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

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—— S U M M A R Y

The impact of current interventions to improve early detection of tuberculosis (TB) seems to have been saturated. Case detection trends have stagnated. TB incidence is falling in most settings worldwide, 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 are likely to improve the situation. However, will these be enough? Or do we also need to reach out more towards people who do not actively seek care with well-recognisable TB symptoms? There have recently been calls to revisit TB screening, particularly in high-risk groups. The World Health Organization (WHO) recommends screening for TB in people with human immunodeficiency virus infection and in close TB contacts. Should other risk groups also be screened systematically? Could mass, community-wide screening, which the WHO has discouraged over the past four decades, be of benefit in some situations? If so, what screening tools and approaches should be used? The WHO is in the process of seeking answers to these questions and developing guidelines on systematic screening for active TB. In this article, we present the rationale, definitions and key considerations underpinning this process.

KEY WORDS: tuberculosis; active case finding; policy; guidelines

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

Since then, the 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 to those of mass miniature radiography (MMR) performed at 2–3 yearly intervals, while screening many 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]

Screening in specific risk groups has been part of the Stop TB Strategy since its launch, namely for people with human immunodeficiency virus infection (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] although these lack specific advice on when and how to screen for active TB. Screening in these and other risk groups has been implemented, particularly in low-burden countries with concentrated TB epidemics, but also in some high-burden

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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 prioritise risk groups, and how to choose an appropriate screening approach are not yet available. The 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. Screening may therefore be a logical way to intensify TB control, particularly when a country is striving for TB elimination and needing to invest additional resources to effectively reach those who 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, alternative interventions to reach these goals, the cost-effectiveness, feasibility and affordability of screening and the risk of doing harm.

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

TERMINOLOGY

Screening

The WHO has defined screening as:

> the presumptive identification of unrecognised 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 that can be applied rapidly. Among those with suspected TB, the diagnosis needs to be established through the 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 (because they do not perceive that they have a health problem that warrants medical attention, due to access barriers or for 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 by screening, for example if TB symptoms are systematically asked about among all people seeking care in a general out-patient 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. Screening may therefore also be partly patient-initiated. 'Active' case finding is often used as a synonym for screening, although it usually implies screening outside the health services.[18]

Risk group

A TB risk group may be defined as any group of people with significantly higher TB 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 a high burden of TB. It is not necessary that the characterising factor be a causal risk factor for TB. The association of a risk marker with TB may be confounded by other factors, but is still valid as an identifier for higher TB risk. An absolute level of TB prevalence or incidence may be used to define a risk group in a given epidemiological situation,[19,20] but it 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 (Table 1). The list is not exhaustive, and risk groups may be reachable in different localities and settings depending on the local epidemiological and health system context.

RATIONALE FOR REVISITING 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

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 populations, etc.) Household contacts, other close contacts
Hospital out-/in-patients and primary health care 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 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 workplaces

TB = tuberculosis; CXR = chest radiography; HIV = human immunodeficiency virus.

elimination target of <1 case per million in 2050, an average rate of decline of 20% per year is required.[22]

There are two principal explanations for the lack of rapid decline in incidence. First, missed or late diagnosis of active TB leads to long duration of infectiousness and sustained transmission,[23–25] particularly 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 TB infection (LTBI),[31] and/or addressing the underlying risk factors for progression.[26]

In theory, screening for both active TB disease and LTBI can help reduce incidence. However, screening for LTBI is only relevant if LTBI diagnosis can be made with reasonable accuracy, while excluding active TB, and if those who would enjoy significantly more benefits from preventive treatment than risk of harm (e.g., due to side effects) can be identified.[32] The accuracy of the available tests for LTBI is not known with certainty, as there is no reliable gold standard for LTBI diagnosis. Furthermore, available tests, while providing an indication of the likelihood of infection, cannot reliably identify those persons with the highest risk of progression to active TB disease.[33] The decision to treat LTBI can therefore only be based on im-

precise tests in combination with the identification of risk markers for progression to active disease. The 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 to provide 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 article does not specifically address screening for LTBI, although it will highlight how ruling out active TB can help identify persons eligible for LTBI treatment.

Passive case finding using sputum smear microscopy is not enough

There is now abundant direct evidence from TB prevalence surveys to suggest that a large pool of infectious TB cases remains in many settings despite the scale-up of diagnosis and treatment. Many surveys in countries with well-performing national TB programmes (NTPs) have consistently demonstrated that the majority of people with undiagnosed bacteriologically positive pulmonary TB cases have smear-negative TB, and that ≥50% do not spontaneously report symptoms that correspond to the commonly used criteria for suspecting TB (cough of more than 2–3 weeks). A large proportion do not report any symptoms at all.[34–36] 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 have been conducted for some high-risk groups, including PLHIV,[38] TB contacts,[39,40] prisoners[41] and the homeless,[42] all of which report a high prevalence of undetected TB. These reviews suggest that there is a large pool of undiagnosed TB cases in many risk groups and that they can be identified through screening.

Early diagnosis and treatment of smear-positive TB in persons with chronic cough is of highest priority for reducing TB transmission.[43] Smear-positive TB with productive cough is associated with a 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. This has recently been demonstrated through repeat prevalence surveys in China, where prevalence has fallen 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, although it will probably not exceed 15–20% of 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 -negative cases earlier.[47] Screening for active TB is a possible means of achieving this, but better access to diagnostic tests that are more sensitive than smear microscopy is an essential first step.

Reaching the hardest to reach

There are many barriers to passive case finding.[17] The poorest are at the highest risk of not accessing quality care, and they also face the highest costs of illness and health care.[26] Screening may help improve access and reduce costs for these groups.

Earlier TB detection in particularly vulnerable groups

PLHIV, children, the elderly, people with diabetes, alcohol abusers, drug users and immune-compromised individuals have an elevated risk of poor treatment outcomes, including high death rates.[25,48–50] Screening and early initiation of treatment may be particularly beneficial for these groups.

Goals and objectives of screening for active tuberculosis

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

1 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.
2 Reduce TB transmission by shortening 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 aged <5 years.

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 and alcohol/drug abuse, who may require repeat screening. In some settings, some of these risk groups may be eligible for LTBI treatment if an 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 of improving 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 and 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 who screen positive, apart from excluding them from the healthy cohort.[51] Such practices raise significant ethical concerns.

APPROPRIATENESS OF SCREENING FOR TUBERCULOSIS

Generally agreed criteria for when disease screening is appropriate are summarised in Table 2. Screening for disease is only relevant if it can efficiently detect disease at an early stage, and if early treatment has better outcomes than later treatment.[60,61] In the case of communicable diseases, the outcomes of interest are both at the individual and community levels through impact on transmission. Disease screening is particularly relevant for conditions that are non-symptomatic or have only vague symptoms at 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 the initiation of treatment earlier

Table 2   Assessment of the appropriateness of screening for active TB against WHO generic screening criteria

Wilson's and Jungner's criteria for screening[15]	Assessment for TB	
	Fulfilled	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, as each TB case is a potential outbreak to be contained
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 and 20% for smear-negative TB;[52] anti-tuberculosis treatment can reduce case fatality to about 3% among HIV-negative individuals;[53] 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.[54] 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 has not been established.[55] Active TB can arise from 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.[56] However, there is insufficient evidence on 1) the natural rate of progression of signs and symptoms, 2) the rate of natural recovery, 3) the natural rate of progression of infectiousness, and 4) the association between these parameters
The natural history of the disease should be adequately understood	Conditional	
There should be a latent or early symptomatic stage	Yes	
There should be a suitable and acceptable screening test	Yes	Symptom screening and/or CXR screening are suitable[57] and acceptable[58] tools in most risk groups and most settings
Facilities for diagnosis and treatment should be available	Conditional	Appropriate diagnostic tools, highly effective treatments, and internationally agreed standards for diagnosis and treatment are available;[59] however, quality of service provision and accessibility varies across settings. These criteria therefore need to be assessed locally
There should be an agreed policy on whom to treat as patients	Yes	There is an internationally agreed TB case definition, although uncertainty remains with regard to culture-negative pulmonary TB, extra-pulmonary 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 the 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	Conditional	Cost may be assessed in relation to 1) additional cases detected, 2) reduced transmission, 3) reduced suffering and death, and 4) social and economic impact for the 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 cost therefore needs to be assessed locally and separately for different risk groups

TB = tuberculosis; WHO = World Health Organization; CXR = chest radiography.

and thus reducing the risk of poor treatment outcomes, including long-term sequelae and socio-economic consequences. If screening for active TB reduces delays, for which there is some evidence,[62] it is plausible that it should help reduce the risk of poor outcomes, particularly in groups with a high baseline risk of poor treatment outcomes. However, there is very little direct evidence that screening, as compared to passive case finding, improves outcomes.[62]

Screening for primary prevention (reducing TB transmission) is an important goal but it is 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 *Mycobacterium tuberculosis*. If smear-positive disease develops quickly in predisposed individuals alongside rapidly progressive TB symptoms, while patients with smear-negative disease tend to progress slowly over long periods of time,[2] then in the context 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 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.[62] Challenges for such trials include high cost and the 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 the incidence[63,64] and future cost of TB care[65] under certain assumptions, and that screening in transmission hot-spots may be particularly efficient in reducing transmission within and outside poor urban areas[66] and prisons.[67] 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:

- The natural history of TB infection and disease progression, although known in general, lacks sufficient precision to allow definitive conclusions.
- The availability of quality diagnosis and treatment varies greatly in different settings. Assessment of this criterion needs to be made locally.
- 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 could potentially fulfil all generic screening criteria, notably where TB burden is high and where the 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.

DECIDING IF, WHEN, WHOM 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

Table 3 Basic prerequisites before TB screening is initiated

1 Quality TB diagnosis, treatment, management and patient support is in place, and there is capacity for further scale-up. 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 complement. The following interventions have already been pursued:
- Access to free-of-charge TB services of good quality
- Optimisation 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 minimise 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 functions of the health system.

TB = tuberculosis.

frameworks, is required. Table 3 lists conditions that need to be met before initiating TB screening.

Prioritising risk groups

The prioritisation of risk groups for screening depends on locally adapted goals of screening. The following factors should be considered for the prioritisation 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 being diagnosed with TB without actually having TB (false-positive) or being declared as not having TB when one does in fact have TB (false-negative). Furthermore, the inconvenience and cost for the individual of going through screening and diagnosis also need to be considered for those people who are correctly identified as not having TB (true-negative). Finally, for the true-positive cases, unintended negative consequences (e.g., stigma and discrimination) may 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 performed as an outreach activity among people who have not requested the service provided.

2 Potential impact on transmission, within and beyond the risk group: the 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 NNS to detect a previously undetected case of TB. The NNS provides an indication of both the prevalence of undetected TB (NNS = 1/prevalence, if the diagnostic precision is very high) and the efforts (time, manpower, cost) required to diagnose one case of TB.

4 Feasibility and acceptability: barriers to screening, diagnosing and initiating and adhering 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 regard 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 the screening and diagnostic algorithm

The yield of true-/false-positive/negative cases varies with the TB prevalence as well as with the sensitivity and specificity of the screening and diagnostic algorithm. Figure 1 shows a flow chart for the estimation of these numbers from a hypothetical scenario using a screening and diagnostic algorithm with very high combined sensitivity and specificity in a population with a TB prevalence of 500 per 100 000 population. 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.
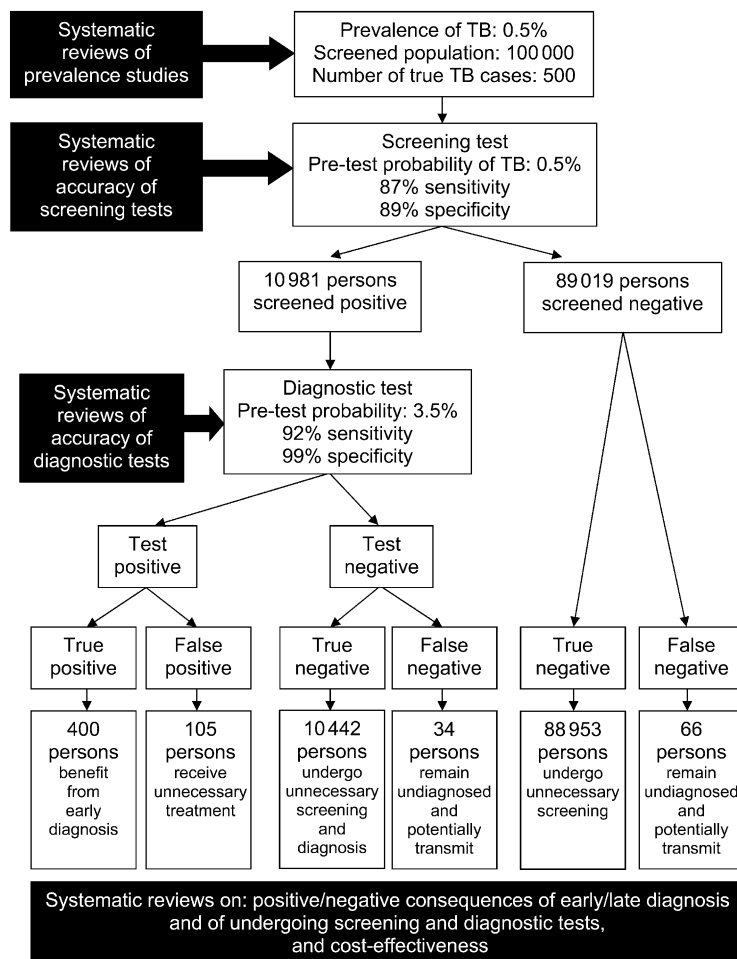

Figure 1 Estimated numbers of true-positive, false-positive, true-negative and false-negative TB cases when using a screening tool with 87% sensitivity and 89% specificity and a diagnostic test with 92% sensitivity and 99% specificity in a screened population of 100 000 in which the prevalence of TB is 500/100 000. TB = tuberculosis. Black boxes show required information for assessing the accuracy of a screening and diagnostic algorithm, and for assessing the consequences of different test results.
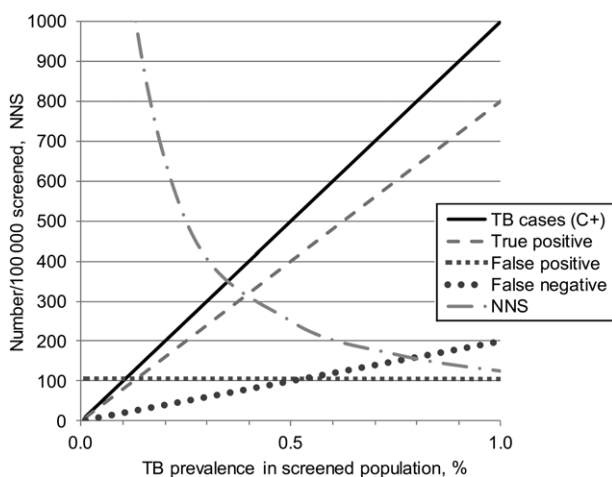
Figure 2 Estimated NNS, and numbers of true-positive, false-positive and false-negative cases (culture-positive pulmonary TB) when using a screening tool with 87% sensitivity and 89% specificity and a diagnostic test with 92% sensitivity and 99% specificity in a screened population of 100 000 in which the prevalence of TB varies between 0% and 1%. NNS = number needed to screen; TB = tuberculosis; C+ = culture-positive.

Sensitivity is a first key consideration when choosing the algorithm. For a 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 NNS accelerates at lower prevalence levels. For example, when the prevalence is 100/100 000, more than 1200 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 (i.e., the positive predictive value) decreases with falling prevalence. It therefore 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 Figures 1 and 2, there would be more false-positive than true-positive cases when the prevalence is <140/100 000, unless additional efforts are put in place to verify the diagnosis. If the specificity is 98% instead of 99%, the number of false-positive cases is doubled, and the number of false-positives equals the number of true-positives when the 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 consequences of being treated unnecessarily for TB. For example, a higher proportion of false-positive cases may be acceptable among PLHIV 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.[68] 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 a high prevalence of multidrug-resistant TB (MDR-TB), drug susceptibility testing (DST) 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 DST.

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,[69] 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 minimise discomfort, time loss, indirect costs, discrimination and stigmatisation. For example, the legal status of migrants, with regard both to access to health services and to risk of expatriation in case of TB diagnosis, needs to be fully considered. Similarly, screening among specific occupational groups needs to consider the legal protection of workers' rights to maintain their employment as well as their right to treatment and care if TB is detected.[70]

Coordinated delivery

TB screening within health facilities needs to consider coordination and integration within an existing health care structure.[71] 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, the homeless, refugees, persons living in remote areas, slum dwellers, etc., may be considered. Integration may improve both the efficiency and relevance of screening.[72]

TOWARDS GUIDELINES

As part of the 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 the prioritisation of risk groups for screening and the choice of screening tools and algorithms will be developed based on the findings in these reviews. However, it is already clear that the evidence base is very weak. The most critical research gap was uncovered by the review by Kranzer et al.[62] More research is needed, particularly to determine the positive and negative impact on individual and population level in relation to cost. Careful monitoring and evaluation of all screening activities is an essential part of developing a better evidence base. As new diagnostic tools become available (also for LTBI), further research is needed on the sensitivity and specificity of different screening and diagnostic algorithms. Operational research on acceptability and feasibility is needed, from the viewpoint of both the screened population and the health sector, to inform the choice about screening approaches in different risk groups and different settings.

Acknowledgement

References

1 World Health Organization. WHO Expert Committee on Tuberculosis. Ninth report. Technical Report Series no. 552. Geneva, Switzerland: WHO, 1974.

2 Rieder H. What is the role of case detection by periodic mass radiographic examination in TB control? In: Frieden T, ed. Toman's Tuberculosis. Geneva, Switzerland: WHO, 2004.

3 Krivinka R, Drapela J, Kubik A, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia. Second report (1965–1972). Bull World Health Organ 1974; 51: 59–69.

4 Roelsgaard E, Iversen E, Bløcher C. Tuberculosis in tropical Africa—an epidemiological study. Bull World Health Organ 1964; 30: 459–518.

5 World Health Organization. WHO Expert Committee on Tuberculosis. Eighth report. Technical Report Series no. 290. Geneva, Switzerland: WHO, 1964.

6 Meijer J, Barnett G D, Kubik A, Styblo K. Identification of sources of infection. Tuberculosis Surveillance Research Unit. Report no. 2. Bull Int Union Tuberc 1971; 45: 5–54.

7 World Health Organization. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, Switzerland: WHO, 2011.

8 World Health Organization. Recommendations for the investigation of contacts of persons with infectious tuberculosis in low- and middle-income countries. WHO/HTM/TB/2012.9. Geneva, Switzerland: WHO, 2012.

9 Tuberculosis Coalition for Technical Assistance and International Committee of the Red Cross. Guidelines for the control of tuberculosis in prisons. The Hague, The Netherlands: TBCTA, 2009.

10 World Health Organization. Tuberculosis care and control in refugee and displaced populations. WHO/HTM/TB/2007.377. Geneva, Switzerland: WHO, 2007.

11 Stop TB Department, World Health Organization/International Union against Tuberculosis and Lung Disease. Provisional collaborative framework for care and control of tuberculosis and diabetes. WHO/HTM/TB/2011.15. Geneva, Switzerland: WHO, 2011.

12 Corbett E L, Bandason T, Duong T, et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. Lancet 2010; 376: 1244–1253.

13 Eang M, Satha P, Yadav R, et al. Early detection of tuberculosis through community-based active case finding in Cambodia. BMC Public Health 2012; 12: 469.

14 Miller A C, Golub J E, Cavalcante S C, et al. Controlled trial of active tuberculosis case finding in a Brazilian *favela*. Int J Tuberc Lung Dis 2010; 14: 720–726.

15 Wilson J M G, Jungner G. Principles and practice of screening for disease. Geneva, Switzerland: WHO, 1968. Originally appearing in: Commission on Chronic Illness. Chronic illness in the United States: Volume I. Prevention of chronic illness. Cambridge, MA, USA: Harvard University Press, 1957: p 45.

16 World Health Organization. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis programmes. WHO/HTM/TB/2008.401. Geneva, Switzerland: WHO, 2008.

17 World Health Organization. Early detection of tuberculosis: an overview of approaches, guidelines and tools. WHO/HTM/STB/PSI/2011.21. Geneva, Switzerland: WHO, 2011.

18 Golub J E, Mohan C I, Comstock G W, Chaisson R E. Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis 2005; 9: 1183–1203.

19 European workshop on tuberculosis control. 2nd Wolfheze Conference. Wolfheze, The Netherlands, 1994.

20 Royal Netherlands Anti-tuberculosis Association. Tuberculosis control in high-risk groups in the Netherlands. The Hague, The Netherlands: KNCV, 1997.

21 Raviglione M, Marais B, Floyd K, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. Lancet 2012; 379: 1902–1913.

22 World Health Organization. Global tuberculosis control 2012. WHO/HTM/TB/2012.6. Geneva, Switzerland: WHO, 2012.

23 Luelmo F. What is the role of case detection in tuberculosis control? In: Frieden T, ed. Toman's tuberculosis. Geneva, Switzerland: WHO, 2004.

24 Lin X, Chongsuvivatwong V, Lin L, Geater A, Lijuan R. Dose–response relationship between treatment delay of smear-positive tuberculosis patients and intra-household transmission: a cross-sectional study. Trans R Soc Trop Med Hyg 2008; 102: 797–804.

25 Lönnroth K, Castro K, Chakaya J M, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet 2010; 375: 1814–1829.

26 Lönnroth K, Jaramillo E, Williams B G, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med 2009; 68: 2240–2246.

27 Storla D G, Yimer S, Bjune G A. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 2008; 8: 15.

28 Sreeramareddy C, Panduru K, Menten J, Ven der Ende J. Time delay in diagnosis of pulmonary tuberculosis: a systematic review of the literature. BMC Infect Dis 2009; 9: 91.

29 Dye C, Williams B. Eliminating human tuberculosis in the twenty-first century. J R Soc Interface 2008; 5: 653–662.

30 Hoft D F. Tuberculosis vaccine development: goals, immunological design, and evaluation. Lancet 2008; 372: 164–175.

31 Ginsberg A M, Spigelman M. Challenges in tuberculosis drug research and development. Nat Med 2007; 13: 290–294.

32 Marchetti S M, Cook D, Smaill F M. Isoniazid for preventing

tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev 2000; (2): CD001363.

33 Rangaka M X, Wilkinson K A, Glynn J R, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12: 45–55.

34 Hoa N B, Sy D N, Nhung N V, Tiemersma E W, Borgdorff M W, Cobelens F G J. A national survey of tuberculosis prevalence in Vietnam. Bull World Health Organ 2010; 88: 273–280.

35 Cambodia Ministry of Health. National TB Prevalence Survey, 2002, Cambodia. Phnom Penh: Ministry of Health, 2002.

36 Ayles H, Schaap A, Nota A, et al. Prevalence of tuberculosis, HIV and respiratory symptoms in two Zambian communities: implications for tuberculosis control in the era of HIV. PLoS ONE 2009; 4: e5602.

37 Shapiro A, Golub J. A systematic review of active case-finding strategies in risk groups for tuberculosis and the relationship to the number needed to screen. Report to WHO. Geneva, Switzerland: WHO, 2012.

38 Getahun H, Kittikraisak W, Heilig C M, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. PLoS Med 2011; 8: e1000391.

39 Morrison J, Pai M, Hopewell P C. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis 2008; 8: 359–368.

40 Fox G J, Barry S E, Britton W J, Marks G. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J 2013; 41: 140–156.

41 Baussano I, Williams B G, Nunn P, Beggiato M, Fedeli U, Scano F. Tuberculosis incidence in prisons: a systematic review. PLoS Med 2010; 7: e1000381.

42 Beijer U, Wolf A, Fazel S. Prevalence of tuberculosis, hepatitis C virus, and HIV in homeless people: a systematic review and meta-analysis. Lancet Infect Dis 2012; 12: 859–870.

43 Styblo K, Bumgarner R. 1. Tuberculosis can be controlled with existing technologies: evidence. The Hague, The Netherlands: Tuberculosis Surveillance Research Unit, 1991.

44 Behr M A, Warren S A, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 1999; 353: 444–449.

45 Tostmann A, Kik S V, Kalisvaart N A. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clin Infect Dis 2008; 47: 1135–1142.

46 China Centre for Disease Control. [The 5th National Prevalence Survey in China—2010]. Beijing, China: Ministry of Health, 2011. [Chinese]

47 Dowdy D, Chaisson R. The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection. Bull World Health Organ 2009; 87: 296–304.

48 Chaisson R E, Schechter G F, Theuer C P, Rutherford G W, Echenberg D F, Hopewell P C. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. Am Rev Respir Dis 1987; 136: 570–574.

49 Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet 2007; 369: 2042–2049.

50 Baker M A, Harries A D, Jeon C Y, et al. Systematic review: the impact of diabetes on tuberculosis treatment outcomes. BMC Med 2011; 9: 81.

51 Haygood T M. Radiologic history exhibit: chest screening and tuberculosis in the United States. Radiographics 1994; 14: 1151–1166.

52 Tiemersma E W, van der Werf M J, Borgdorff M W, Williams B G, Nagelkerke N J D. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV-negative patients: a systematic review. PLoS ONE 2011; 6: e17601.

53 Straetemans M, Glaziou P, Bierrenbach A L, Sismanidis C, van der Werf M J. Assessing tuberculosis case fatality ratio: a meta-analysis. PLoS ONE 2011; 6: e20755.

54 Waitt C J, Squire S B. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis 2011; 15: 871–885.

55 Miller T L, McNabb S J N, Hilsenrath P, et al. Personal and societal health quality lost to tuberculosis. PLoS ONE 2009; 4: e5080.

56 Rieder H. Epidemiological basis of tuberculosis control. Paris, France: International Union Against Tuberculosis and Lung Disease, 1999.

57 van't Hoog A H, Langendam M W, Mitchell E, et al. A systematic review of the sensitivity and specificity of symptoms and chest radiography as screening tools for active pulmonary tuberculosis. Report to WHO. Geneva, Switzerland: WHO, 2012.

58 Mitchell E, Shapiro A, Golub J, et al. Acceptability of TB screening among at-risk and vulnerable groups: a systematic qualitative/quantitative literature metasynthesis. Report to WHO. Geneva, Switzerland: WHO, 2012.

59 Hopewell P C, Pai M, Maher D, Uplekar M, Raviglione M C. International standards for tuberculosis care. Lancet Infect Dis 2006; 6: 710–725.

60 McKeown T, ed. Screening in medical care: reviewing the evidence. Oxford, UK: Oxford University Press, 1968.

61 Holland W W, Stewart S. Screening in disease prevention. What works? Oxford, UK: Radcliff Publishing, 2005.

62 Kranzer K, Afnan-Holmes H, Tomlin K, et al. A systematic literature review of the benefits to communities and individuals of screening for active tuberculosis disease. Int J Tuberc Lung Dis 2013. [In press]

63 Murray C J L, Salomon J A. Modeling the impact of global tuberculosis control strategies. Proc Natl Acad Sci USA 1998; 95: 13881–13886.

64 Borgdorff M W, Floyd K, Broekmans J. Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries. Bull World Health Organ 2002; 80: 217–227.

65 Dodd P J, Whit R G, Corbett E L. Periodic active case finding for TB: when to look? PLoS ONE 2011; 6: e29130.

66 Dowdy D, Golub J, Chaisson R, Saraceni V. Heterogeneity in tuberculosis transmission and the role of geographical hotspots in propagating epidemics. Proc Natl Acad Sci USA 2012; 109: 9557–9562.

67 Legrand J, Sanchez A, Le Pont F, Camacho L, Larouze B. Modelling the impact of tuberculosis control strategies in highly endemic overcrowded prisons. PLoS ONE 2008; 3: e2100.

68 Lewis J J, Charalambous S, Day J H, Fielding K L, Grant A D, Hayes R J. HIV infection does not affect active case finding of tuberculosis in South African gold miners. Am J Respir Crit Care 2009; 180: 1271–1278.

69 World Health Organization. Guidance on ethics of tuberculosis prevention, care and control. WHO/HTM/TB/2010.16. Geneva, Switzerland: WHO, 2010.

70 World Health Organization. Working together with businesses: guidance on TB and TB/HIV prevention, diagnosis, treatment and care in the workplace. WHO/HTM/TB/2012.3. Geneva, Switzerland: WHO, 2010.

71 World Health Organization. Contributing to health system strengthening—guiding principles for national tuberculosis programmes. WHO/HTM/TB/2008.400. Geneva, Switzerland: WHO, 2008.

72 Suthar A B, Klinkenberg E, Ramsay A, et al. Community-based multi-disease prevention campaigns for controlling human immunodeficiency virus-associated tuberculosis. Int J Tuberc Lung Dis 2012; 16: 430–436.

RÉSUMÉ

L'impact des interventions actuelles en vue d'améliorer une détection précoce de la tuberculose (TB) semble être arrivé à saturation. Les tendances de détection des cas stagnent. L'incidence de la TB baisse dans la plupart des contextes au niveau mondial, mais le taux de décroissance est beaucoup plus faible que ce que l'on attendait. Il y a des preuves croissantes, provenant d'enquêtes nationales de surveillance de la TB et d'autres recherches, qu'il existe un ensemble important de cas de TB non détectées dans la collectivité. Des efforts intensifiés afin de rompre les barrières d'accès et d'étendre de nouveaux outils de diagnostic rapide sont susceptibles d'améliorer la situation. Toutefois, cela suffira-t-il ? Ou bien devons-nous également nous orienter davantage vers les personnes qui ne recourent pas activement aux soins tout en ayant des symptômes bien reconnaissables de TB ? Récemment, on a fait appel à un réexamen du dépistage de la TB, particulièrement dans les groupes à haut risque. L'Organisation Mondiale de la Santé (OMS) recommande le dépistage de la TB chez les sujets atteints du virus de l'immunodéficience humaine et chez les contacts étroits de cas de TB. Devrait-on dépister systématiquement d'autres groupes à risque ? Un dépistage massif au niveau de l'ensemble de la communauté, que l'OMS a découragé au cours des quatre dernières décennies, serait-il bénéfique dans certaines situations ? S'il en est ainsi, quels sont les outils et les approches de dépistage qui devraient être utilisés ? A l'OMS, un processus de recherche d'une réponse à ces questions est actuellement en cours, de même que l'élaboration de directives sur le dépistage systématique de la TB active. Dans cet article, nous présentons la justification, les définitions et les considérations-clé qui sont à la base de ce processus.

RESUMEN

Pareciera que la repercusión de las intervenciones actuales que tienden a mejorar la detección temprana de la tuberculosis (TB) haya alcanzado un punto de saturación. La tendencia de la detección de casos es estacionaria. La incidencia de TB disminuye en la mayoría de los entornos en todo el mundo, pero la tasa de disminución es muy inferior a las previsiones. Existen cada vez más indicios provenientes de las encuestas de prevalencia y otras investigaciones sobre la existencia de una gran proporción de casos que se pasan por alto en la comunidad. Esta situación se podría mejorar al intensificar las medidas que buscan acabar los obstáculos al acceso a la atención y ampliar la escala de aplicación de los nuevos instrumentos de diagnóstico rápido. Pero ¿son estas medidas suficientes? O ¿sería necesario además tratar de alcanzar a más personas que no acuden activamente en busca de atención y que presentan síntomas claramente reconocibles de TB? Últimamente ha habido llamamientos a reconsiderar la detección sistemática de la enfermedad, sobre todo en los grupos de alto riesgo de contraerla. La Organización Mundial de la Salud (OMS) recomienda esta detección en las personas infectadas por el virus de la inmunodeficiencia humana y los contactos cercanos de los casos de TB. ¿Se debería aplicar la detección sistemática a otros grupos de riesgo? ¿Sería útil en algunas situaciones practicar la detección colectiva a escala de la comunidad, que ha desaconsejado la OMS durante los últimos cuatro decenios? En caso afirmativo, ¿cuáles serían los instrumentos y las estrategias más adecuadas? En la actualidad, la OMS estudia las respuestas a estos interrogantes y elabora directrices sobre la estrategia de detección sistemática de la TB activa. En el presente artículo se presentan los fundamentos, las definiciones y las consideraciones esenciales que respaldan este proceso.