes when diagnosis is delayed** (for example, because their immune system is compromised, such as people living with HIV).

2.3.2 Potential risks and harms for the individual

The screening procedure itself may be inconvenient and have direct and indirect costs for the individual, and these may vary with both the risk group and the screening approach. **Harms associated with the results of screening include the unintended negative effects of being correctly diagnosed (which may include stigmatization or discrimination) and the harms caused by a false-positive or a false-negative diagnosis.** Particular attentions should be paid to these harms for groups such as migrants, who may risk deportation if TB is diagnosed or suspected, and employees who lack legal protection against dismissal if they are diagnosed with TB.

The risk of false positive diagnosis depends on both the prevalence of TB in the screened group, as well as on the screening and diagnostic algorithm used. Screening in groups with low TB prevalence can result in a large proportion with a false-positive result. **Therefore, as a general rule, screening should be avoided in low risk groups.** The importance of choosing an appropriate screening and diagnostic algorithm in order to minimize the number of false positive outcomes is further discussed in section 2.4.

2.3.3 Potential to identify other conditions that need medical attention

When someone is screened for TB, **other conditions that require treatment may be identified** (such as lung cancer or chronic obstructive pulmonary disease); offering treatment for other conditions may not be within the scope of the screening team's responsibilities. Links must be developed with other health programmes to handle these cases.

2.3.4 Potential total yield of true TB cases

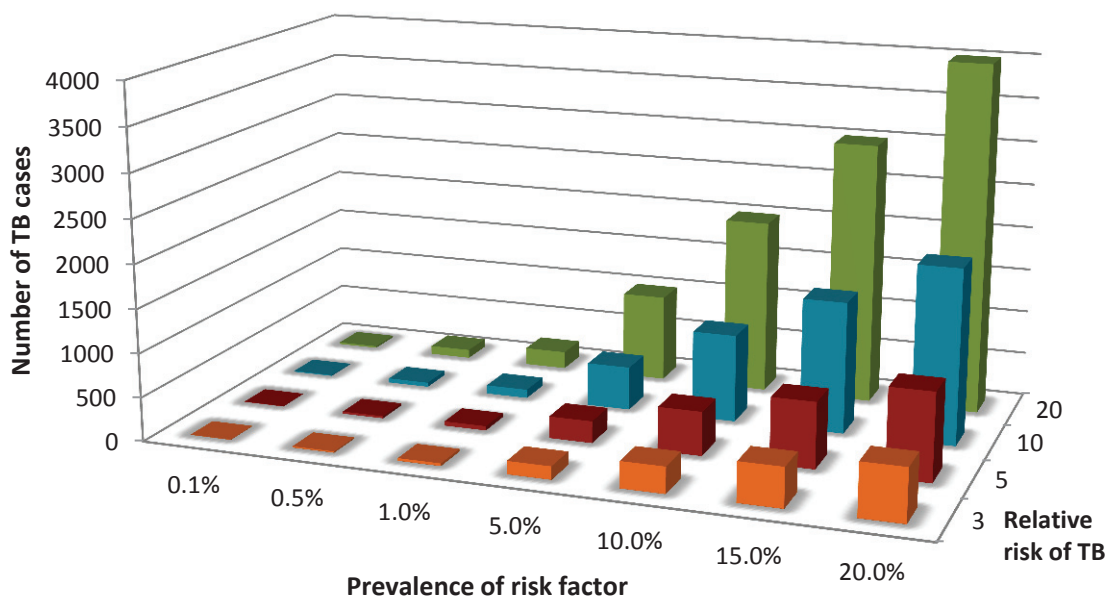
The potential total case-detection yield is a function of:

- **the size of the risk group and the proportion of them that can be reached;**
- **the prevalence of TB in the risk group;**
- **the sensitivity of the screening approach; and**
- **the acceptance of screening in the risk group.**

Figure 3 shows the potential yield of screening across a range of hypothetical risk groups and across a range of relative risks of TB (assuming 100% coverage, acceptance to screening, sensitivity and specificity of screening).

As illustrated in Figure 3, the yield of TB screening in a specific risk group (in terms of the number of TB cases detected) is driven by both the size of the risk group (or the prevalence of the risk factor in the general population) and the prevalence of TB within that risk group.

Figure 3. Potential yield of screening as a function of the prevalence of the risk factor in the population and the relative risk of tuberculosis (TB) in the risk group (baseline incidence, 100 cases/100 000 in a population of 1 000 000)



Often, the groups at the highest risk of TB are also the smallest, and groups with only a moderately elevated risk can be very large. For example, the population prevalence of HIV, which is associated with up to 20-fold risk increase, is normally less than 1% (with the exception of 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 normally a very small fraction of the total population. However, risk factors such as having diabetes or undernutrition, or living in a crowded slum, which normally have moderate relative risks for TB (in the range of 2–3) could affect more than 10% of the total population.

Therefore, screening in the highest risk groups often gives a low total yield. 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 their risk of TB. However, screening in these groups will have a higher NNS and cost per case detected than screening in groups at very high risk. The risk of a false positive diagnosis is also higher in these groups. Therefore, there will often be a difficult trade off between the desire to achieve a large total yield and the cost effectiveness.

2.3.5 Potential impact on transmission within and beyond the risk group

The potential of screening to have an impact on 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 principle, the larger the total yield of screening, the larger the potential impact on transmission in the community. However, when the TB burden is highly concentrated in a few high-risk groups, the largest impact on overall transmission may come from screening carefully selected groups, and these may be small in size.

2.3.6 The number needed to screen to detect a case of TB

The NNS to identify one true case of 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 translate into 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 need to be screened for each case detected, resulting in a lower NNS. *Figure 4* illustrates the idea of the NNS in a risk group.

Figure 4. The number needed to screen (NNS) to diagnose one case in any given risk group is roughly the inverse of the prevalence of the disease in that risk group

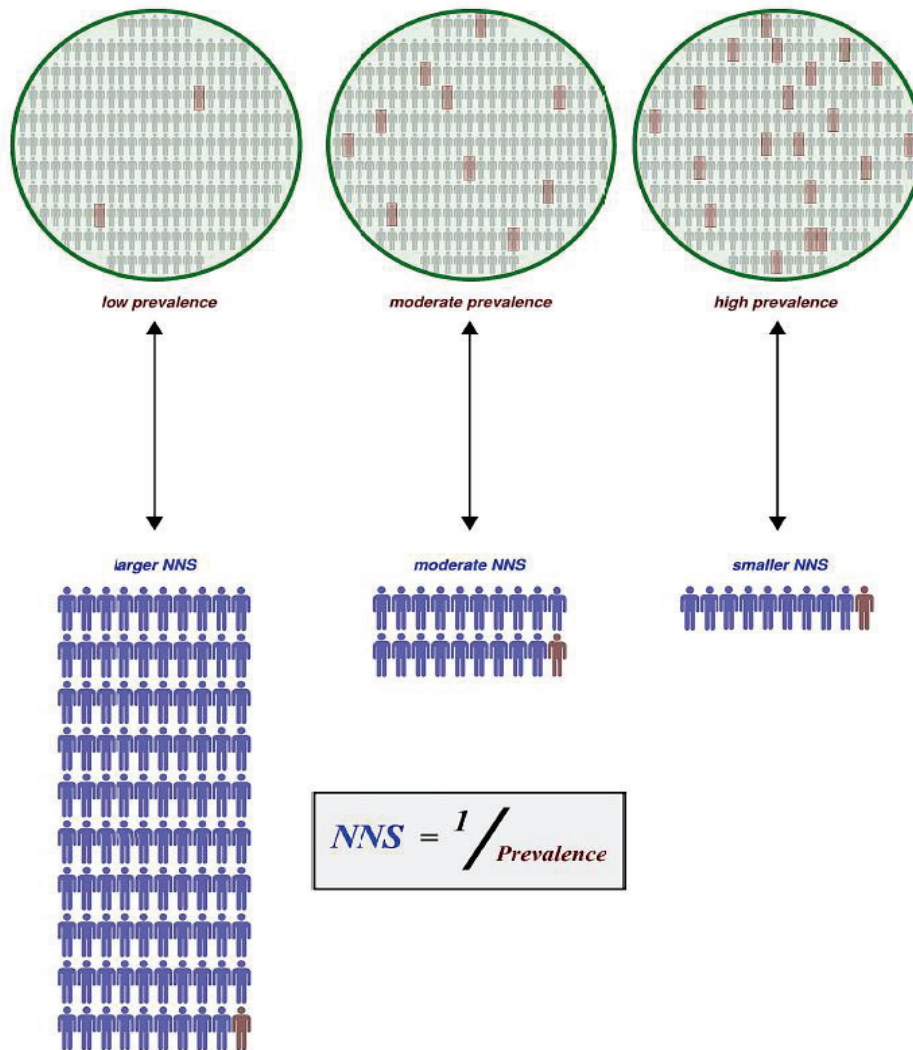
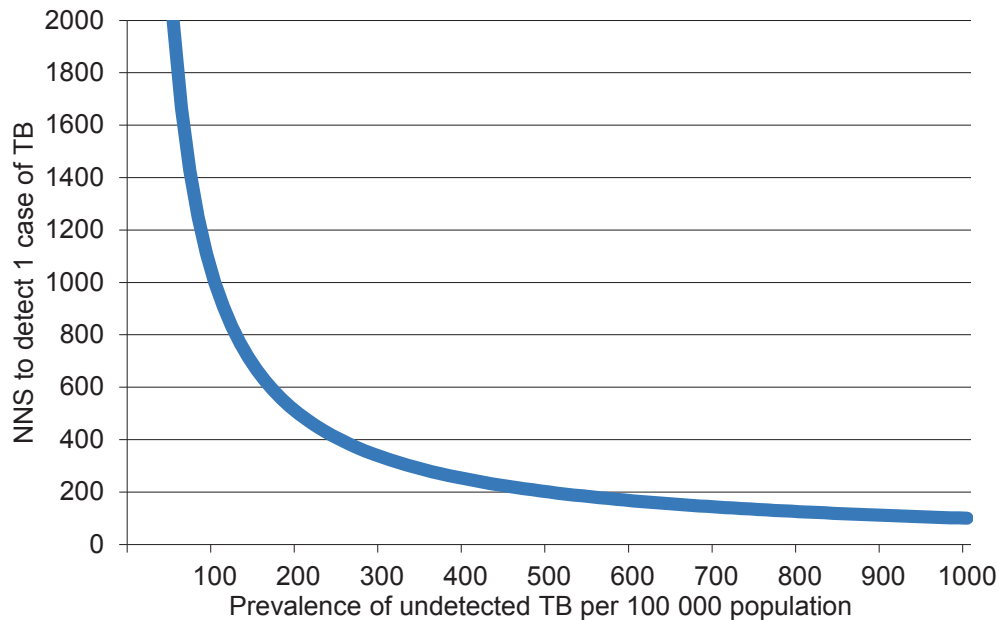


Figure 5 shows the relationship between the prevalence of TB in a risk group (per 100 000 population) and the NNS, assuming 100% sensitivity and specificity in screening and diagnosis. However, this assumption is never met and, therefore, the NNS will always be higher in practice.

Figure 5. Number needed to screen (NNS) at different levels of tuberculosis (TB) prevalence, assuming 100% coverage, sensitivity and specificity



As demonstrated in *Figure 5*, the NNS accelerates at lower levels of TB prevalence. At a prevalence of 200/100 000 population the NNS is at least 500 (in practice, it will be higher when the sensitivity 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 the high burden of TB and, therefore, screening the general population is not usually cost effective.

The NNS is a rough indicator of cost effectiveness and of effort. Comparing the NNS across risk groups provides a measure of relative cost effectiveness if it can be assumed that the cost of screening and treatment, as well as the benefits of early treatment, are the same across risk groups (however, this is rarely the case).

In order to guide the prioritization of risk groups the NNS should be estimated 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 section 3.

2.3.7 Feasibility of identifying, reaching and screening people, and having them start and complete treatment, and the acceptability of screening in a risk group

The feasibility and acceptability of screening need to be assessed in relation to both those who will be screened and those who will provide screening.

Certain risk groups will be harder to reach than others. To some extent, the structure of health and social services will determine 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 that can be identified within health facilities, people who are living in institutions (such as prisons) and people working in high-risk locations (such as mines).

Some people may accept screening more readily than others, depending on the perceived cost and inconvenience of screening as well as the adverse consequences of a TB diagnosis (such as stigmatization or discrimination), compared to the perceived benefits. The reported acceptance rates of screening for different risk groups are available in the web annexes.

Whether screening will be accepted depends on how the programme is designed and implemented, and, therefore, it is difficult to predict based on evidence from previous programmes. The acceptability of screening models may be assessed in advance by organizing focus groups of target populations that, preferably, have an age and sex distribution that matches the populations at highest risk.

2.3.8 Cost–effectiveness and cost–benefit ratios

Pre-implementation, the cost effectiveness of the programme can be modelled based on estimates of the predicted number of additional true TB cases detected, the reduction in morbidity, the reduction in time that a person remains infectious, and the reductions in transmission, incidence and mortality.

The cost–benefit ratio can be estimated in terms of future costs saved for the individual, the health sector or society, or all of these. The total cost depends 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.

To properly determine the cost effectiveness of screening in relation to its impact on public health it is necessary to conduct intervention trials that collect appropriate data on costs of screening interventions as well as data on the epidemiological impact. Such data are unlikely to be available in the foreseeable future in many settings. However, models can be used to estimate how costs relate to the potential impact on TB transmission and epidemiology. Nonetheless, because there is no good empirical evidence about the impact of screening on transmission, such models will be highly speculative. In the interim, section 2.3.9 describes how basic cost effectiveness – that is, the cost per case detected through screening – can be estimated using the tool for prioritizing risk groups described below.

2.4. Choosing algorithms for screening and diagnosis

2.4.1 Algorithm options

An algorithm for systematic screening should combine one or several screening tests and one or several diagnostic tests. Screening tests should distinguish between people with a high likelihood of having active TB and people who are unlikely to have active TB. A screening test is not intended to be diagnostic but rather to identify the subgroup of people with the highest likelihood of disease. People with positive results on a screening test then undergo diagnostic evaluation to bacteriologically confirm or rule out active TB. A negative diagnostic test may have to be followed up with clinical evaluation (mainly based on chest radiography, symptoms and medical history). A positive diagnostic test result may have to be re-confirmed with further testing and clinical evaluation if the positive predictive value (PPV) of the test result is low. The tool described in section 3 can help in selecting an appropriate algorithm.

WHO's guidelines on systematic screening for active TB⁶ includes 10 screening algorithm options, consisting of a combination of one or two screening tests and a diagnostic test (*Annex*). The algorithms have been developed predominantly to detect pulmonary TB. The accuracy of the tests has been assessed using culture-confirmed pulmonary TB as the gold standard. While culture is the gold standard for diagnostic testing for TB, in these algorithms it is not considered as an initial diagnostic test because it demands more resources and requires a much longer wait for results (2–8 weeks) than both the Xpert MTB/RIF test and sputum-smear microscopy, both of which can provide results in less than 1 day. Where resources permit, and where the health system has sufficient capacity to ensure that patients are followed up after culture results are available, culture may be used in parallel with or after testing with the Xpert MTB/RIF assay or sputum-smear microscopy.²⁰ Specimens should undergo culture and drug-susceptibility testing according to the guidelines for diagnosing drug-resistant TB.²⁹

The algorithms each have different sensitivity and specificity, and, therefore, different potential yields of true-positive and true-negative cases and false-positive and false-negative TB. Yields also vary with the prevalence of TB in the population being screened. For all algorithms, the risk of a false-positive diagnosis increases as the prevalence declines; therefore, special attention must be paid to diagnostic accuracy, particularly when the prevalence of TB in the screened population is less than 1%. At a TB prevalence of 0.5% in the screened population, all of the algorithms have a PPV of less than 75% (i.e. 25% have a false positive diagnosis) when clinical diagnosis is used for all or some of those with a negative result from their initial diagnostic test. Even when clinical diagnosis is not considered, the PPV is below 80% for all but one algorithm. Special efforts must therefore be made to ensure high quality of diagnostic procedures and clinical assessment especially when TB prevalence in the screened population is moderate to low.

For each given screening situation it is critical to consider what proportion of false positive and false negative results are unacceptable. Ethical considerations should guide the permissible sensitivity and specificity of the algorithm. Considerations will vary across risk

groups. Especially in groups with a high risk of severe negative effects from missed or delayed diagnosis and treatment, it is important to use an algorithm that has very high sensitivity, although this often leads to lower specificity.

The algorithms 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.

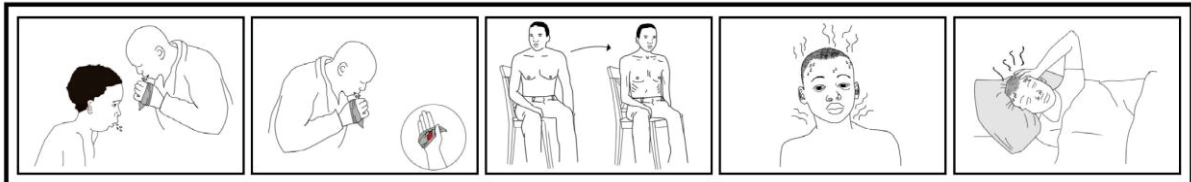
Screening tests

Some commonly used initial screening tests include:

- screening for cough lasting for longer than 2 weeks;



- screening for any symptom compatible with TB, including –
 - cough of any duration
 - haemoptysis
 - weight loss
 - fever
 - night sweats;



- screening with chest radiography.



If symptom screening is used initially, then chest radiography can be used as a second screening to improve the pretest probability of the subsequent diagnostic test and to reduce the number of people who need to undergo a full diagnostic evaluation.

Diagnostic tests

Each screening algorithm also includes one of two options for diagnostic testing for people who screen positive:

- sputum-smear microscopy; or



- a rapid molecular test that has been demonstrated to have high accuracy for both smear-positive and smear-negative pulmonary TB, such as the Xpert MTB/RIF test or any rapid test recommended by WHO in the future that has the same or better accuracy.



Screening algorithms and people living with HIV

As part of the initial screening, each algorithm seeks to identify people living with HIV; these people should be screened and diagnosed by following the algorithm in WHO's *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*.³⁰ Screening can be enhanced by combining screening for TB with screening for HIV, especially in settings with a high burden of HIV.³⁰ In settings with a low prevalence of HIV, it is normally sufficient to ask a patient about their HIV status.

2.4.2 How to choose an algorithm for a particular risk group

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,
- the profile of the prioritized risk groups,
- the TB prevalence in the risk groups,
- the cost, availability and feasibility of using different tests, and
- the ability to engage the population to be screened.

Specific objectives of screening

The specific objectives of screening will partly determine the relative importance of the sensitivity of the algorithm 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 treatment for latent TB (for example, as part of an investigation of contacts), then it is critical to have very high sensitivity (and thus very high negative predictive value of a negative result) but suboptimal specificity may be acceptable (which in this case might lead to treating people for active TB rather than latent TB). In other situations it may be critical to avoid false-positive diagnoses, and a less sensitive but highly specific algorithm may be preferable.

Accuracy and yield of screening and diagnostic tests

Table 4 and Table 5 summarize the published sensitivity and specificity of the screening and diagnostic tests as of 2012 described in section 2.4.1. Table 4 shows the modelled yield of screening in a population with a 1% prevalence of TB using different algorithms.

Table 4. Pooled sensitivity and specificity of different screening tools for pulmonary tuberculosis (TB) using culture-confirmed pulmonary TB as the gold standard⁶

Screening tool	Pooled sensitivity ^a	Pooled specificity ^a
Chest radiography		
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms (any abnormality) ^b	90 (81–96)	56 (54–58)
Symptom screening		
Prolonged cough (lasting >2–3 weeks)	35 (24–46)	95 (93–97)
Any cough	57 (40–74)	80 (69–90)
Any TB symptom (in settings with a low prevalence of HIV)	70 (58–82)	74 (53–95)
Any TB symptom (in settings with a high prevalence of HIV)	84 (76–93)	61 (35–87)
Any TB symptom (in settings with a low prevalence or high prevalence of HIV)	77 (68–86)	68 (50–85)

^a Values are % (95% confidence interval).

^b Results from only one study; data are for any abnormality seen on chest radiography.

Table 5. Pooled sensitivity and specificity of different diagnostic tests for tuberculosis (TB), from systematic reviews using culture-confirmed pulmonary TB as the gold standard⁶

Diagnostic test	Pooled sensitivity ^a	Pooled specificity ^a
Liquid culture (gold standard)	100	100
Conventional sputum-smear microscopy ^b	61 (31–89)	98 (93–100)
Xpert MTB/RIF assay	92 (70–100)	99 (91–100)
Clinical diagnosis	24 (10–51)	94 (79–97)

^a Values are % (95% confidence interval).

^b This refers to conventional light microscopy used to examine direct smears stained with Ziehl–Neelsen. Fluorescence microscopy, including microscopy with light-emitting diodes generally has higher sensitivity than conventional light microscopy.

Table 6. Modelled yield of different algorithms when screening 100 000 persons in a population with a 1% prevalence of culture-positive pulmonary tuberculosis (TB) (1 000 cases). (It is assumed that final diagnosis uses results from sputum-smear microscopy or the Xpert MTB/RIF test, and there is no further diagnostic evaluation)^{a,6}

Screening test	Final diagnostic test	Outcome of screening ^a				Outcome of diagnosis in persons with positive screening ^a						
		TN	FN	NPV ^b (%)	Screened positive ^c	TP	Detected of true cases (%)	FP	PPV ^d (%)	TN ^e (n)	FN ^f	NPV ^g (%)
Cough lasting >2 weeks	SSM	93 753	649	99.3	5 598	214	21	105	67.1	5 142	137	97.4
	Xpert	93 753	649	99.3	5 598	324	32	52	86.0	5 195	27	99.5
1st screen: cough >2 weeks 2nd screen (if 1st screen positive): chest radiography	SSM	96 691	684	99.3	2 625	193	19	46	80.7	2 263	123	94.8
	Xpert	96 691	684	99.3	2 625	291	29	23	92.7	2 286	25	98.9
Any TB symptom	SSM	67 023	230	99.7	32 747	470	47	640	42.3	31 337	300	99.1
	Xpert	67 023	230	99.7	32 747	710	71	320	68.9	31 657	60	99.8
1st screen: any TB symptom 2nd screen (if 1st screen positive): chest radiography	SSM	84 930	307	99.6	14 763	423	42	281	60.0	13 788	270	98.1
	Xpert	84 930	307	99.6	14 763	639	64	141	82.0	13 929	54	99.6
Chest radiography: abnormality suggestive of active TB	SSM	88 506	132	99.9	11 362	529	53	210	71.6	10 284	339	96.8
	Xpert	88 506	132	99.9	11 362	800	80	105	88.4	10 389	68	99.4
Chest radiography: any abnormality compatible with TB	SSM	74 646	22	100.0	25 332	597	60	487	55.1	23 867	381	98.4
	Xpert	74 646	22	100.0	25 332	902	90	244	78.7	24 110	76	99.7

TN, true negative; FN, false negative; NPV, negative predictive value; TP, true positive; FP, false positive; PPV, positive predictive value; SSM, sputum-smear microscopy; Xpert, Xpert MTB/RIF test.

^a Values are numbers unless otherwise indicated.

^b The negative predictive value for screening is the likelihood that someone whose screening test is negative does not have TB.

^c This is the number of people whose screening test would be positive, which equals the number of people who should have the diagnostic test

^d The positive predictive value is the likelihood that a person with a final diagnosis of TB has true culture-positive TB. It summarizes the specificity and sensitivity of the entire algorithm, not just the diagnostic part.

^e The number of true negatives among people whose screening test is positive is the number of people correctly diagnosed as not having TB among those whose screening test is positive and who have a diagnostic test.

^f The number of false negatives among people whose screening test is positive is the number of people falsely diagnosed as not having TB among those whose screening tests are positive and who have a diagnostic test.

^g The negative predictive value for diagnosis among people whose screening test is positive is the likelihood that a person whose screening test is positive and who is not diagnosed with TB does not have culture-positive TB.

Profile of the prioritized risk groups

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, chest X-rays, Xpert and sputum-smear microscopy have lower sensitivity in people living with HIV).

TB prevalence in the risk groups

The prevalence of TB in a risk group has a direct impact on the predictive values of all tests and, therefore, on the yield of true-positive and false-positive cases and true-negative and false-negative cases. The lower the prevalence, the more important it is for the algorithm to have very high specificity in order to avoid a high proportion of false-positive cases.

Cost, availability and feasibility of using different tests

The total cost of an algorithm depends on the unit cost of each test (including both start-up costs and running costs), the total number of tests required and the overhead costs for delivering the services. Different algorithms require different numbers of different tests for any given population with any given TB prevalence.

Table 6 provides estimated number of tests required for different algorithms, and displays these inputs in relation to outputs in terms of case-detection yield. The tool described in section 3 can be used to generate cost estimates for each algorithm and risk group based on local cost assumptions. This information can be used to conduct a simple cost–effectiveness analysis that focuses on the cost per true case detected.

However, the availability, cost and feasibility of tests may vary considerably in different parts of the health-care system. Outreach screening requires special considerations with regards to mobility and field conditions. For example, digital chest X-ray technology offers lower running costs and higher mobility than conventional chest X-ray, but requires high initial investment costs. Symptom screening may be relatively low cost, especially in integrated services, but it also has low sensitivity. Sputum examination (either by smear microscopy or using the Xpert MTB/RIF assay) may become more feasible under outreach conditions if proper sputum collection and transportation can be organized.

Ability to gain access to the population to be screened

Although the algorithm used in the population that is screened will have significant implications for the budget and logistics, so too will the approach that is used to conduct the screening. Implementing contact investigation may require home visits or it can be done by requesting that individuals with TB bring their contacts to a health facility to be tested. Although the latter option may be far cheaper, the number of people actually screened may be far smaller. Similarly, community outreach may involve setting up mobile treatment teams and laboratories, engaging in home visits or simply using loudspeakers to announce the availability of testing services. Different approaches work differently in different settings, and their impact will vary depending on the number of people reached and tested, and on the yield.

2.5 Planning, budgeting and implementing

2.5.1 Requirements for planning, human resources, commodities and budgeting

As noted in the assessment section, consideration should be given to the extra resources, both human and financial, that will be needed to prepare for, carry out, and monitor screening, and to accommodate the extra cases that may be identified by screening.

Determining which cadre(s) of staff will be involved in screening will require review of the current terms of reference, workload and capacity of different staff, including supervisory staff and staff enabling provision of commodities for the front-line screening workers. Lessons should be assessed from other programmatic experience in screening within health facilities as well as outreach efforts. The model of staffing and supervision can be highly context-specific (even within countries), and could vary between urban and rural settings and risk groups targeted.

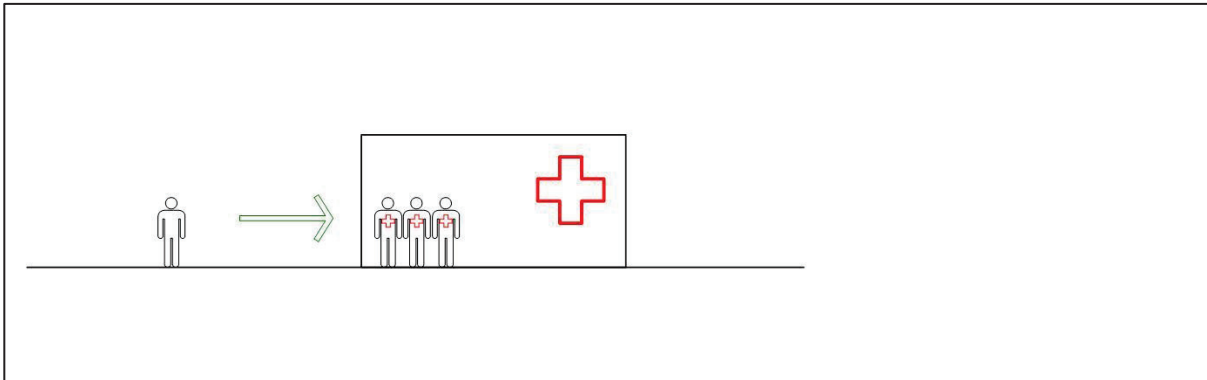
New forms or registers may be required and training will certainly be needed. Screening can be conducted by a variety of personnel, depending on which tests are being used. For instance, symptom screening can be conducted by community health workers or volunteers. Also, new diagnostic equipment or additional reagents and tests may be required for the additional activities. In many cases, the logistics of gaining access to and testing the target population will also require significant resources. Finally, 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; it will also be important to ensure that patients receive adequate support during treatment.

2.5.2 Choosing a screening programme model

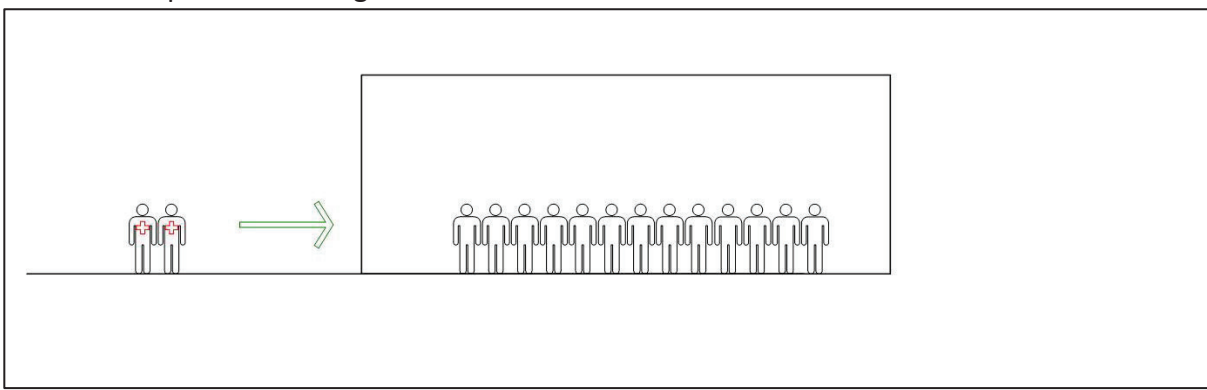
The choice of screening programme will have implications for the resources required and the potential reach and effectiveness of the programme. The decision about which model to use should be based on determining which approach will be most effective at reaching the targeted risk group with the resources available.

Programmes that conduct screening in locations where people gather for other purposes, such as health centres or workplaces, can limit the effort and resources required to reach the target population. However, not all populations can be reached using this method.

- Screening health centre attendees

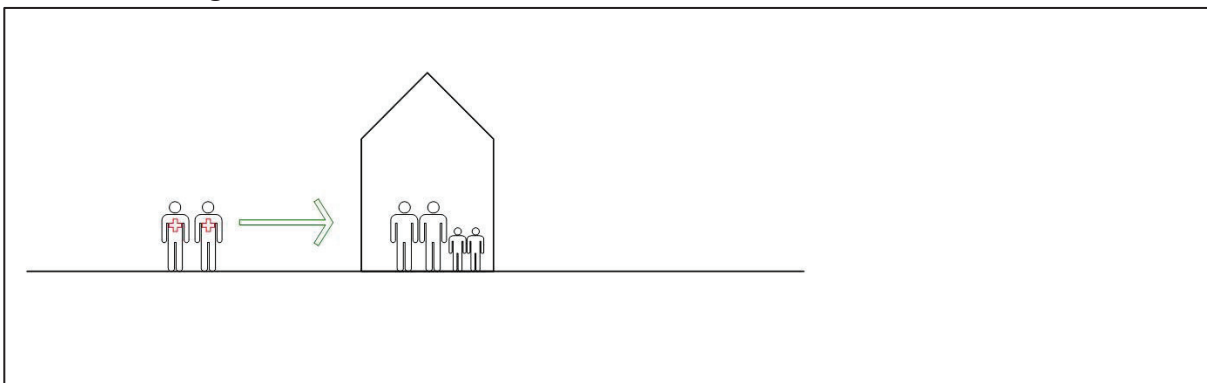


- Workplace screening

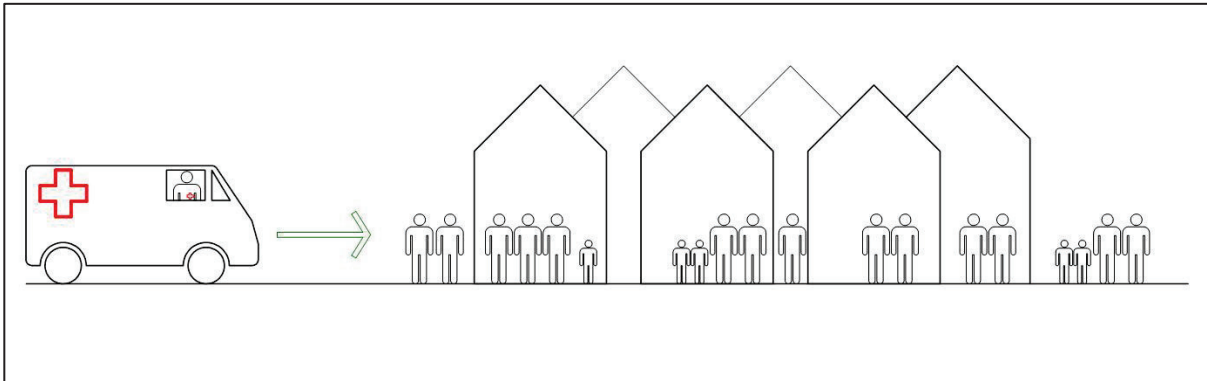


Programmes that bring screening to places where people live or work can reach more vulnerable populations, particularly those for whom there are barriers to accessing care, but these programmes require more resources. Such programme models can include home visits, mobile outreach screening campaigns and community-based screening events, such as health fairs.

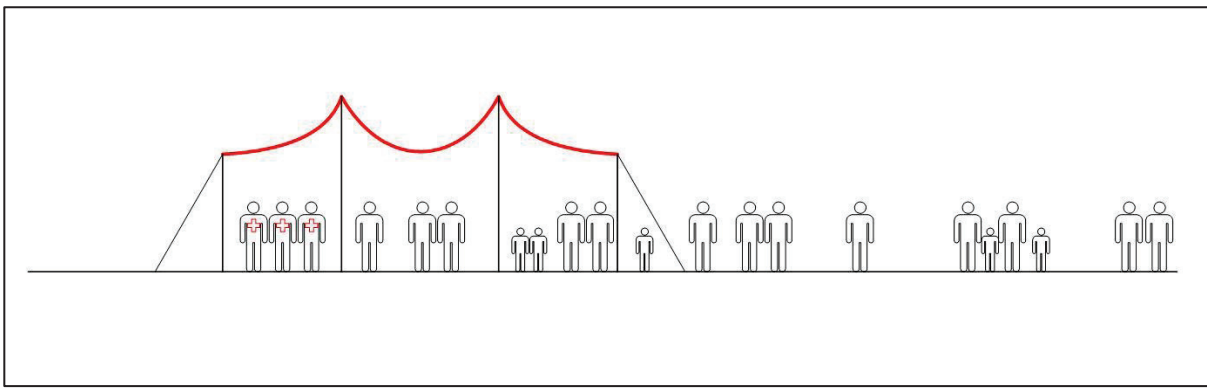
- Screening in the home



- Mobile outreach screening campaign



- Community-based screening events (health fairs)



2.5.2 Ethical considerations

Ethical issues should be considered from the onset of the planning process, which, preferably, should include the involvement of end-users. The process of designing screening interventions for specific risk groups should involve discussions with those 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 and 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. The privacy and confidentiality of all information related to screening should be ensured.

The risks of discrimination and stigmatization should be carefully assessed prior to initiating screening. Depending on the risks identified for different target groups, measures may be adapted to minimize the consequences. In particular, the legal status of migrants, both with regards to their access to health services and the risk of expatriation if they are diagnosed with TB, need to be fully considered when the screening approach is designed. Similarly, when plans are made to screen specific occupational groups, it should be determined whether workers have legal protection to ensure their right to care and to maintain employment.

2.5.3 Involving partner organizations and dividing roles

Many different partners can be involved in screening for TB, and it is preferable to integrate TB screening into other screening and outreach activities to improve both the efficiency of screening and the relevance for the users. Identifying appropriate entry points for screening is critical, and this requires mapping the health-care providers and social-service providers for relevant groups – for example, endocrinology departments caring for people with diabetes or non-governmental organizations providing social support for vulnerable groups. To offer screening in prisons, links must be established with correctional services, and, likewise, screening in workplaces requires establishing dialogue with employers and departments of occupational health.

The planning for and management of the required financial and human resources should account for all possible stakeholders that 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 screened receive appropriate care. Good coordination between stakeholders is required in order to ensure complementary and avoid overlap or that conflicting approaches being implemented.

It is not effective to implement TB screening unless treatment, care and support services are of high quality. Implementing an effective systematic screening programme for TB provides opportunities to enhance support for patients receiving treatment as part of the overall outreach efforts, and this may improve not only detection but also treatment results.

If human resources are limited, those who are engaged to help in case-finding can and should also support patients who are receiving TB treatment, especially patients who are members of high-risk groups who may face more barriers to completing treatment.¹⁰ For example, lay workers employed to screen people living with HIV can also provide treatment support at the same facilities.

2.5.4 Mobilizing resources

Many times, national TB programmes will not have extra money in their core budgets to carry out screening activities, and these funds will need to come from other sources. However, once some screening activities have been shown to be effective, funding may be made available from programme budgets for screening to form part of national TB programmes' activities (PLHIV, contact investigation).

As part of efforts to detect and treat all people with TB, screening activities need to be prioritized in accordance with findings in the initial situation analysis. A national strategic plan should be written to position for external funding for screening activities, and careful planning and initial assessments should be readily available to support any planned activities.

2.5.5 Pilot testing

It is critical to pilot test a newly designed screening programme to ensure that it operates as designed. Piloting provides a valuable opportunity to test and refine new instruments, protocols, data systems and management structures. It also allows for an 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 and to allow the design or the protocol to be modified if necessary.

2.6 Monitoring, evaluating and modifying the programme

A monitoring and evaluation plan should be developed as 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, or cost per case detected, or some combination of these.

Indicators need to be chosen and forms for collecting data need to be created for or adapted to the specific objectives and local conditions. In order to monitor yield and the NNS in each targeted risk group, an appropriate information system needs to 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 within each group may change over time, and prioritization for screening will have to be adapted accordingly.

Because some members of any particular risk population will eventually find their way to diagnosis through the patient-initiated pathway if not screened, it is of interest to evaluate what impact screening in a particular group has on overall additional notification 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 activities are simply concentrating case-finding in a few facilities, which may occur 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.

Because one objective of screening is early detection, it may also be useful to measure delays in diagnosis and treatment. This, however, will require special surveys.

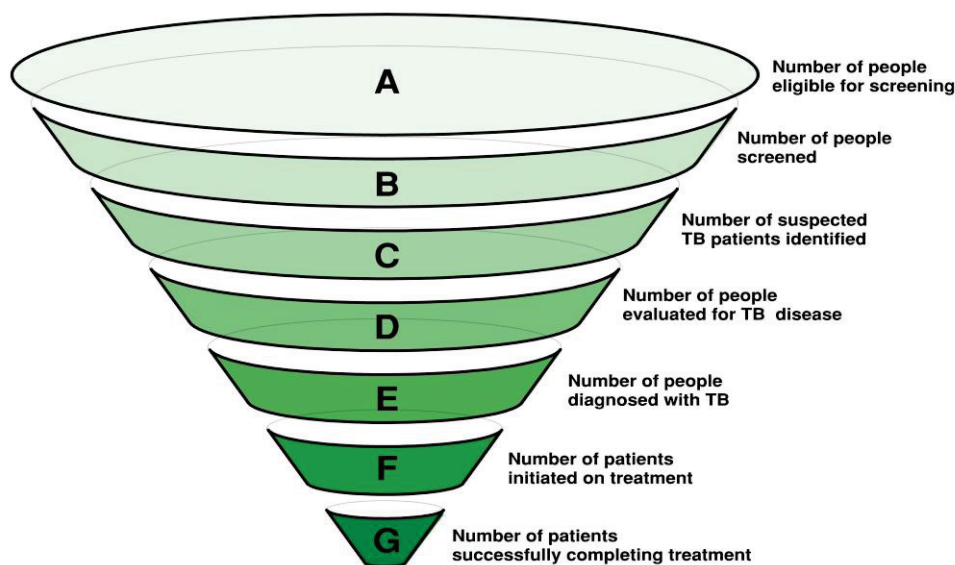
2.6.1 Developing a plan for monitoring and evaluation

Monitoring and evaluating systematic screening should be incorporated into the monitoring and evaluation programmes used within the national TB programme. Targets should be set for the expected yield, the NNS and costs in relation to benefits.

2.6.2 Proposed indicators

Approaches to screening will vary for different groups, and intervention-specific indicators should be developed for each approach. In general, however, data on the indicators shown in *Figure 10* should be collected for each targeted risk group.

Figure 10. Data to be collected for most systematic screening programmes for tuberculosis (TB)



From the data collected in *Figure 10*, the following basic indicators can be calculated for each respective risk group:

- the proportion of people screened among those eligible (B/A);
- the proportion of people suspected of having TB among those screened (C/B);
- the proportion of people tested or evaluated for TB among patients suspected of having TB (D/C);
- the proportion of people diagnosed among those screened (E/B) and tested (E/D);
- the proportion of people initiating treatment among those diagnosed (F/E);

- the proportion of people successfully completing treatment among those who initiated treatment (G/F).

It is critical to monitor the yield of bacteriologically confirmed TB versus bacteriologically unconfirmed TB. A high proportion of TB cases that have not been confirmed with a bacteriological test may indicate over-diagnosis and should lead to a closer evaluation of screening and diagnostic routines.

Data may also be disaggregated by age and sex – but this requires that detailed data be collected for each individual screened.

Additional indicators of process (such as the number of people reached and screened per day, the time required for each step of the screening and diagnostic procedure, and the number of people requiring referral) should be collected during the pilot phase of a screening programme to ensure that it is operating as designed. However, once the programme has been established, these additional indicators should be discarded and the focus should be shifted to streamlining the programme and scaling it up.¹⁵

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. Normally, it is possible to obtain the relevant information for screening that is conducted in health facilities, closed settings (such as prisons) and through contact investigations. However, it is often difficult to obtain this information from outreach screening programmes – for example, when screening is done in the community – although the estimated population of a targeted community may be used to obtain a rough estimate of the eligible population.

Whenever screening occurs, a baseline should be developed using historical data, if available.³¹

2.6.3 Routines for recording and reporting

In order to obtain the information required for the indicators described above, a recording and reporting system for TB screening needs to include:

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

- a column in the treatment register to note whether the patient was identified through screening and to which risk group the patient belongs;
- other forms may be necessary depending on the approach used and the existing registers. For example, if contact investigation will be implemented, there should be specific forms to properly track this activity.

2.6.4 Programmatic evaluations

Based on the results from monitoring the indicators discussed above, a special assessment may be needed to explore, for example, the reasons for a low uptake of screening, an unexpectedly low proportion of people suspected of having TB identified by screening, a low proportion of those suspected of having TB who had a diagnostic investigation, a higher than expected NNS, or a high proportion of cases that are not bacteriologically confirmed.

Additional quantitative and qualitative analyses may be needed to determine whether there are barriers to screening, to identify opportunities to improve the screening approach and whether there have been any social consequences from the screening activities. 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.

2.6.5 Monitoring time trends for rescreening and reprioritization

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 as well as changes in the profile of TB patients in the community (for example, a trend towards fewer patients with symptomatic TB and fewer cases of smear-positive TB) can lead to a reduction in the yield from screening, an increase in the NNS, a reduction in cost effectiveness, and a change in the ratio of benefits to harms. Trends in all of these indicators need to be monitored, and the prioritization of risk groups, choice of screening approach, and screening interval should be reassessed regularly. Criteria for stopping screening should be established before a screening initiative is implemented.

2.6.6 Research

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

- assessing the accuracy and performance of different algorithms for screening and diagnosis;
- identifying operational challenges and solutions;
- identifying the best ways to improve the acceptability of screening and minimize the harms;
- establishing the effectiveness and cost effectiveness of screening in different risk groups and in different epidemiological situations.

For a number of algorithms it may be useful to evaluate the PPV. Evaluating the PPV can be much simpler than assessing accuracy, which includes evaluating the sensitivity of the algorithm. Evaluating sensitivity requires testing a large number of persons with the reference standard, but assessing the PPV requires only that those diagnosed as having TB are tested with a reference standard.

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

3. Web-based tool to assist risk group prioritization and algorithm choices

3.1 Introduction to the tool

The most desirable screening strategy would be 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 tend to run in opposite directions, so a multifactorial analysis is needed.

An online tool has been developed to assist with the process of prioritizing risk groups for screening and choosing appropriate screening and diagnostic algorithms. The tool allows users to select one or a number of risk groups for exploration, and for each risk group selected the tool estimates the yield and costs of screening and diagnosis for each different screening algorithm.

The tool is intended as an aid to explore which risk groups that may potentially be screened and which screening and diagnostic algorithms may be most appropriate to use. The tool must not be used as the only source of information for prioritization, planning and budgeting. Rather it can be used as a starting point for these processes, which are outlined in section 2. The limitations of the tool are further discussed in section 3.3.

The online tool builds on a previous tool which was developed before the WHO issued guidelines on systematic screening for active TB.³² The present tool models yields for the screening algorithm options listed in the WHO guideline based on data from systematic reviews of accuracy of different screening and diagnostic tests and assumed prevalence of culture positive pulmonary TB among screened risk groups.³³

All calculations are made for specific country settings. Some of the necessary information (including TB prevalence in the general population and the sensitivity and specificity of different screening and diagnostic tests) is prepopulated with estimates from various data sources, while some information must be provided by the user. It is important to note that much of the prepopulated generic data is based on point estimates from systematic reviews (including studies up to 2012) and may not be applicable in a given setting. The accuracy of diagnostic tests varies in certain groups and settings, and technologies are improving. The user must therefore review all prepopulated estimates to ensure they are appropriate, and make changes as required. The collection of relevant data to enter into the tool should be part of the situation assessment (see section 2.1.3). Moreover, it is always advisable to perform sensitivity analyses using confidence intervals or plausibility ranges for key assumptions.

Users who are unfamiliar with interpretation of sensitivity, specificity and predictive values of screening and diagnostic tests are advised to seek assistance from persons with expertise in clinical epidemiology.

3.2. How to use the tool

The user begins by selecting the country for which screening will be modelled, and then selects the risk groups to explore. The user then provides estimates, or confirms prepopulated data, for the following inputs:

- **Population size and TB prevalence of general population** – The user can rely on national estimates provided or can enter other estimates if better data is available or for subnational calculations.
- **Size of selected risk groups** – This should be provided either as an absolute number or as a proportion of the general population (equivalent to the prevalence of the risk factor in the country).
- **TB prevalence in selected risk groups** – This should be provided either as an absolute figure (per 100 000 population) or as the relative risk for TB in the group compared with the risk in the general population. Relative risks for certain groups have been provided based on data from systematic reviews; these estimates are prepopulated in the tool. The user should review any prepopulated estimates to ensure they are appropriate, and update as necessary with national estimates.
- **Reachability and acceptability of screening** – This is the proportion of each selected risk group that may be reached by a screening programme, and then once reached, the proportion of each selected risk group that may accept screening.
- **Costs of screening and diagnostic tests** – This is the estimated cost per screening or diagnostic test performed in a screening programme. Estimates for the running costs of test are provided for chest X-rays, sputum-smear microscopy and the Xpert MTB/RIF assay, stratified by global region. The user should review test costs and add start-up, operational and overhead costs.

The tool then generates the following estimates for each risk group selected:

- **the number of people expected to be screened;**
- **the number of prevalent culture positive pulmonary TB cases;**
- **the number of true culture positive TB cases that may be detected, according to the sensitivity of the screening algorithm used;**
- **the number of cases missed;**
- **the number of false-positive diagnoses expected, according to the specificity of the screening algorithm used;**
- **the NNS to detect one true case of pulmonary TB; and**
- **the total cost and cost per true case detected for screening the selected risk group, according to the screening algorithm used.**

To allow for easy visual comparison across risk groups and across screening algorithms, the tool produces graphs of the potential yield of true-positive and false-positive cases (Figure 6), the NNS (Figure 7), the cost per case detected (Figure 8), and the costs versus yield comparison of various potential screening algorithms (Figure 9).

In order to understand how variations in the estimated parameters and the targeted populations affect estimates of size, yield and cost, the user should repeat the process of generating estimates while varying some or all of the inputs and risk groups.

Figure 6. Potential yield of true-positive and false-positive cases of TB in three risk groups, per screening algorithm used (Algorithms can be found in the annex)

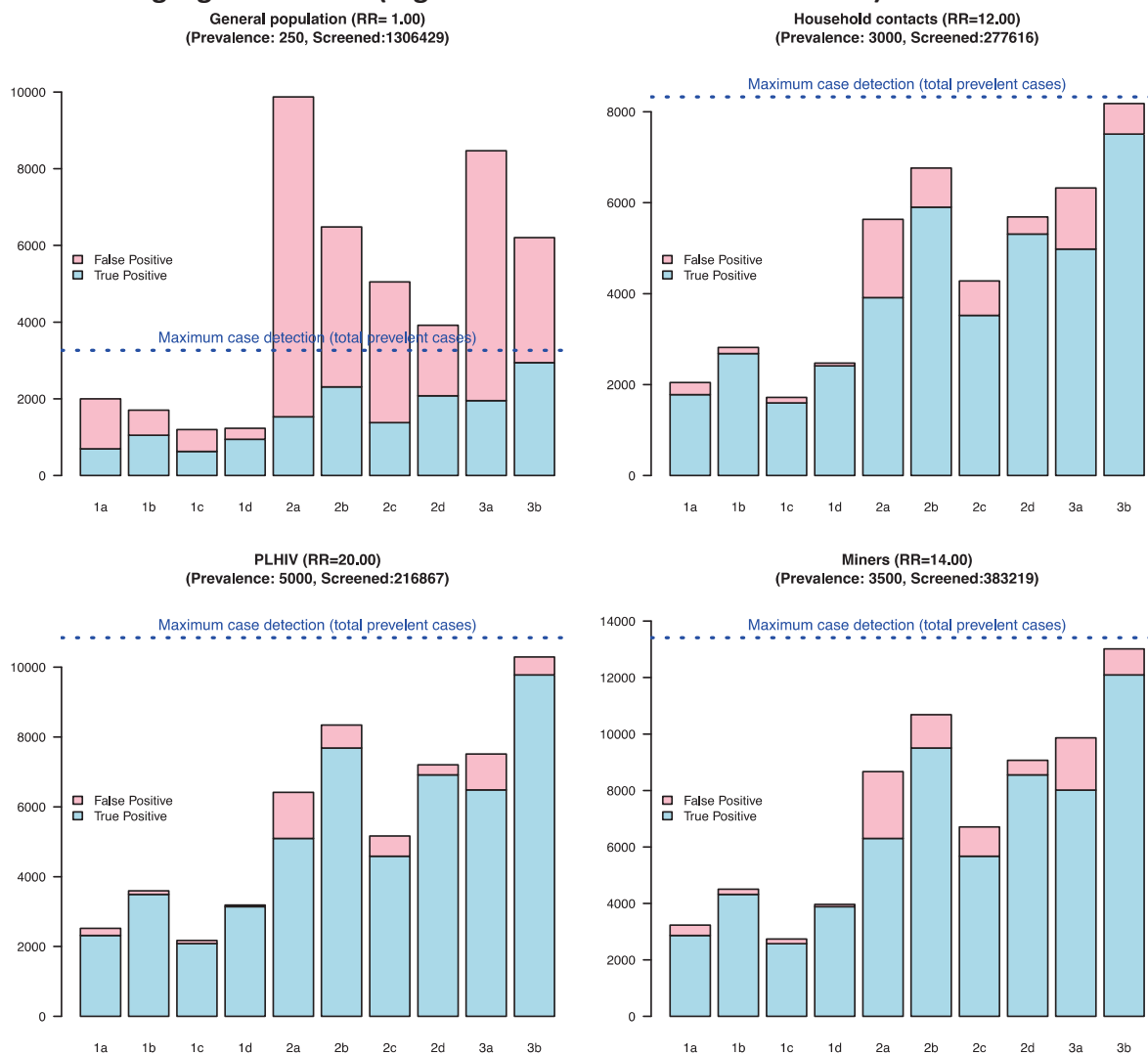


Figure 7. The number needed to screen (NNS) to detect one true case of TB in three risk groups with specified relative risks of TB, per screening algorithm used (Algorithms can be found in the annex)

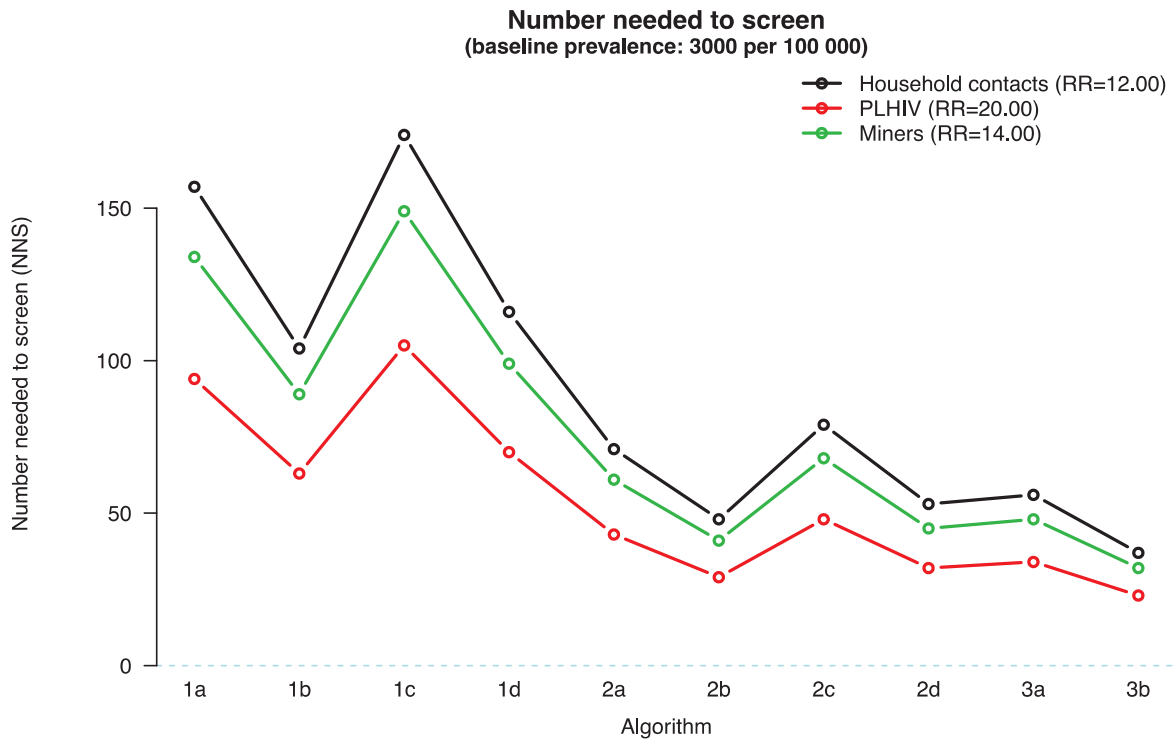


Figure 8. Screening and diagnostic costs per true case detected in three risk groups with specified relative risks of TB, per screening algorithm used (Algorithms can be found in the annex)

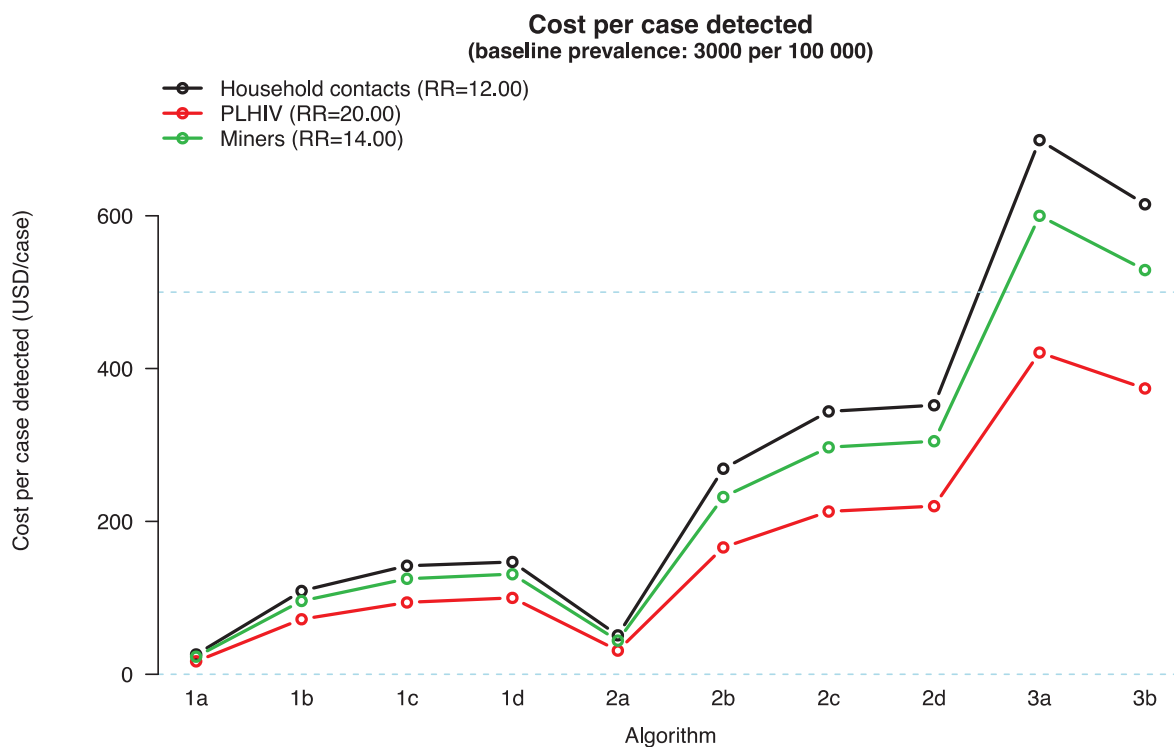
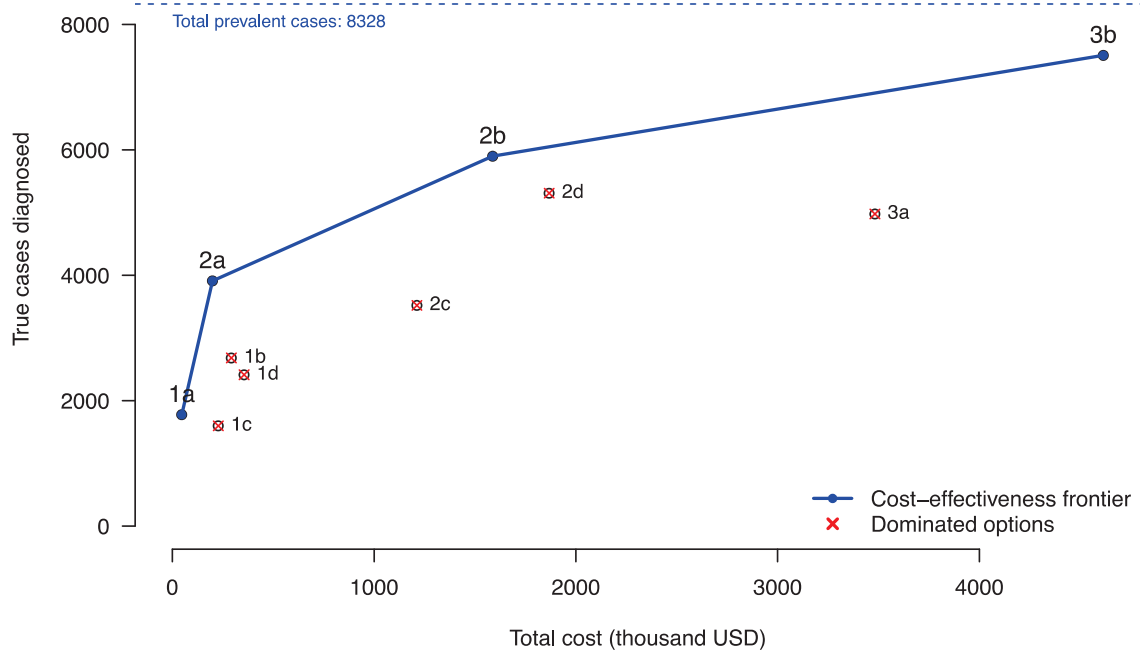
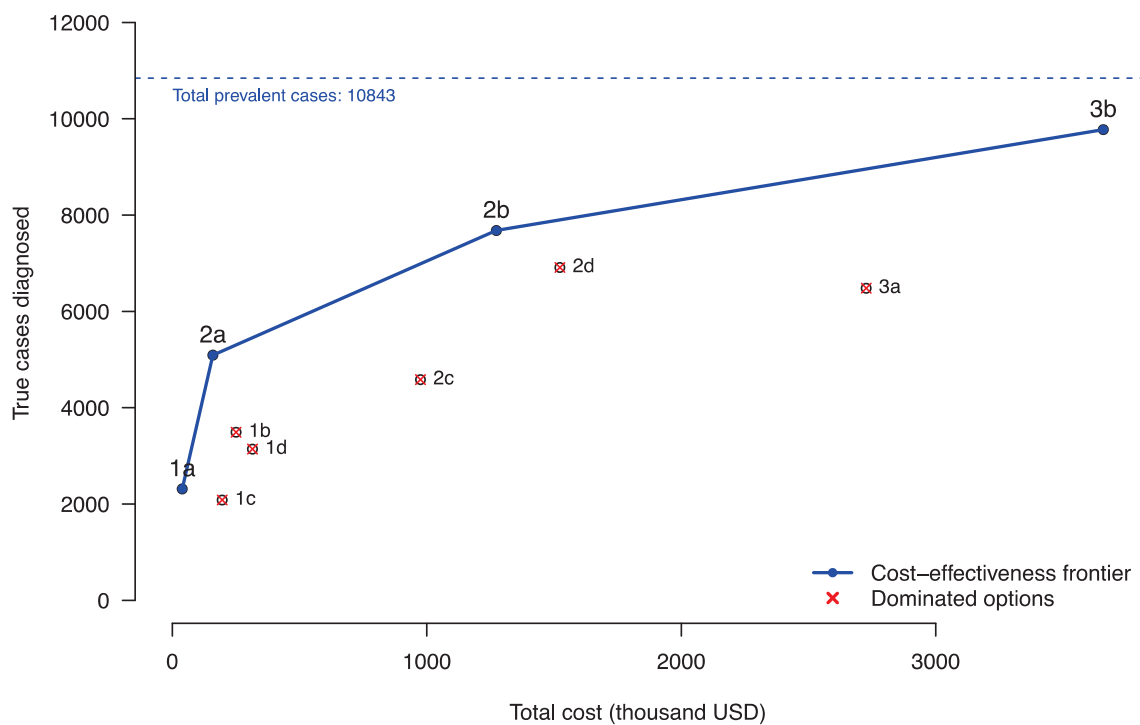


Figure 9. Incremental costs and incremental yield of screening across screening algorithms in two risk groups of specified size and TB prevalence, per screening algorithm used (Algorithms can be found in the annex)

Household contacts (RR=12.00)
(Prevalence: 3000, Screened:277616)



PLHIV (RR=20.00)
(Prevalence: 5000, Screened:216867)



3.3 Limitations of the tool

There are several limitations to this tool that include but are not limited to the following:

- ***The estimates produced by the tool are based on a series of assumptions.*** Each parameter entered into the tool is an estimate with inherent uncertainty. The uncertainty across all of the parameters used in the tool compounds the overall uncertainty of the estimates produced by the tool.
- ***The tool requires significant input from the user.*** Using the tool requires specific inputs from the user, and some of these inputs can be difficult to estimate. The resulting outputs from the tool are only as good as the data provided, both by the tool and by the user.
- ***The tool does not account for overlaps among risk groups.*** It is likely that people who belong to a risk group selected for targeted screening will also have other risk factors and, therefore, will be part of one or several other risk groups. If a screening programme includes many potentially overlapping risk groups, this overlap should be adjusted for. It may also be prudent to consider and incorporate the potentially increased risk for TB among people with many risk factors.
- ***The tool does not estimate the potential additional number of cases detected through screening, nor the relative effectiveness compared with interventions to improve the patient-initiated pathway.*** The estimated number of true cases that can be detected through screening can not be assumed to be equal to additional case detection since a proportion of them would be detected through health seeking. The tool does not estimate additional case detection from efforts to improve the patient-initiated pathway.
- ***The tool does not model the impact of screening on the future prevalence or incidence of TB.*** Estimates are cross-sectional and do not incorporate any future changes in the epidemiology of TB. When screening is repeated in the same population at regular intervals, the prevalence and incidence of TB may diminish, especially in confined populations, such as in prisons. The tool only estimates the yield of the first screening round. For subsequent screening rounds the user will have to adjust inputs in line with assumed change in TB prevalence. The tool cannot be used to predict impact on TB transmission and long term effects on TB incidence. For this, dynamic transmission modelling is required.
- ***The tool does not estimate impact on diagnostic delay, disease severity at time of diagnosis, or improvement in treatment outcomes from early treatment initiation.***
- ***The tool does not incorporate elements of equity and fairness.***

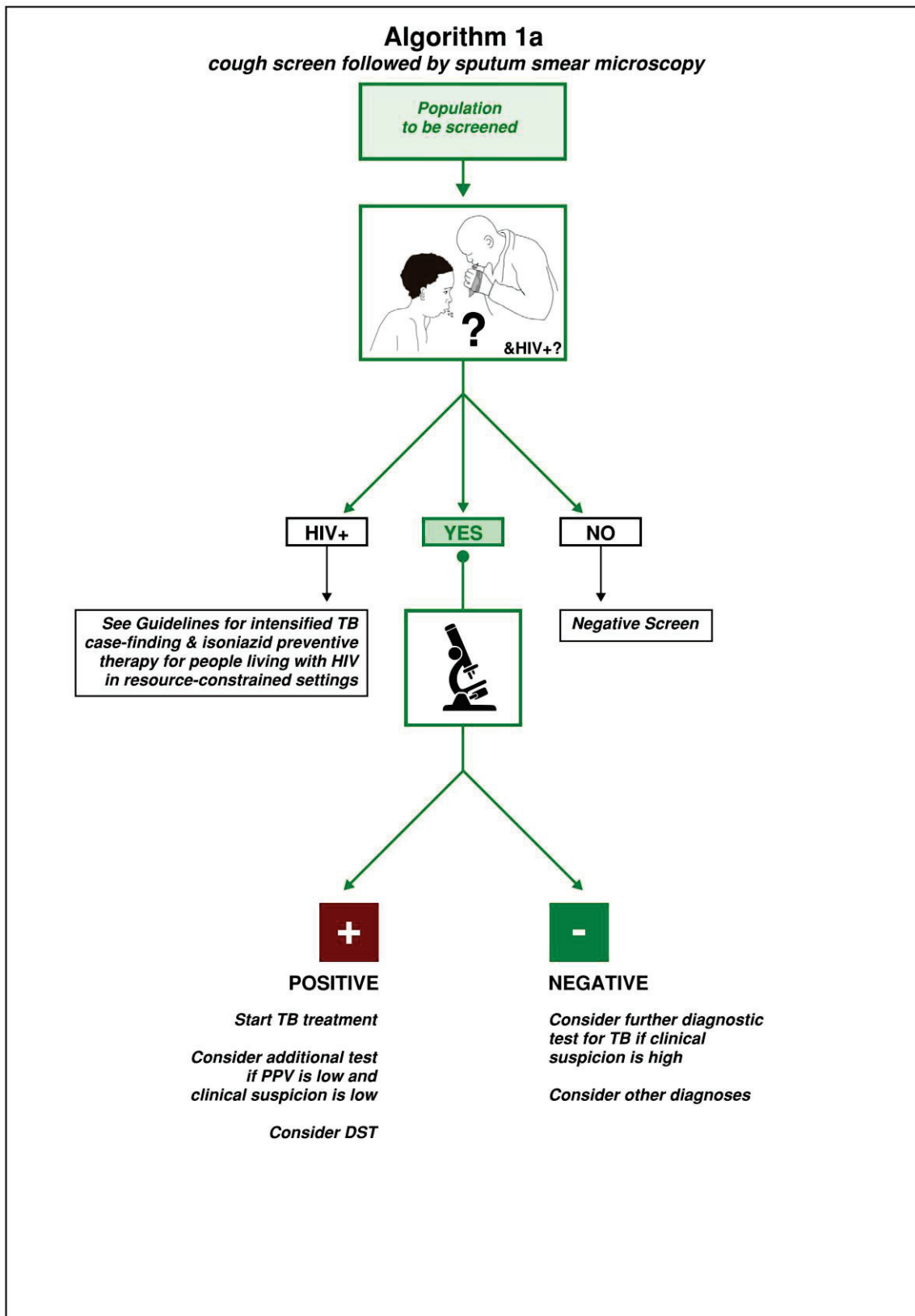
For these reasons ***the tool is meant to serve only as an aid in the process of prioritizing risk groups for screening and choosing screening algorithms.*** It should not be used for detailed planning, or for projection of future impact on TB epidemiology. See section 2 for other elements of the planning and implementation process.

References

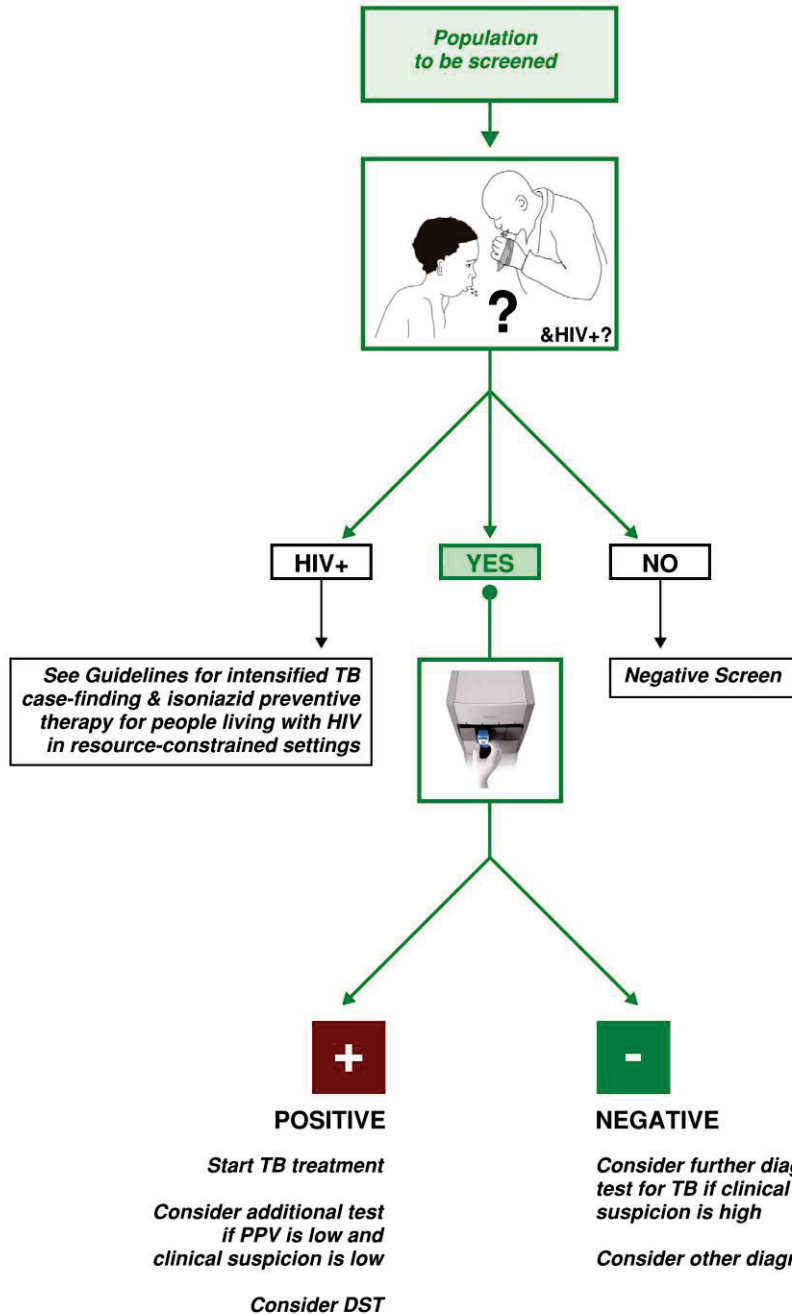
1. World Health Organization. Global Tuberculosis Report, 2013. Geneva: World Health Organization, 2013.
2. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC public health* 2008; **8**: 15.
3. Raviglione M, Marais B, Floyd K, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. *Lancet* 2012; **379**(9829): 1902-13.
4. World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015: Post-2015 global tuberculosis strategy framework. Geneva: World Health Organization, 2014.
5. Uplekar M, Weil D, Lonnroth K, et al. WHO's new End TB Strategy. *Lancet* 2015.
6. World Health Organization. Systematic screening for active tuberculosis: Principles and recommendations. Geneva: World Health Organization, 2013.
7. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet* 2006; **367**(9514): 952-5.
8. World Health Organization. An expanded DOTS framework for effective tuberculosis control. Geneva: World Health Organization, 2002.
9. Corbett EL, MacPherson P. Tuberculosis screening in high human immunodeficiency virus prevalence settings: turning promise into reality. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(9): 1125-38.
10. Golub JE, Dowdy DW. Screening for active tuberculosis: methodological challenges in implementation and evaluation. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(7): 856-65.
11. Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(4): 432-46.
12. Lönnroth K, Corbett E, Golub J, et al. Systematic screening for active tuberculosis: rationale, definitions and key considerations. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(3): 289-98.
13. Uplekar M, Creswell J, Ottmani SE, Weil D, Sahu S, Lönnroth K. Programmatic approaches to screening for active tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(10): 1248-56.
14. Zenner D, Southern J, van Hest R, et al. Active case finding for tuberculosis among high-risk groups in low-incidence countries. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013; **17**(5): 573-82.
15. World Health Organization. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, 2012. WHO/HTM/TB/2012.9.
16. World Health Organization. Early detection of tuberculosis: An overview of approaches, guidelines, and tools. Geneva, 2011. WHO/HTM/STB/PSI/2011.21.

17. World Health Organization. Engaging all health care providers in TB control: Guidance on implementing public-private mix approaches. Geneva: World Health Organization, 2006.
18. World Health Organization. Practical approach to lung health (PAL): A primary health care strategy for integrated management of respiratory conditions in people of five years of age and over. Geneva: World Health Organization, 2005.
19. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Geneva, 2007. WHO/HTM/TB/2007.379 & WHO/HIV/2007.1
20. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test: Technical and operational "how-to": Practical considerations. Geneva: World Health Organization, 2011. WHO/HTM/TB/2011.2.
21. World Health Organization. Tuberculosis prevalence surveys: a handbook. Geneva: World Health Organization, 2011.
22. World Health Organization. Understanding and using tuberculosis data. Geneva: World Health Organization, 2014.
23. World Health Organization. Framework for conducting reviews of tuberculosis programmes. Geneva: World Health Organization, 2014.
24. World Health Organization. Public–Private Mix for TB Care and Control: A tool for national situation assessment. Geneva: World Health Organization, 2007.
25. World Health Organization. ENGAGE-TB: integrating community-based tuberculosis activities into the work of nongovernmental and other civil society organizations. Geneva: World Health Organization, 2012.
26. Tuberculosis Coalition for Technical Assistance. The Tool to Estimate Patients' Costs 2008.
27. Contributing to health system strengthening - Guiding principles for national tuberculosis programmes. WHO/HTM/TB/2008.400. Geneva: World Health Organization, 2008.
28. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization, 2015.
29. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. Geneva: World Health Organization, 2011.
30. World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva: World Health Organization, 2010.
31. Blok L, Creswell J, Stevens R, et al. A pragmatic approach to measuring, monitoring and evaluating interventions for improved tuberculosis case detection. *International health* 2014; **6**(3): 181-8.
32. Nishikiori N, Van Weezenbeek C. Target prioritization and strategy selection for active case-finding of pulmonary tuberculosis: a tool to support country-level project planning. *BMC Public Health* 2013 Feb 2;13:97
33. van 't Hoog AH, Onozaki I, Lönnroth K. Choosing algorithms for TB screening: a modelling study to compare yield, predictive value and diagnostic burden. *BMC Infectious Diseases* 2014; **14**: 532. doi: 10.1186/1471-2334-14-532.

Annex 1. Ten potential screening and diagnostic algorithms.

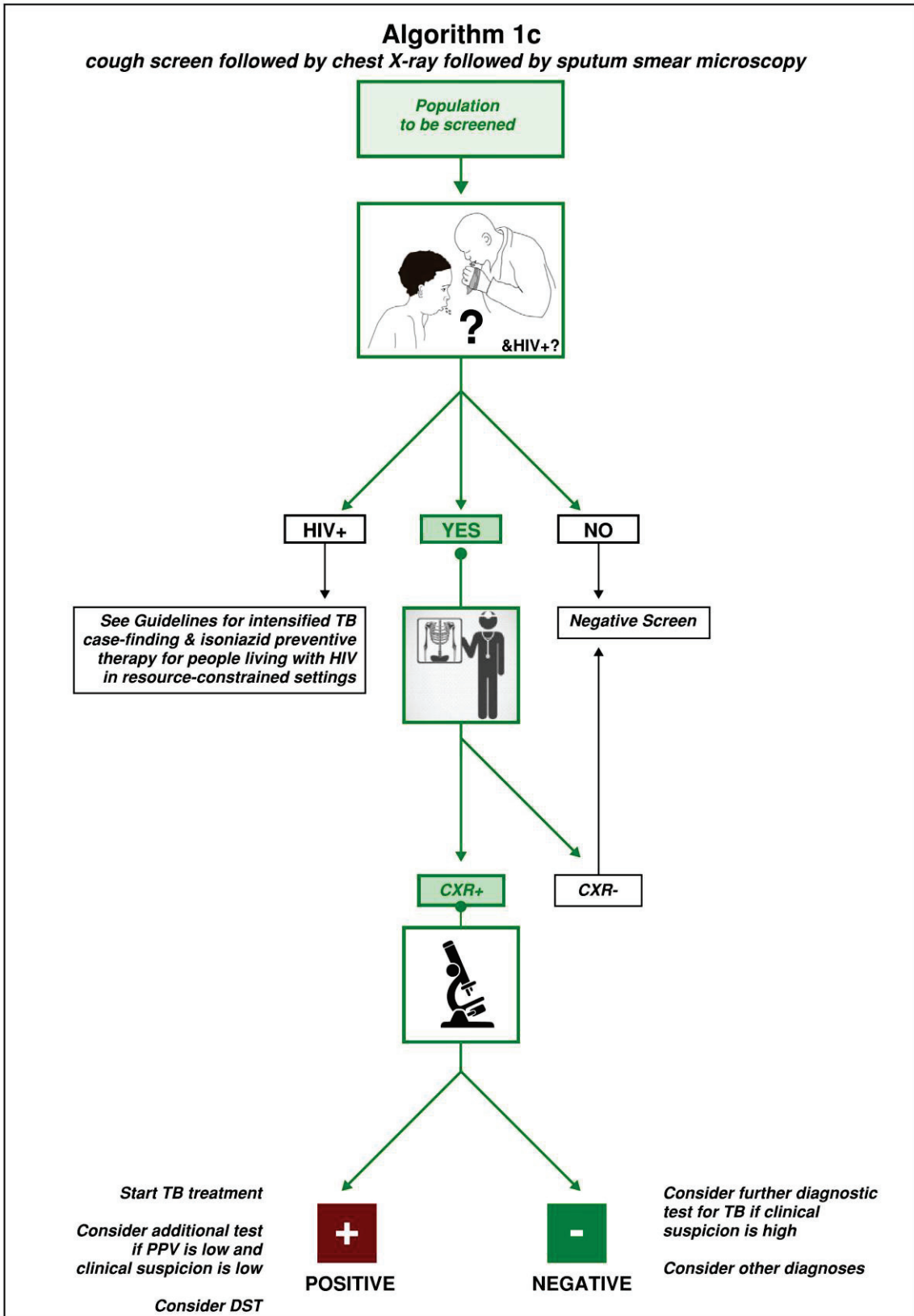


Algorithm 1b
cough screen followed by GeneXpert

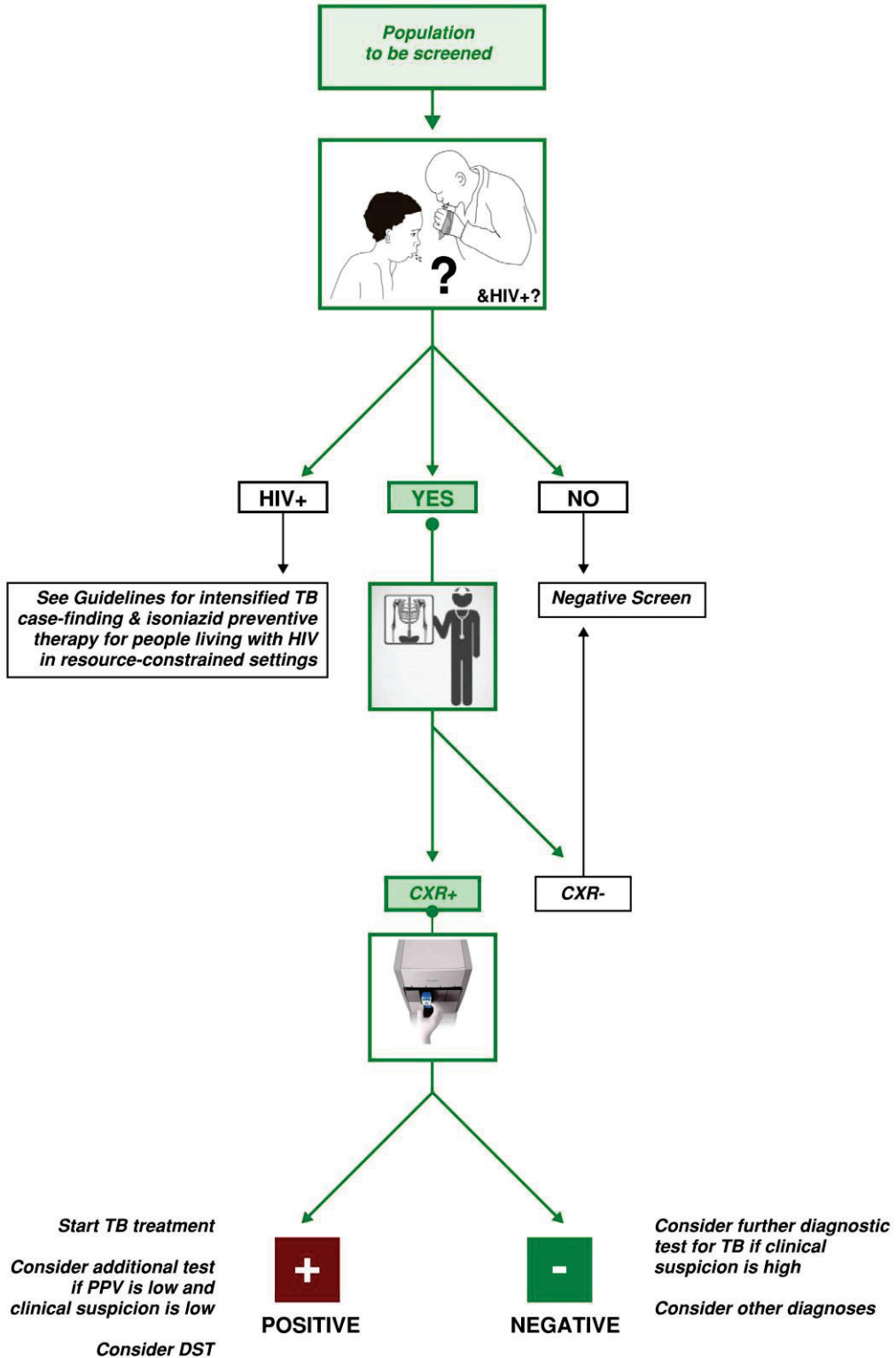


Algorithm 1c

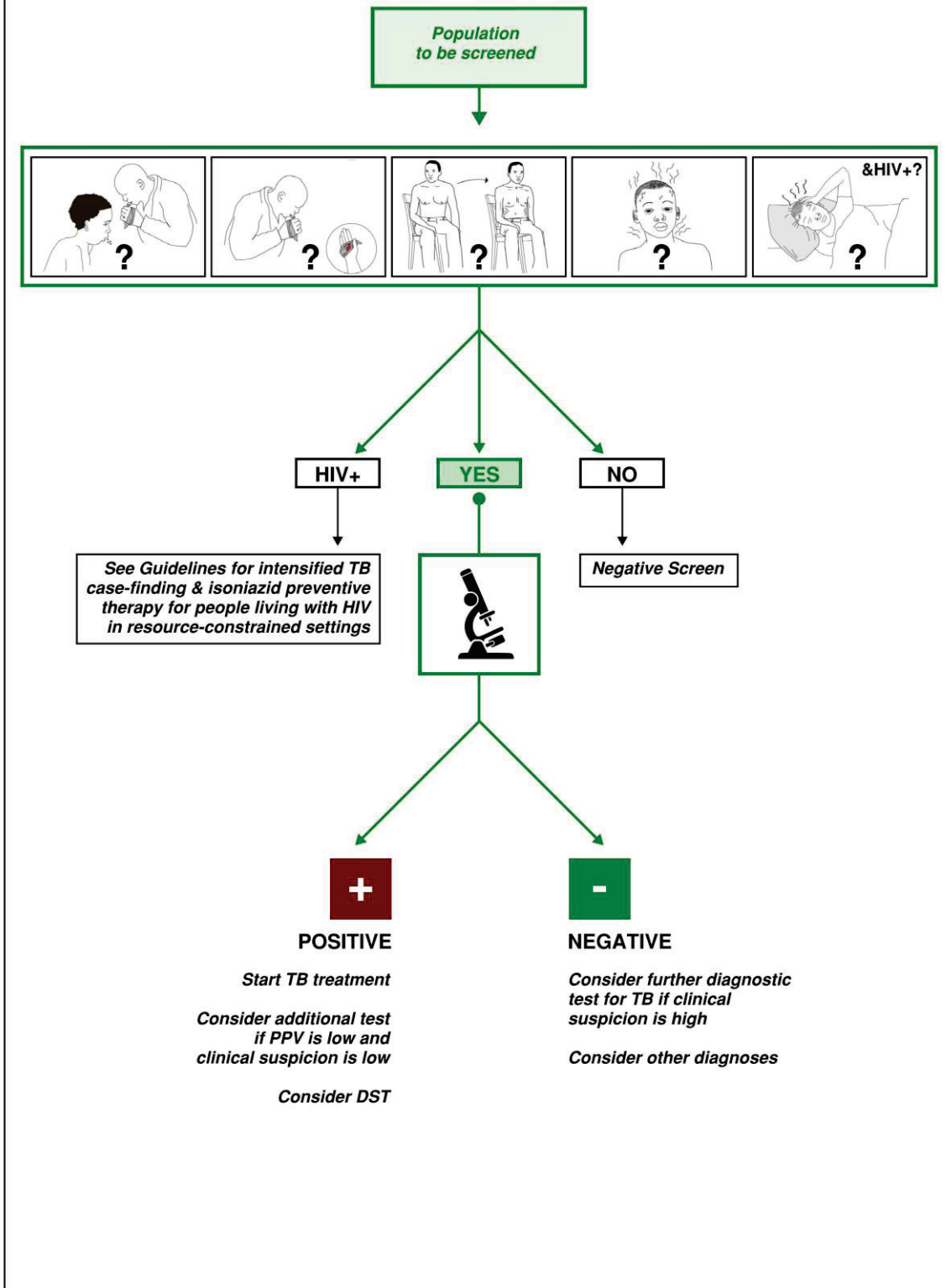
cough screen followed by chest X-ray followed by sputum smear microscopy



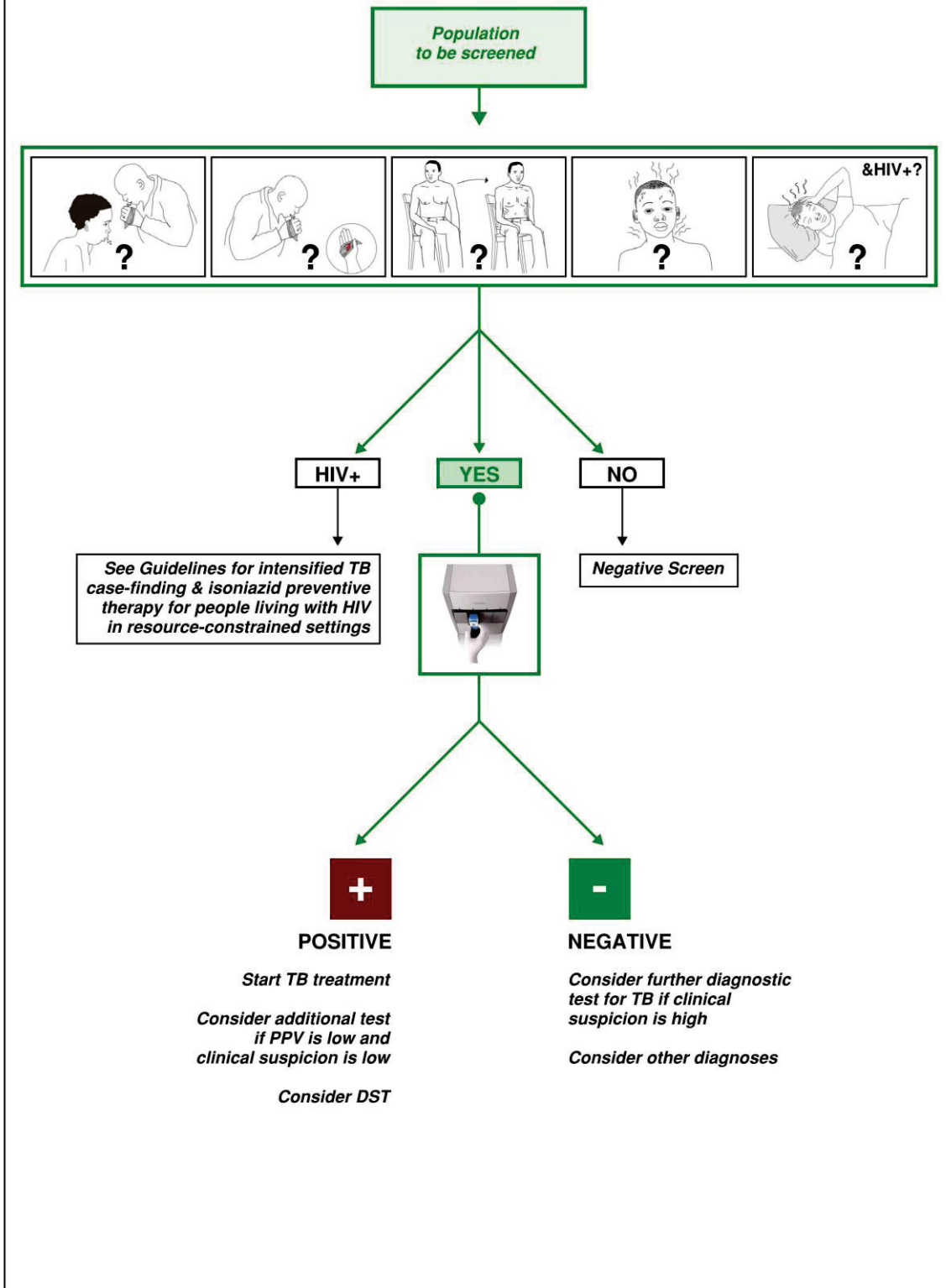
Algorithm 1d
cough screen followed by chest X-ray followed by GeneXpert



Algorithm 2a
any TB symptom screen followed by sputum smear microscopy

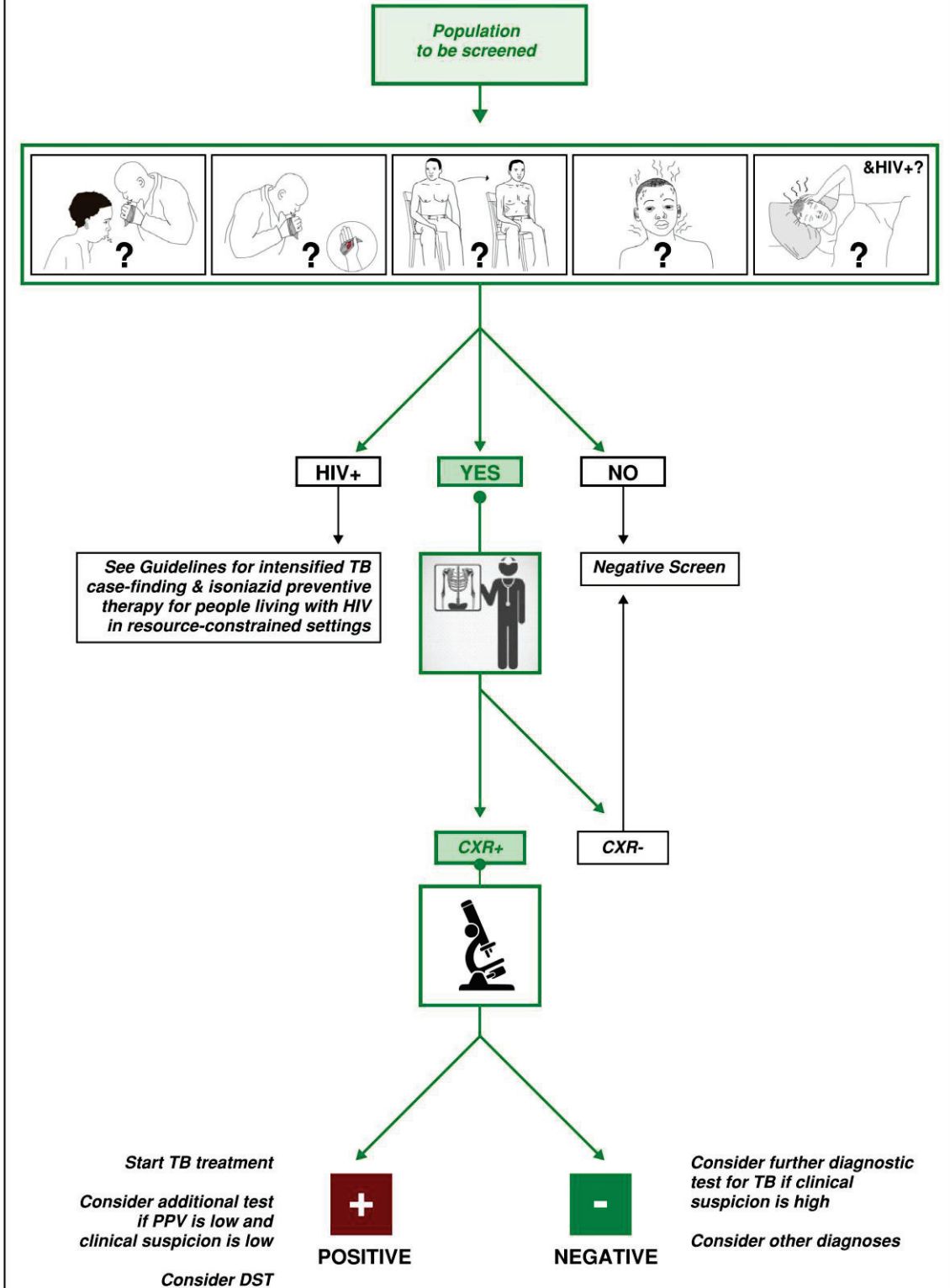


Algorithm 2b
any TB symptom screen followed by GeneXpert



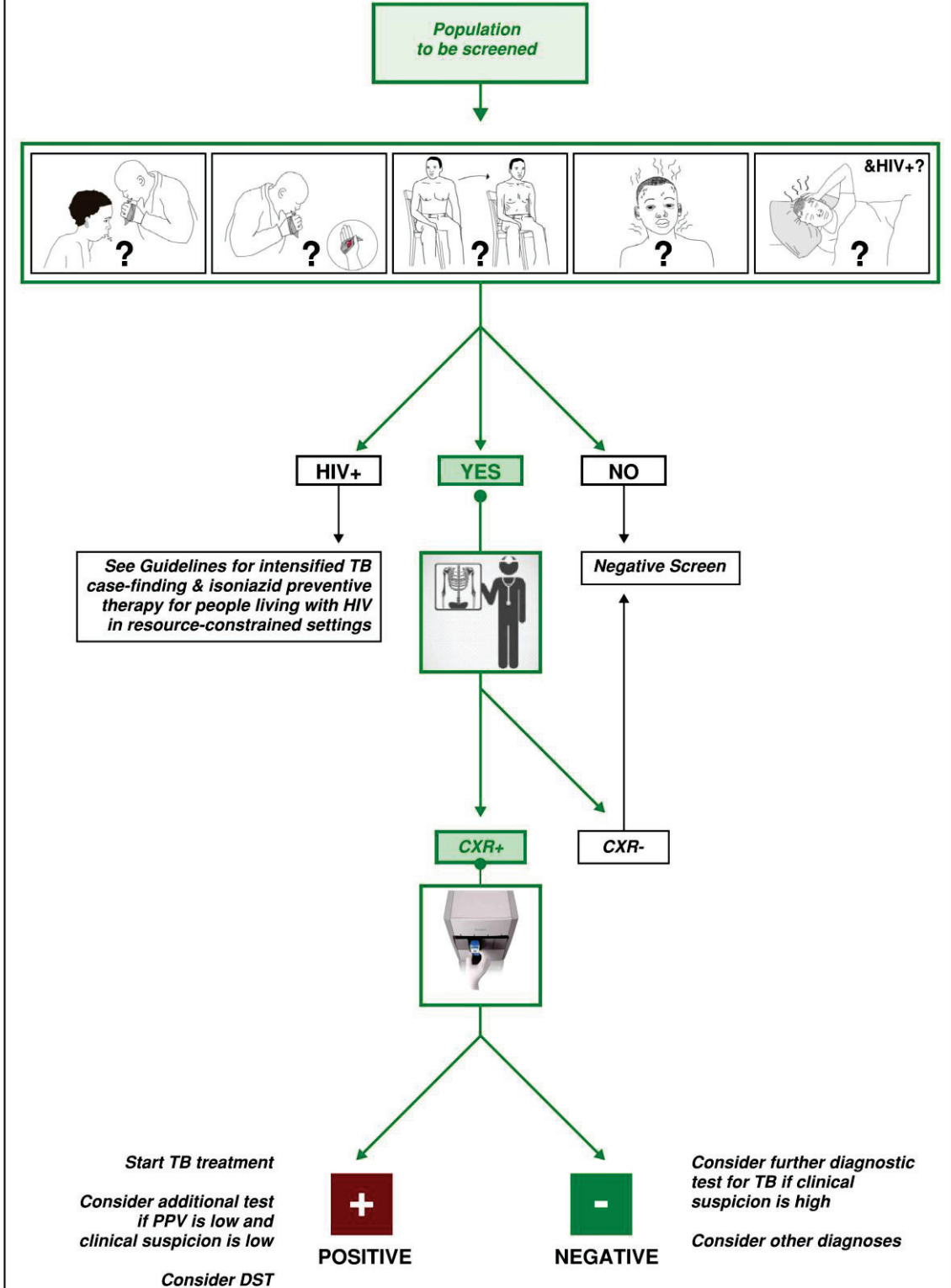
Algorithm 2c

any TB screen followed by chest X-ray followed by sputum smear microscopy

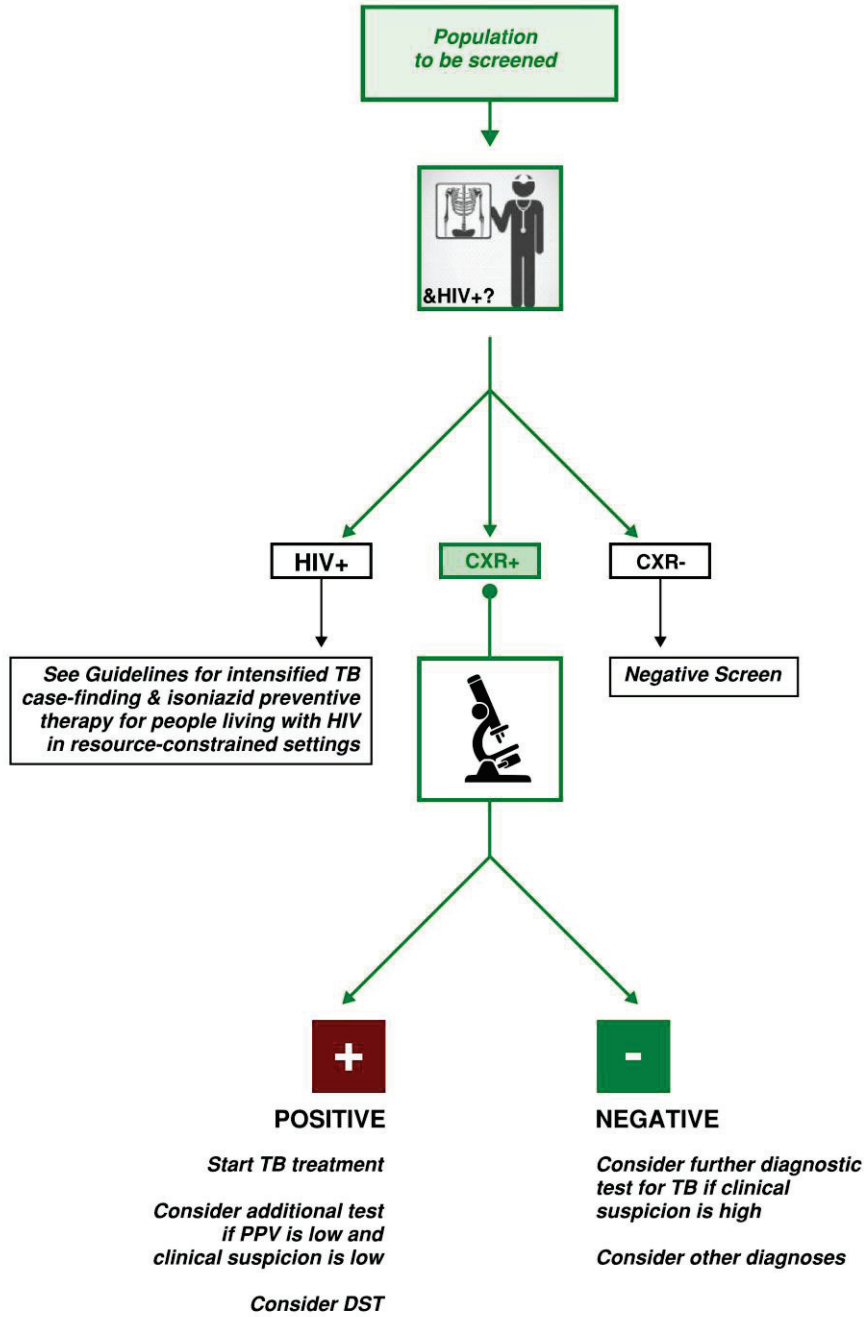


Algorithm 2d

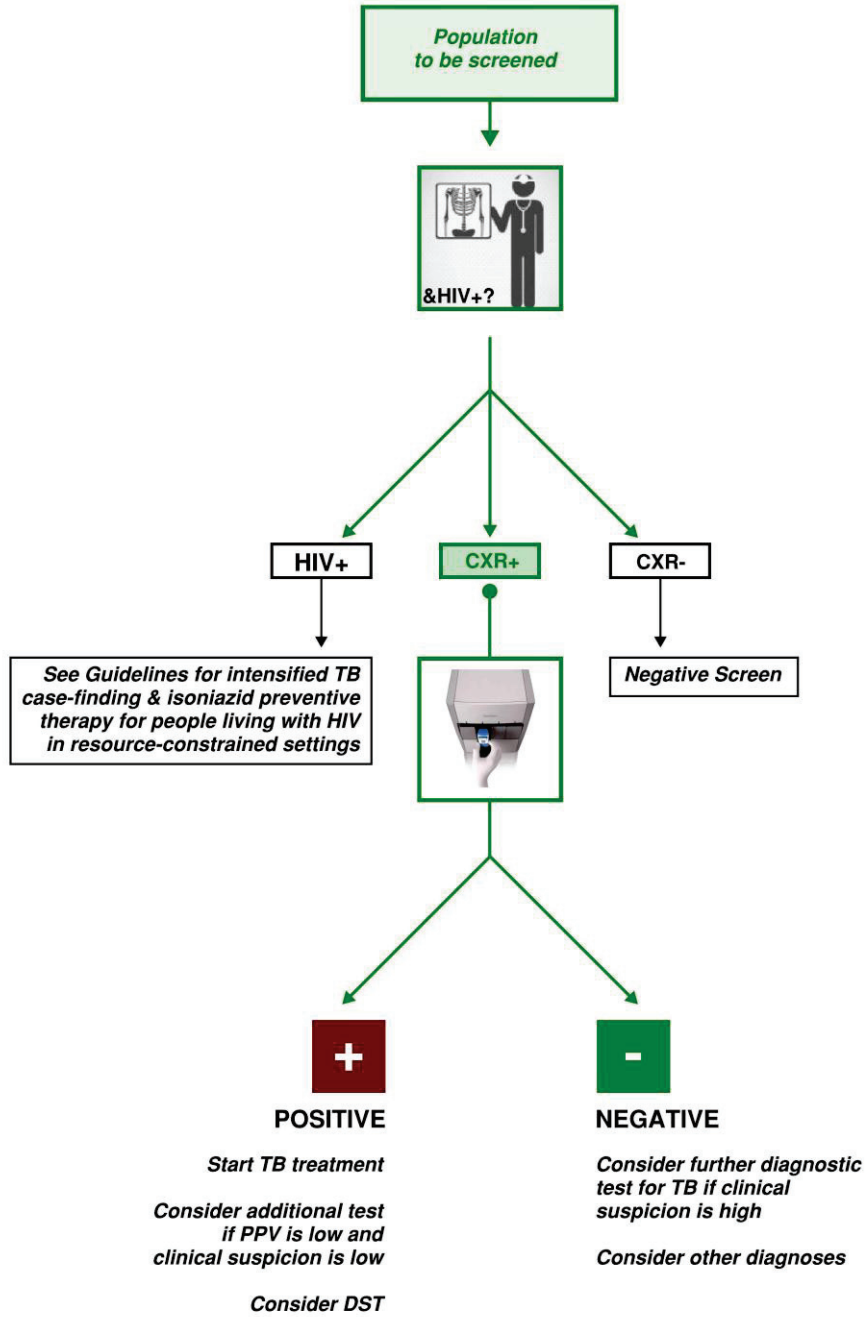
any TB screen followed by chest X-ray followed by GeneXpert



Algorithm 3a
chest X-ray followed by sputum smear microscopy



Algorithm 3b
chest X-ray followed by GeneXpert



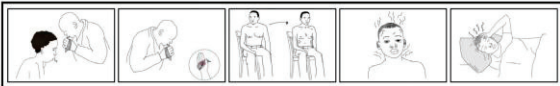
Algorithm Key

TB	Tuberculosis
HIV	Human Immunodeficiency Virus
PPV	Positive Predictive Value
DST	Drug Susceptibility Testing
CXR	Chest X-Ray

Algorithm Legend



Cough Screen



Any TB Symptoms Screen



Chest X-Ray



Sputum Smear Microscopy



GeneXpert MTB/RIF

