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Systematic screening for active tubeculosis: rationale, definitions and key considerations

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Title: Systematic screening for active TB: rationale, definitions and key considerations

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Summary

The impact of current interventions to improve early detection of TB seems to have been saturated. Case detection trends have stagnated. Incidence of TB is falling in most settings world-wide, but the rate of decline is far lower than expected. There is growing evidence from national TB prevalence surveys and other research of a large pool of undetected TB in the community. Intensified efforts to further break down access barriers and scale up new and rapid diagnostic tools is likely to improve the situation. However, would this be enough? Or, do we also need to reach out more towards people who do not actively seek care with well-recognisable TB symptoms? Recently, there have been calls to revisit TB screening, particularly in high risk groups. WHO recommends screening for TB in people living with HIV and in close TB contacts. Should other risk groups also be screened systematically? Could community-wide mass screening, which WHO has discouraged during the past four decades, be of benefit in some situations? If so, what screening tools and approaches should be used? WHO is in the process of seeking to answer these questions and developing guidelines on systematic screening for active TB. In this paper, we present the rationale, definitions, and key considerations underpinning this process.

Introduction

In 1974, the 9th report of the WHO's Expert Committee on Tuberculosis stated that "the policy of indiscriminate tuberculosis case finding by mobile mass radiography should now be abandoned"[1(p.16)]. Evidence demonstrating the inefficiency of mass screening had mounted, mainly from assessments in populations with low TB prevalence and good access to high quality regular health services[2,3]. In low-income settings screening was deemed inappropriate because basic diagnostic and treatment services were not yet widely available[4,5].

Since then, WHO has advised against mass screening. However, screening per se was never abandoned. "Indiscriminate" is a key word in the negative WHO recommendation from 1974, and the report recommended continued screening of selected risk groups, as long as it was not "at the expense of development of adequate diagnostic and treatment services"[1]. An extensive review of outcomes of screening programmes in Czechoslovakia, The Netherlands and Canada in the 1950 and 1960s had found that selective chest radiography (CXR) screening in specific risk groups yielded similar numbers as mass miniature radiography (MMR) done at 2-3 yearly intervals, while screening much fewer people[6]. The authors concluded that "radiography might be a more efficient instrument in TB control, provided that its indiscriminate mass use is replaced by a discriminate one"[6(page 41)]

Indeed, screening in specific risk groups has been part of the Stop TB Strategy since its launch, namely for people with HIV[7] and household contacts[8]. There are also WHO guidelines on TB diagnosis and management in prison populations[9], among refugees[10] and in people with diabetes[11], though these lack specific advice on when and how to screen for active TB. Screening in those and other risk groups has been implemented especially in low-burden countries with concentrated TB epidemics, but also in some high-burden countries. Recent studies in Zimbabwe[12], Cambodia[13], and Brazil[14] have reported improved case detection and declining TB burden associated with screening. However, guidelines on when screening is appropriate, how to prioritize risk groups, and how to choose an appropriate screening approach are not yet available. WHO is in the process of developing such guidelines.

Low-TB burden countries tend to have concentrated epidemics of TB in specific risk groups and their close contacts, such as selected clinical risk groups, immigrants, prisoners, homeless

people and the elderly. When resources are available, TB screening in selected risk groups may be affordable and have relatively low opportunity costs. Therefore, screening may be a logical way to intensify TB control, especially when a country is striving for TB elimination and needing to invest additional resources to effectively reach those that are hardest to reach.

But, does screening make sense for a high-TB burden country with a more generalised epidemic? And, if it does, which risk groups should be targeted and with what approach? To answer these questions, one needs to examine the intended goals of screening; the alternative interventions to reach those goals; the cost-effectiveness, feasibility and affordability; and the risk of doing harm.

In this paper, while not directly answering these questions, we will define basic screening concepts, review the rationale, and outline key considerations and data requirements for deciding if, when, who and how to screen for active TB.

Terminology

Screening

The WHO has defined screening as *"the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred for diagnosis and necessary treatment."*[15].

We propose that systematic screening for active TB be defined as the *systematic identification of people with suspected active TB in a predetermined target group by the application of tests, examinations, or other procedures which can be applied rapidly*. Among those with suspected TB, the diagnosis needs to be established through application of diagnostic tests and clinical assessment with high combined specificity.

Systematic screening for active TB can, in principle, target the whole population ("mass screening"), or selected risk groups. It can target both people who seek health care (with or without symptoms/signs compatible with TB) and people who do not seek care (either

because they do not perceive that they have a health problem that warrants medical attention, because of access barriers, or other reasons). The latter group might be reached through door-to-door outreach, or by invitation to be screened at a mobile or stationary clinic.

"Passive case finding" has conventionally meant that TB is looked for mainly among people who actively seek care due to symptoms compatible with TB[16]. It is in principle a "patient-initiated" pathway to TB diagnosis[17]. However, it can be complemented with screening, for example if TB symptoms are systematically asked about among all people seeking care in a general outpatient department. Screening and passive case finding are therefore not mutually exclusive. Screening is in principle "provider-initiated", and offered to a pre-determined target group. However, once made available, a screening test may be requested by patients. Therefore, screening may also be partly "patient-initiated". "Active case finding" is often used as a synonym for screening, though mainly implying screening outside health services[18].

Risk group

TB risk group may be defined as any group of people with significantly higher incidence or prevalence than the general population. It may be a group of people sharing a specific individual-level risk factor (e.g. HIV infection), or people living in a specific geographical location (e.g. urban slum) or institution (e.g. prison) associated with high burden of TB. It is not necessary that the characterizing factor is a causal risk factor for TB. The association of a risk marker with TB may be confounded by other factors, but still valid as an identifier for higher TB risk. An absolute level of TB prevalance or incidence may be used to define a risk group in a given epidemiological situation[19,20] but may need to change over time with changing TB burden.

For practical purposes it may be useful to categorise risk groups according to the place where they can be reached for screening, see table 1. The list is not exhaustive and risk groups may be reachable in different localities and settings depending on local epidemiological and health system context.

Table 1 here

Rationale for re-visiting screening

Insufficient impact of current interventions

Global TB prevalence and TB death rates are in steady decline. The scale-up of high quality TB diagnosis and treatment have greatly contributed to this through improved cure rates and reduced case fatality[21]. The estimated global TB incidence is, however, declining very slowly, at about 2% per year[22]. To reach the TB elimination target of <1 case per million in 2050 one would need to reach an average rate of decline of 20% per year[22].

There are two principal explanations for the lack of rapid incidence decline. First, missed or late diagnosis of active TB leads to long duration of infectiousness and sustained transmission[23,24,25] especially where population density is high and where living and working environments are crowded and poorly ventilated[26]. Long average delay to diagnosis is common in many countries[27,28,] as are poor living and working conditions. More intensified efforts are needed to address both.

Second, the large pool of latently infected individuals generates many TB cases, and will continue to do so for many decades even if transmission is stopped, unless the risk of progression to active disease is diminished[29], for example through a new potent post-exposure vaccine[30], better treatment of latent infection[31], and/or addressing the underlying risk factors for progression[26].

In theory, screening for both active TB disease and latent TB infection (LTBI) can help reduce incidence. However, screening for LTBI is only relevant if the LTBI diagnosis can be made with reasonable accuracy, while excluding active TB, and if those who would enjoy significantly more benefit from preventive treatment than risk of harm (e.g. due to side-effects) can be identified[32]. Accuracy of available tests for LTBI is not known with certainty because there is no reliable gold standard for LTBI diagnosis. Furthermore, available tests, while providing an indication of the likelihood of infection, cannot reliably identify persons with the highest risk of progression to active TB disease[33]. Therefore, the decision to treat LTBI can only be based on imprecise tests in combination with the identification of risk markers for progression to active disease. WHO recommends that People living with HIV (PLHIV)[7] and TB contacts under the age of 5 years[8] should receive LTBI treatment. In

resource-constrained moderate and high TB-burden settings the decision of LTBI treatment in these two risk groups can be based on assumed infection, after ruling out active TB, rather than on LTBI test results[7,8]. There is a need to examine the evidence on LTBI treatment in other groups in high burden countries. This paper is not specifically addressing screening for LTBI, though it will highlight how ruling-out active TB can help identify people eligible for LTBI treatment.

"Passive case finding" using sputum smear microscopy is not enough

There is now abundant direct evidence from TB prevalence surveys that the pool of infectious TB cases remains large in many settings despite scale-up of diagnosis and treatment. Many surveys in countries with well-performing national TB programmes (NTP) have consistently demonstrated that the majority of people with undiagnosed bacteriologically positive pulmonary TB cases have smear-negative TB, and that 50% or more do not spontaneously report symptoms that correspond to the commonly used criteria for suspecting TB (cough for more than 2-3 weeks). A large proportion do not report any symptoms at all[34,35,36]. Those individuals are less likely to seek care and when they do seek care they are less likely to be diagnosed.

A systematic review of the number needed to screen (NNS) to detect one case of active TB found a large range in NNS across risk groups in different epidemiological situations[37]. Low NNS (i.e. high prevalence of previously undiagnosed TB) was reported from many risk groups in diverse epidemiological settings. Specific reviews of the TB burden and screening yield has been done for some high-risk groups, including people with HIV[38], TB contacts[39,40], prisoners[41], and homeless[42], all reporting high prevalence of undetected TB. These reviews suggest that the pool of undiagnosed TB cases is large in many risk groups, and that they can be identified through screening.

Early diagnosis and treatment of smear-positive TB in people with chronic cough is of highest priority for reducing TB transmission[43]. Smear positive TB with productive cough is associated with 4-5 times higher rate of transmission than smear-negative pulmonary TB[44,45]. An anticipated effect of introducing an effective DOTS programme in a setting with a previously weak NTP is that the proportion of smear positive chronic coughers out of the total prevalent pool gradually diminishes, which has recently been demonstrated through repeat prevalence surveys in China (fall from 78% in 2000 to 56% in 2010)[46].

With an increasing proportion of smear-negative TB, the relative transmission contribution from this group would gradually increase, though probably not reach above 15-20% of the total transmission[44,45]. When high case detection and treatment success of smear-positive cases with chronic cough have already been achieved, increased impact on transmission may be unlikely unless additional efforts are put in place to detect both smear-positive and smear-negative cases earlier[47]. Screening for active TB is one possible interventions to achieve this, but better access to more sensitive diagnostic tests than smear-microscopy is a first essential step.

Reaching the hardest to reach

There are many barriers for "passive case finding"[48]. The poorest are at the highest risk of not accessing quality care, and they face the highest cost of illness and health care[49]. Screening may help improve access and reduce costs for these groups.

Detecting particularly vulnerable groups earlier

People living with HIV, children, the elderly, people with diabetes, alcohol abusers and drug users, and immune-compromised individuals have elevated risk of poor treatment outcomes, including high death rate[50,51,52]. Screening and early initiation of treatment may be particularly beneficial for these groups.

Goals and objectives of screening for active TB

The *primary objective* of screening is to improve early detection of active TB, which would contribute to two ultimate goals:

a) To reduce the risk of poor treatment outcomes, health sequelae, and adverse social and economic consequences of TB for the individual. This would directly contribute to reduced suffering, TB prevalence and TB death rates.
b) To reduce TB transmission through shortening of the duration of infectiousness. This would contribute to reduced TB incidence.

A *second objective* of screening for active TB is to help identify, by ruling out active disease, people who are eligible for LTBI treatment, for example among PLHIV and TB contacts under the age of 5.

A third objective is to identify people at particularly high risk of developing active disease in the future, such as people with untreated fibrotic CXR lesions and people with other risk factors for active TB, such as HIV infection, undernutrition, smoking, diabetes, alcohol/drug abuse, who may require repeat screening. In some settings, some of these risk groups may be eligible for LTBI treatment, if a LTBI diagnosis can be established with reasonable accuracy.

A *fourth objective* of screening is to help map out individual or community-level risk factors and socio-economic determinants that need to be addressed to prevent TB in a given population.

Not all TB screening is done with the aim to improve general TB care and control. Screening has been used also to "screen out" people with high likelihood of TB with the prime objective of identifying a cohort of healthy individuals, for example among army recruits, at pre-employment and pre-immigration screening. Such screening may be (and has been) done without necessarily having a clear strategy for how to deal with those screened positive, apart from excluding them from the healthy cohort[53]. Such practices raise significant ethical concerns.

Appropriateness of TB screening

Generally agreed criteria for when disease screening is appropriate are summarized in table 2. Screening for disease is only relevant if it can efficiently detect disease in an early stage, and if early treatment has better outcomes than later treatment[54,55]. In the case of communicable diseases, the outcomes of interest are both at individual and community level through impact on transmission. Disease screening is particularly relevant for conditions that are non-symptomatic or have only vague symptoms in early stages of the disease. While many diseases can be detected early, the critical question is if the disease can be detected and treated early enough, and at a reasonable cost, to significantly change the outcomes of disease.

In theory, screening for active TB can improve tertiary prevention (reduce negative consequences of disease) by enabling initiation of treatment earlier and thus reducing risk of poor treatment outcomes, including long-term sequelae and socio-economic consequences. If

screening for active TB reduces delay, for which there is some evidence[56], it is plausible that it should help reduce the risk of poor outcomes, especially in groups with high baseline risk of poor treatment outcomes. However, there is very little direct evidence that screening, as compared to "passive case finding", improves outcomes[56].

Screening for primary prevention (reducing TB transmission) is an important goal, but also the most uncertain of the potential benefits due largely to some critical gaps in our understanding of the relationship between TB symptoms and TB transmission. The exact timing of transmission events and proportion preventable by early case-detection through systematic screening is not fully understood, and may differ between groups and between different lineages of *M. tuberculosis*. If smear-positive disease develops quickly in predisposed individuals alongside with rapidly progressive TB symptoms, while patients with smear-negative disease tend to progress slowly over long periods of time[2], then in the contest of readily accessible health services for those who feel ill, screening would have relatively little impact on transmission, regardless of screening interval. At the other extreme, if smear-positivity develops early on in the course of TB disease despite a prolonged subclinical stage, and/or smear-negative TB patients almost all convert to being smear-positive over time, then screening even at moderate to long intervals will prevent substantial amounts of "smear-positive time", thereby preventing secondary infections. Ultimately, the proof that screening impacts on transmission needs to be established through randomised trials comparing screening with alternative interventions. However, very few controlled trials have been conducted to date, with mixed approaches, quality and findings, and the evidence remains very weak[56]. Challenges for such trials include high cost and lack of an established approach to measuring changes in TB transmission.

Mathematical modelling can help judge the likely impact of different scenarios, assisting in the development of interventions. Modelling suggests that screening for active TB can help reduce incidence[57,58] and future cost of TB care[59] under certain assumptions, and that screening in transmission hot-spots may be particularly efficient to reduce transmission within and outside poor urban areas[60] and prisons[61]. However, given our imperfect understanding of the natural history of TB, and the paucity of data showing impact on transmission from empirical studies, such models should be interpreted with caution.

Using available evidence, table 2 summarises an assessment of the appropriateness of screening for active TB, judged against WHO generic screening criteria. Three of the nine generic criteria for screening are only conditionally fulfilled for screening for active TB:

1. The natural history of TB infection and disease progression, although known in general, lacks sufficient precision to allow definitive conclusions.
2. Availability of quality diagnosis and treatment vary greatly in different settings. Assessment of this criterion needs to be made locally.
3. The final criterion of benefit in relation to cost depends on many factors, including local TB epidemiology, targeted risk groups, screening approach, and alternative interventions.

There are several scenarios under which TB screening potentially could fulfil all generic screening criteria, notably where TB burden is high and where baseline delay to diagnosis and treatment is long. However, there are also situations in which TB screening can do more harm than good even without considering opportunity costs, for example in populations with low to moderate TB burden if the screening and diagnostic algorithm has suboptimal specificity. The screening criteria therefore need to be assessed separately for different epidemiological situations.

Table 2 here

Deciding if, when, who, and how to screen: Key considerations

Prerequisites

Screening is inappropriate unless diagnostic and treatment services of sufficient quality are available or can be made available in parallel with implementing a screening initiative. If there is a large case detection gap despite good availability of TB diagnosis and treatment, screening for active TB may be relevant, but the potential benefits of screening need to be judged against alternative interventions, relative cost-effectiveness, affordability, and risk of doing harm. For this, an assessment of the epidemiological situation, current TB programme performance, general health system capacity, and public health law and other legal frameworks, is required. Box 1 lists conditions that need to be met before initiating TB screening.

Box 1 here

Prioritizing risk groups

The prioritization of risk groups for screening depends on locally adapted goals of screening. The following factors should be considered for the prioritization of risk groups;

1. Potential benefits vs. harm for the individual. The potential benefit (health, social and/or economic) is likely to be larger if people in the risk group are at high risk of delaying diagnosis due to poor health care access and/or if they are at high risk of poor treatment outcomes due to underlying vulnerability. For any given risk group the potential benefits of improving early access to quality treatment need to be balanced against the risk of getting a TB diagnosis without actually having TB (false positive), or being declared not to have TB when in fact having TB (false negative). Furthermore, the inconvenience and cost for the individual of going through screening and diagnosis need to be considered, also for those people who are correctly identified as not having TB (true negative). Finally, for the true positive cases there may be unintended negative consequences (e.g. stigma and discrimination) that need to be considered. The severity of negative consequences will vary across risk groups. The risk of harm is particularly important to consider when screening is done as an outreach activity among people who have not requested the provided service.

2. Potential impact on transmission, within and beyond the risk group. Impact on transmission within a risk group is likely to be highest in congregate settings. If there is large in- and out-migration, such settings may serve as transmission amplifiers for the larger community. The larger the risk group covered, the larger the population transmission impact.

3. The number needed to screen (NNS) to detect a previously undetected case of TB. The NNS provides an indication of both the TB prevalence of undetected TB (NNS=1/prevalence) and the efforts (time, manpower, cost) required to diagnose one case of TB.

4. Feasibility and acceptability. Barriers to screen, diagnose and initiate and adhere to treatment may vary considerably across settings and across risk groups. It is quite likely that the groups that would benefit the most from screening are also those that are hardest to reach.

5. Cost in relation to impact. Cost is a function of the screening approach and the NNS. Cost-effectiveness may be measured with regards to individual benefits and/or transmission. Cost-benefit may be assessed in relation to possible future cost reductions for the individuals, the health system, and society.

Choosing screening and diagnostic algorithm

The yield of true/false positive/negative cases varies with the TB prevalence as well as the sensitivity and specificity of the screening and diagnostic algorithm. Figure 1 shows a flowchart for the estimation of those numbers from a hypothetical scenario using a screening and diagnostic algorithm with very high combined sensitivity and specificity in a population with TB prevalence 500/100,000. Figure 1 also indicates the data requirements for estimating the number of people with each outcome and for assessing the consequences of each outcome. Figure 2 shows the output for the same algorithm, and the NNS, at different prevalence levels, as well as the number of false positive cases when specificity of the diagnostic test is 98% instead of 99%.

Figure 1 here

Figure 2 here

Sensitivity is a first key consideration when choosing algorithm. For high yield of true positive cases, high sensitivity of both the screening and the diagnostic tool is required. Even with a highly sensitive algorithm, the number needed to screen accelerates at lower prevalence levels. For example, when prevalence is 100/100,000 more than 1,200 people need to be screened to detect one TB case with the algorithm in figure 2.

A second key consideration is the expected number of false positive cases, which theoretically changes very little with TB prevalence, whereas the number of true positive cases detected is directly proportional to the prevalence (figure 2). A consequence is that the proportion of true cases out of all cases detected (=the positive predictive value) decreases with falling prevalence. Therefore, it becomes more critical to use an algorithm with high specificity when prevalence is low. Even with a highly specific algorithm, there is likely to be a lower threshold under which screening becomes problematic. With the hypothetical algorithm in figure 1 and 2 there would be more false positive than true positive cases when prevalence is <140/100,000 unless additional efforts are put in place to verify the diagnosis. If specificity is 98% instead of 99%, the number of false positive cases is doubled and the numbers of false positive equals the number of true positive when prevalence is 280/100,000.

The benefit/risk ratio will be different for different risk groups depending on the added value of early treatment vs. the adverse consequence of being treated unnecessarily for TB. For example, a higher proportion of false positive cases may be acceptable among people with HIV and other risk groups where the potential benefit of early treatment is high. Conversely, even a small fraction of false positive cases may be unacceptable in groups that are at risk of unintended negative impact of a TB diagnosis (true or false).

When screening is repeated over time, the prevalence of TB may decrease and the profile of prevalent undetected cases may gradually shift towards cases that are difficult to detect with the initial screening approach used[62]. The sensitivity and specificity may therefore change over time, and the expected number of true/false positive/negative cases with different algorithms needs to be continuously re-estimated.

When screening in a risk group with high MDR-TB prevalence, drug-susceptibility testing should be considered as a part of the diagnosis. Conversely, when MDR-TB prevalence is low and the diagnostic tool also tests for drug-resistance, there should be capacity for confirmatory drug-susceptibility testing.

Ethics and human rights considerations

The paramount principle of "first, do no harm" is particularly important in screening. Before initiating screening, the mechanisms for informed consent and confidentiality should be carefully planned[63], while considering that TB notification may be compulsory under existing public health laws. Persons offered screening should be well aware of the consequences of all possible test results. The screening approach should be designed to minimize discomfort, time loss, indirect costs, discrimination and stigmatization. For example, the legal status of migrants, both with regards to access to health services and risk of expatriation in case of TB diagnosis, needs to be fully considered. Similarly, screening among specific occupational groups need to consider legal protection of workers' right to maintain employment as wel as righ to treatment and care given detection of TB[64].

Coordinated delivery

TB screening within health facilities needs to consider coordination and integration with existing health care structure[65]. Existing platforms for outreach and health promotion activities outside health care facilities may already be in place, e.g. screening programmes for non-communicable diseases, childhood malnutrition, malaria, HIV, etc. Similarly, existing health and social services, including non-governmental and civil society led services, for special populations such as prisoners, homeless, refugees, persons living in remote areas, slum dwellers, etc, may be considered. Integration may improve both efficiency and relevance of screening[66].

Towards guidelines

As part of WHO's ongoing work to develop screening guidelines, four systematic reviews have been commissioned, covering: (1) The general benefits of TB screening (impact on case detection; delay; treatment outcomes; and TB epidemiology); (2) The sensitivity and specificity of different screening tools and algorithms; (3) The number needed to screen to detect a case of active TB in different risk groups; and (4) The acceptability of screening in different risk groups.

Recommendations on prioritization of risk groups for screening and choice of screening tools and algorithms will be developed based on findings in these reviews. However, it is already clear that the evidence base is very weak. The most critical research gap was uncovered by

459 review 1[56]. More research is needed especially to determine positive and negative impact on
460 individual and population level, in relation to cost. Careful monitoring and evaluation of all
461 screening activities is an essential part of developing a better evidence base. As new
462 diagnostic tools become available (also for LTBI) further research is needed on the sensitivity
463 and specificity of different screening and diagnostic algorithms. Operational research on
464 acceptability and feasibility is needed, both from the screened population's and the health
465 sector's viewpoint, in order to inform the choice about screening approaches in different risk
466 groups and different settings.
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476 Table 1. Possible risk groups to consider for screening

Potential site of Screening	Risk group
Community level	High prevalence sub- population (poor areas, urban slums, indigenous/tribal pop, etc)
	Household contacts, other close contacts
Hospital out/in-patients & primary healthcare centres	People previously treated for TB
	People with untreated fibrotic CXR lesions
	People living with HIV / attending HIV testing clinic
	People with diabetes mellitus
	People with chronic respiratory disease / smokers.
	Undernourished people
	People with gastrectomy/ jejunoileal by-pass
	People with alcohol/drug use disorder
	People with chronic renal failure
	People with other immunocompromising disorders/treatments
	Elderly
	People in mental health clinics/institutions
Residential institutions	Prisoners and prison staff
	People residing in shelters
	Other congregate institutions
Immigration and refugee services	Immigrants from high prevalence settings
	People in refugee camps
Workplaces	Health care workers
	Miners/workers with high silica exposure
	Other high TB prevalence work-places

477

478 **Table 2.** Assessment of the appropriateness of screening for active TB against WHO generic
479 screening criteria

Wilson's and Jungner's criteria for screening (WHO 1968)	Assessment for TB	
	Ful-filled	Comment
Condition is an important health problem for individual and community.	Yes	In high TB burden settings because of the health and economic burden of TB. In low burden countries since each TB case is a potential outbreak to contain.
There is accepted treatment for patients with the disease.	Yes	Untreated TB is associated with very high case fatality, about 70% case fatality for smear-positive TB and 20% for smear-negative[67]. TB treatment can reduce case fatality to about 3% (among HIV-negative individuals)[68]. Standardised treatment of drug-susceptible TB renders an infectious individual non-infectious within 2-3 weeks. However, there is mixed evidence on the association between case fatality and diagnostic delay[69]. TB is associated with considerable loss of Quality of Life both during and after active TB disease. However, the association between diagnostic delay and risk of sequelae have not been established[70]. Active TB can arise form recent infection or from latent infection. Active TB can have an early subclinical stage during which signs and symptoms are absent, and/or an early symptomatic stage during which signs and symptoms progress from vague and moderate to more prominent. Infectiousness is correlated with degree of signs and symptoms[71,72]. However, there is insufficient evidence on: (a) the natural rate of progression of signs and symptoms; (b) the rate of natural recovery; (c) the natural rate of progression of infectiousness; and (d) the association between these parameters.
The natural history of the disease should be adequately understood.	Condi-tional	
There should be a latent or early symptomatic stage.	Yes	
There should be a suitable and acceptable screening test.	Yes	Symptom screening and/or chest X-ray screening are suitable[73] and acceptable[74] tools in most risk groups and most settings.
Facilities for diagnosis and treatment should be available.	Condi-tional	Appropriate diagnostic tools, highly effective treatments, and internationally agreed standards for diagnosis and treatment are available[75]. However, quality of service provision and accessibility varies across settings. This criteria therefore needs to be assess locally.
There should be an agreed policy on whom to treat as patients.	Yes	There is an internationally agreed TB case definition, though uncertainty remains with regards to culture negative pulmonary TB, extrapulmonary TB and TB in children. In addition, there is no consensus on whether to define a person with positive sputum bacteriology but no symptoms and no CXR abnormalities, as active TB.
Early treatment has more benefit than treatment started later.	Yes	The shorter the period of infectiousness, the less TB transmission. It is plausible that the risk of poor outcomes, death, and subsequent sequelae increases with delay, but the direct evidence on the exact relationship between delay and adverse outcome is weak (see above).
The cost should be economically balanced	Condi-tional	Cost may be assessed in relation to: (a) additional cases detected; (b) reduced transmission; (c) reduced suffering and death; (d) social and economic impact for individual and for society. Cost and cost-effectiveness depends on: the risk group; the screening approach; and the local TB epidemiology. The judgement of benefits in relation to therefore needs to be assessed locally and separately for different risk groups[37,57,74,75]

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Box 1. Basic prerequisites before TB screening is initiated

1. Quality TB diagnosis, treatment, management and patient support is in place, and there is capacity to scale up further. There is capacity to tailor treatment to the specific needs of the screened population.

2. Reasonable individual and/or public health gain can be expected in relation to investment (financial, human resources, etc, as compared to alternative health interventions) and in relation to the risk of doing harm.

3. Opportunities and barriers to further improve the patient-initiated pathway to diagnosis have been analysed, and screening has been judged to be an important compliment. The following interventions have already been pursued:
   - Access to free-of-charge TB services of good quality
   - Optimization of the accuracy of TB diagnosis within existing TB diagnostic facilities
   - Training of health staff to identify people with suspected TB within health facilities
   - Efforts to minimize initial loss to follow-up
   - Enforced comprehensive notification of all detected TB cases, and engagement of all relevant public and private health providers in TB diagnosis, referral and notification

4. Sufficient additional resources are available or can be made available without adverse impact on other key function of the health system

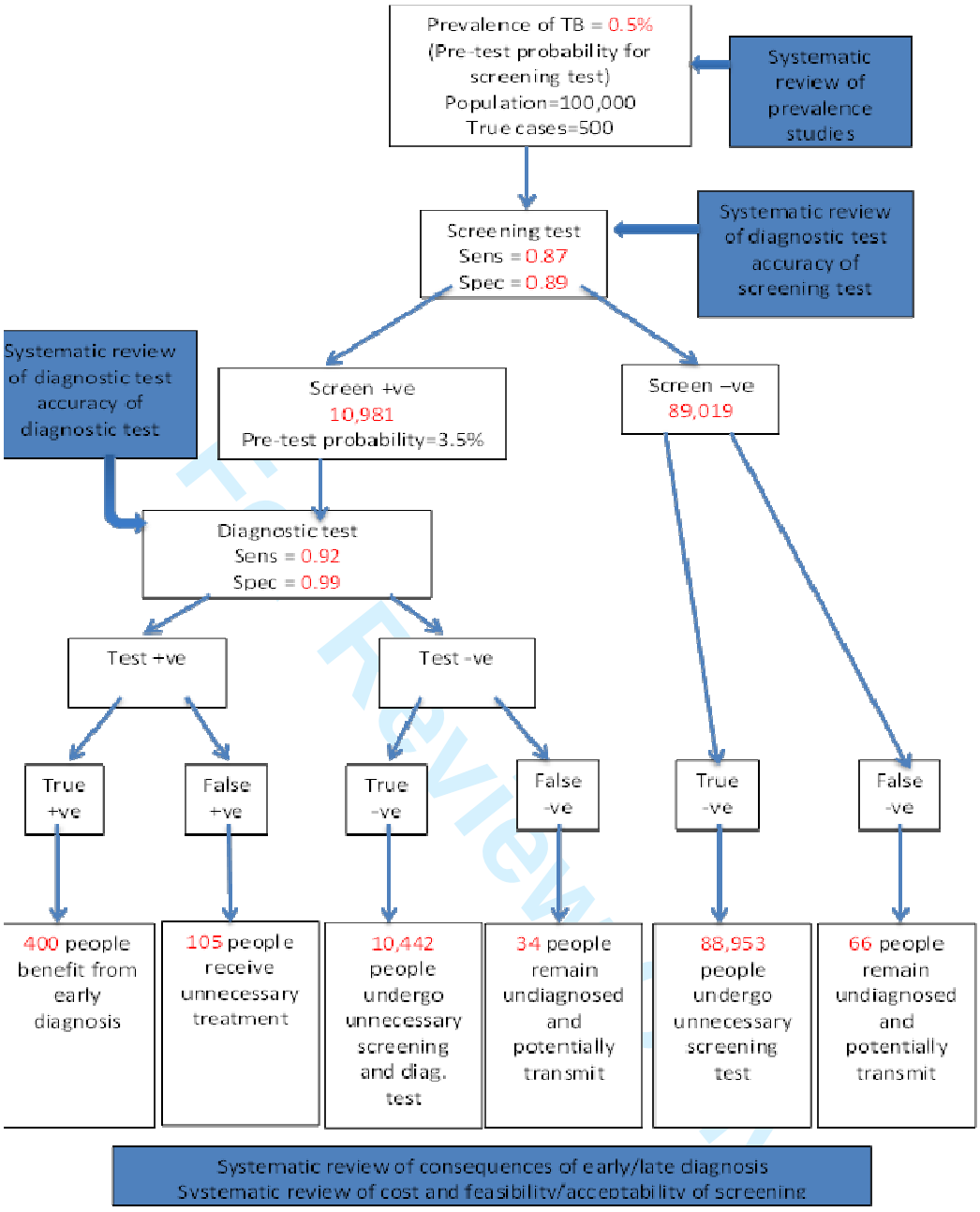

Figure 1. Estimated numbers of true positive, false positive, true negative and false negative TB cases when using a screening tool with 87% sensitivity and 89% specificity and a diagnostic test with a 92% sensitivity and 99% specificity, in a screened population of 100,000 people in which the prevalence of TB is 500/100,000.

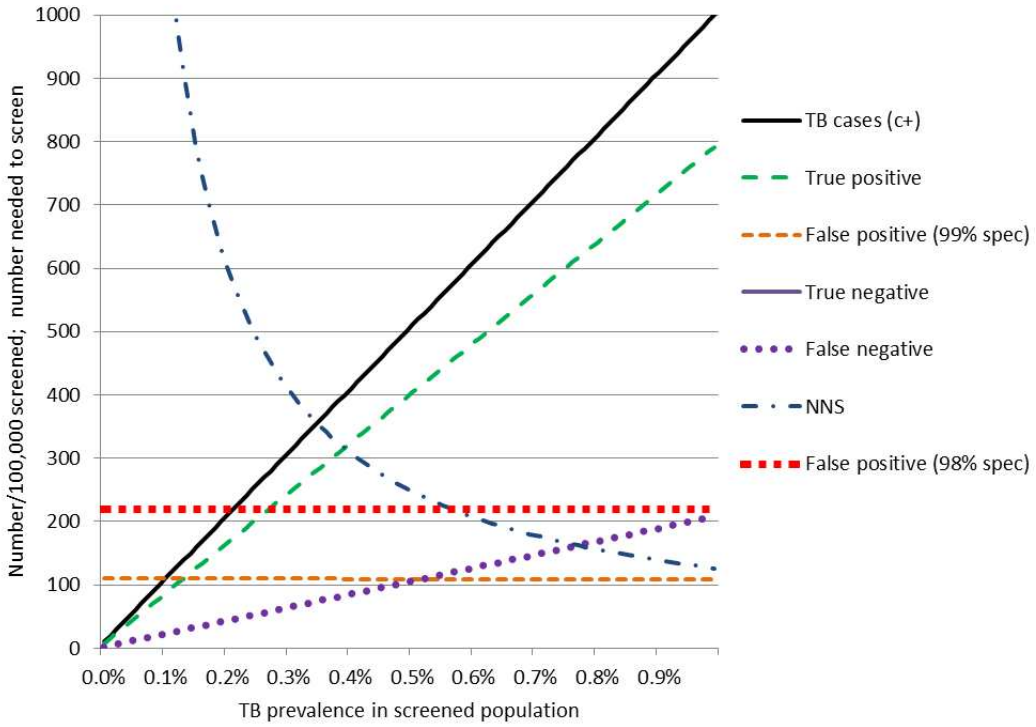

Figure 2. Estimated number needed to screen (NNS), and numbers of true positive, false positive, and false negative cases (culture positive pulmonary TB) when using a screening tool with 87% sensitivity and 89% specificity and a diagnostic test with a 92% sensitivity and 99% specificity, in a screened population of 100,000 in which the prevalence of TB varies between 0% and 1%. Number of false positive if specificity of the diagnostic test is 98% is also shown.

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