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Screening for active tuberculosis: methodological challenges in implementation and evaluation

J. E. Golub, D. W. Dowdy

Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

SUMMARY

As active screening strategies for tuberculosis (TB) continue to rise globally, it has become increasingly important to consider the methodological challenges in designing and implementing these strategies. The key challenges associated with TB screening can be summarized in terms of four continua or spectra, namely those of 1) TB disease and diagnostic yield, 2) TB risk and resource availability, 3) TB screening strategies,

and 4) outcomes and impact measurements of screening programs. In this review, we provide a discussion of these challenges to help guide development of TB screening strategies that will be effective in a given epidemiological setting.

KEY WORDS: tuberculosis; epidemiology; diagnostic techniques and procedures

SINCE 1995, the DOTS strategy recommended by the World Health Organization (WHO)¹ and its successor, the 2006 Stop TB Strategy,² have combined to save over five million lives.³ Nevertheless, despite the fact that nearly 70% of all tuberculosis (TB) cases worldwide are now detected under these programs, the annual number of new TB cases is higher today than in 1995, and incidence is falling at only 2% per year.^{4,5} The primary rationale for screening individuals for active TB has been discussed earlier in this series.⁶ At the individual (clinical) level, it may be assumed that earlier diagnosis facilitates TB treatment at a stage that incurs fewer negative treatment outcomes, health sequelae, and social/economic conse-

quences; at the population (public health) level, it should reduce the period of infectiousness, thus averting transmission. Although data to support any single strategy for active TB screening are weak,⁷ evidence that current practice will not suffice to meet aggressive targets for TB control is overwhelming.⁸ Nevertheless, screening programs for active TB have not been widely implemented on a global scale. Here, we discuss the methodological challenges inherent in screening for active TB, both in terms of implementation and scale-up as well as monitoring and evaluation. These challenges can be summarized in terms of four continua or spectra, namely those of 1) TB disease and diagnostic yield, 2) TB risk and resource availability, 3) TB screening strategies, and 4) outcomes and impact measurements of screening programs. Choosing implementation and evaluation approaches that fall at appropriate points along these spectra is critical for the development of a TB screening strategy that will be effective in a given epidemiological setting. Through these spectra, we will discuss methodological challenges and knowledge gaps that need to be assessed if screening strategies are to successfully improve individual health and have an impact at the population level.

Previous articles in the series Editorial: Borgdorff M W, Yew W W, Marks G. Active tuberculosis case finding: why, when and how? *Int J Tuberc Lung Dis* 2013; 17(3): 285. **No. 1:** Lönnroth K, Corbett E, Golub J, Godfrey-Faussett P, Uplekar M, Weil D, Raviglione M. Systematic screening for active tuberculosis: rationale, definitions and key considerations. *Int J Tuberc Lung Dis* 2013; 17(3): 289–298. **No. 2:** Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013; 17(4): 432–446. **No. 3:** Zenner D, Southern J, van Hest R, deVries G, Stagg H R, Antoine D, Abubakar I. Active case finding for tuberculosis among high-risk groups in low-incidence countries. *Int J Tuberc Lung Dis* 2013; 17(5): 573–582.

Correspondence to: Jonathan Golub, Johns Hopkins University, 1550 Orleans St, 1M.10, Baltimore, MD 21231, USA. Tel: (+1) 443 287 2969. Fax: (+1) 410 955 0547. e-mail: jgolub@jhmi.edu

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SPECTRUM OF TUBERCULOSIS DISEASE AND DIAGNOSTIC YIELD

Many infectious diseases, including malaria, bacterial pneumonia and diarrheal disease, are characterized by an incubation period that is closely followed by a well-defined symptomatic period during which transmission largely occurs. Such diseases may be easier to control without using screening measures.⁹ Other diseases, including the human immunodeficiency virus (HIV) and syphilis, are characterized by prolonged latent periods during which individuals are infectious and microbial burden is high, making screening with standard diagnostic tests (e.g., antibody and antigen assays) appropriate. By contrast, TB is relatively unique among major infectious diseases as being characterized by a prolonged subclinical phase during which a substantial amount of transmission may occur, but the most commonly used diagnostic approaches and tests are much less effective (Figure 1).

Screening strategies such as untargeted door-to-door campaigns, with universal culture, targeting individuals at all stages along the TB disease spectrum, will not only be cost-inefficient if scaled up on a population level, they will also identify an unacceptably high number of false-positive cases and individuals who cannot be placed on treatment. By contrast, screening strategies that target only those individuals who are sufficiently ill that they would soon otherwise present for passive case detection are unlikely to have an important individual- or population-level impact. Failure to diagnose individuals sufficiently early in disease may explain the lack of effect on TB incidence seen in

the ‘enhanced case finding’ arm of the Zambia/South Africa TB and AIDS Reduction (ZAMSTAR) trial, which consisted of open laboratory access, mobile sputum collection and school mobilization,¹⁰ in Zambia and South Africa,¹¹ although such ‘enhanced’ strategies may not be any less effective than population-based strategies (e.g., door-to-door) in finding TB cases. These need to be evaluated further.^{12,13}

Methodological challenges for tuberculosis screening

A fundamental challenge to TB screening is to identify strategies that can detect cases far enough to the ‘left’ of the TB disease spectrum (Figure 1) that TB disease burden and transmission are averted, yet sufficiently to the ‘right’ that affordable, high-specificity strategies for case detection will be effective. As a further complication, individuals with particular vulnerability to TB, such as those suffering from HIV,¹⁴ malnutrition,¹⁵ silicosis¹⁶ and diabetes,¹⁷ and tobacco smokers,¹⁸ may progress along this spectrum more rapidly than others, requiring less time for diagnosis of early forms of TB. In the general population, earlier disease forms of TB are difficult to distinguish from other causes of chronic cough, such as smoking;¹⁹ the prevalence of chronic cough may exceed 10% in many populations.²⁰ In high-risk populations such as the HIV-infected, TB may be difficult to distinguish from other comorbidities to which individuals are also susceptible. Microbiological tests with higher sensitivity for early diagnosis of TB include culture and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA).²¹ However, these tests are too expensive to deploy for

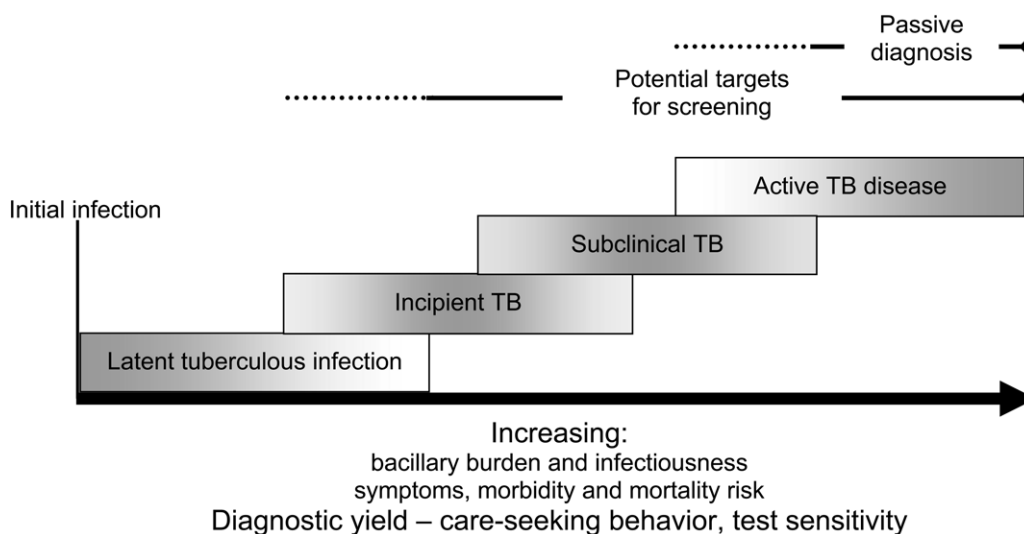


Figure 1 The spectrum of TB disease and diagnostic yield. TB disease activity falls along a spectrum that is not necessarily linear over time, acquiring different names as bacillary burden, symptom severity and infectiousness progress over time. This spectrum also overlays on the ability to diagnose TB: some diagnostic approaches (e.g., four-item symptom screen) and tests (e.g., sputum smear microscopy) that are highly effective at the right-hand side of this spectrum are relatively less effective in the center, where TB screening seeks to have greatest impact, whereas other diagnostic approaches (e.g., screening all individuals at the time of a new human immunodeficiency virus diagnosis) and tests (chest X-ray) may be more effective throughout the spectrum. Whereas passive diagnosis under the DOTS strategy can rely on approaches and tests that are effective only toward the right of this spectrum, effective TB screening requires methods that are effective across a broader range. TB = tuberculosis.

indiscriminate screening (Xpert costs at least US\$15 per test in most settings²²), and their sensitivity when used in active screening may be substantially lower than when used for passive diagnosis. For example, while these results may not be generalizable to all settings, sensitivity for culture-confirmed TB was estimated at ~60% in a prevalence survey among gold miners in South Africa,²³ vs. 90% as a passive case-detection tool in a multicenter implementation study.²⁴ Screening every member of a high-burden population (undiagnosed TB prevalence of 200 per 100 000 population) using Xpert MTB/RIF might therefore cost US\$12 500 per identified case [$\$15/(0.002 \times 0.6)$] for the diagnostic test alone. Taking into account the logistical costs of conducting the survey²⁵ and the treatment costs of false-positives⁶ would more than double this estimate. New diagnostic tests on their own are often not a ‘magic bullet’ for TB screening, but rather must be part of a more comprehensive response.

To reduce disease burden and transmission, therefore, TB screening strategies must find individuals in the ‘center’ of the TB disease spectrum—individuals who are readily diagnosable with cost-efficient algorithms, but antecedent to most transmission and morbidity. Existing algorithms largely lack sufficient accuracy (either sensitivity or specificity) to achieve the ideal balance. In population-based prevalence surveys, the sensitivity of classic symptom screening (any one of prolonged cough, fever, night sweats and weight loss) is often <50%.^{26–30} While sputum smear microscopy remains a useful tool among those with such symptoms,³¹ its sensitivity may be less than one in four among individuals with asymptomatic, microbiologically confirmed TB.²⁸ Although smear-negative, culture-positive disease may resolve spontaneously, it may make an important contribution to transmission,³² and the great majority of high-risk individuals, such as the HIV-infected, progress to symptomatic, active disease if followed over time.^{28,33} As such, the impact of screening strategies that depend on tools such as sputum smear microscopy that have

little ability to detect these early forms will inherently be limited. Other tools, including chest X-ray (CXR)³¹ and broader symptom screens,^{26,34} are more sensitive in detecting early forms of TB, but lack sufficient specificity, and thus often require secondary screening and microbiological or other clinical confirmation before anti-tuberculosis treatment can be initiated. Both existing (e.g., CXR, digital X-ray³⁵) and novel (e.g., soluble intracellular adhesion molecule 1)³⁶ diagnostic tools capable of rapid ‘triage’ with high sensitivity for early forms of TB²⁹ may also help facilitate such effective screening strategies in the future.

SPECTRUM OF TUBERCULOSIS RISK AND RESOURCE AVAILABILITY

Effective TB screening strategies should not only target individuals at an appropriate stage in the disease course, they should also be performed at an appropriate level of the continuum of resource availability (Figure 2). As discussed earlier in this series, TB screening is most efficient, and likely to have the greatest impact at the individual level, when targeted at specific risk groups, including high-prevalence sub-populations such as urban slums,³⁷ contacts of active cases,³⁸ health-care settings such as hospitals,³⁹ congregate settings such as prisons,⁴⁰ and immigrants/migrants from high-prevalence areas.⁴¹ Not only is the prevalence of active TB higher in these populations, but a greater proportion of disease is due to recent transmission, and those without TB are more likely to have characteristics, such as malnutrition, exposure to smoke, socio-economic disadvantage, that may increase their risk of developing active TB disease on infection.⁴² However, populations that stand to benefit most from TB screening are also those in which individuals are most difficult to identify and contact for screening, follow-up (if found to have TB), start on appropriate anti-tuberculosis treatment (poor stability of drug supply, risk of drug resistance, poor availability of drug susceptibility testing and

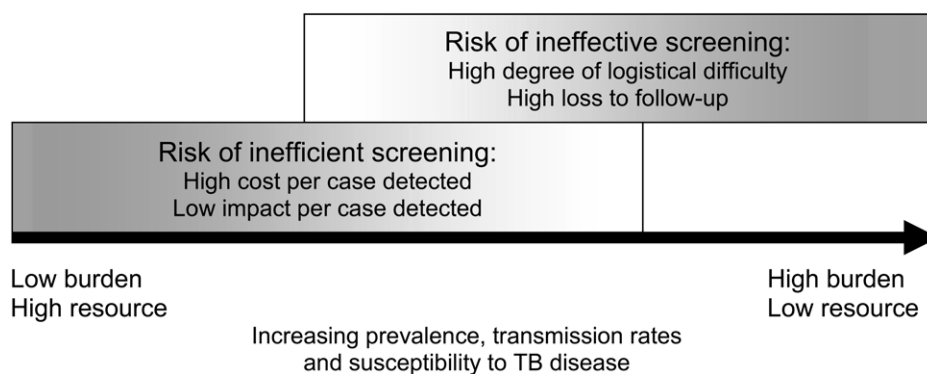


Figure 2 The spectrum of TB risk and resource availability. Screening for active TB is most efficient in high-burden areas, but factors that increase the risk of TB transmission and disease, such as poverty, stigma and migration, are also those that make screening programs least likely to succeed in finding individuals with TB, following up those who screen positive, and initiating and maintaining those people on appropriate anti-tuberculosis treatment. TB = tuberculosis.

second-line drugs) and maintain on treatment until completion.

Methodological challenges

The spectrum of TB risk and resource availability raises two key challenges for implementing TB screening programs: selection of appropriate risk groups and integration with the broader health care system. Regarding risk group selection, screening programs in high-risk groups may 1) identify more prevalent TB cases per 1000 people screened; 2) avert a greater individual-level disease burden per case detected, as people in these groups have fewer social and economic resources to compensate; 3) reduce more TB transmission per infectious person-year averted, through early diagnosis and treatment, as transmission rates are higher in such crowded and congregate settings; and 4) prevent more TB disease per transmission averted, as contacts are more likely to develop active disease once infected. These arguments all suggest that TB screening programs should be carried out at the 'right' end of the spectrum in Figure 2. However, treatment success is more difficult to attain in high-risk populations, including the socio-economically disadvantaged,⁴³ prison inmates⁴⁴ and injection drug users.⁴⁵ Furthermore, existing resources for TB control are generally weakest in those areas that serve these populations. Thus, targeting high-risk populations for active TB screening—while likely to have greatest impact and efficiency—also runs the greatest danger of identifying individuals with active TB without providing the necessary resources to initiate and complete treatment, and of diverting scarce resources away from other TB control activities, such as passive case detection, surveillance, diagnosis and treatment of drug-resistant TB for screening. The most effective TB screening programs will target individuals as far to the 'right' of the TB risk and resource availability spectrum as possible, without compromising the ability to initiate and maintain treatment for all individuals identified with active TB through screening, and without diverting resources from other essential TB control activities.

In addition to selecting appropriate risk groups for screening, it is important to consider that screening for active TB is one of many TB control activities, and that it is rarely the most cost-effective in isolation. TB screening programs thus generally cannot be implemented in isolation, but must be implemented as part of a broader health system. For example, screening for active TB will not have any impact if systems such as specimen transport or communications are not in place to translate the results of screening tests into treatment decisions.⁴⁶ Furthermore, there are many risk group-specific health programs, including the justice system,^{47,48} occupational health,⁴⁹ immigration⁵⁰ and HIV care,⁵¹ into which screening for active TB can theoretically be incorporated in a cost-effective manner that provides meaningful bene-

fits at the individual and population levels. Ultimately, TB screening and other critical interventions for TB control will only reach such high-risk populations if they are successfully integrated into broader health systems, often those targeting specific groups who are at high risk of having active TB.

SPECTRUM OF TUBERCULOSIS SCREENING STRATEGIES

After considering the trade-offs related to disease stage/diagnostic yield and TB risk/resource availability, an actual screening strategy should be selected. In making this selection, implementers must balance additional trade-offs that largely fall along a third spectrum of breadth. Specifically, screening strategies should include a target population, an approach for selecting members of that target population for screening and diagnostic test(s) with which to screen (Figure 3). At each of these stages, implementers should choose between options that are narrowly focused and those that are broader in scope; narrow strategies are more efficient and less costly, whereas broad strategies may have the greatest epidemiological impact (Figure 4). In general, narrow screening strategies should be implemented first, with broader strategies added as resources allow.

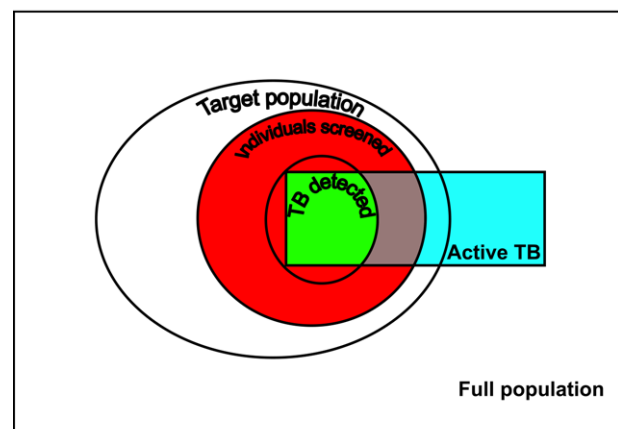


Figure 3 Strategies of screening for active TB. Screening strategies must select a target population, a method of identifying individuals for screening, and a diagnostic test. At each stage, people with active TB will be 'lost'; the goal of an effective screening strategy is to maximize both efficiency (number needed to screen and cost-effectiveness) and yield (proportion of total prevalent cases detected, impact on incidence). Efficiency can be visualized as the green area (true-positive TB cases detected) proportional to the red area (false-positives + true-negatives), whereas yield is represented by the size of the green area alone and often conceptualized in relation to the total burden of prevalent TB (blue area). Broader strategies will increase yield at the cost of efficiency and individual risk to the patient (i.e., more false-positives), whereas narrow strategies maximize the efficiency and likelihood of benefit to those treated at the expense of lower yield. TB = tuberculosis. This image can be viewed online in colour at <http://www.ingentaconnect.com/content/iatld/ijtld/2013/00000017/00000007/art00003>

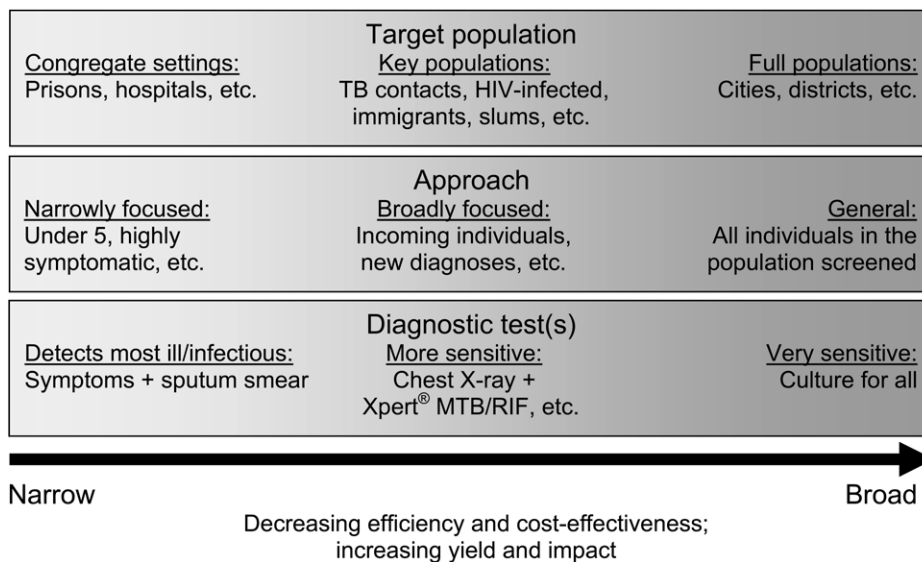


Figure 4 The spectrum of TB screening strategies. Strategies of screening for active TB range from narrow to broad in terms of the target population and the approach and diagnostic test(s) used. Choosing a strategy that is too narrow may have little epidemiological impact, whereas choosing one that is too broad may overwhelm existing capacity. Narrow strategies are generally recommended as being the most efficient, but in areas where more resources exist, broader strategies should also be undertaken. TB = tuberculosis; HIV = human immunodeficiency virus.

Methodological challenges

The success of a screening strategy can hinge upon the selection of the target population, but determining the most appropriate population is challenging, as a close understanding of a setting's epidemiologic profile and resource availability is not always readily available. As TB is not randomly dispersed in a population, random screening strategies are unlikely to be most effective. Rather, screening should start among populations perceived to be at highest risk and broaden to lower-risk populations as resources allow. Although risk profiles differ by setting, the populations at highest risk often include people living with HIV or other immunocompromised conditions,^{52–54} contacts of newly diagnosed active TB cases⁵⁵ and prison inmates, among whom TB incidence is 20–25 times, and often up to 100 times, higher than in the general population.^{56,57} Geographic areas of intense risk include health care settings (high density of immunocompromised individuals, annual risk of tuberculous infection among health care workers up to 14%⁵⁸), and congregate settings such as mines (annual incidence of active TB often over 1%/year⁵⁹). Although these highest-risk groups may account for up to 50% of TB cases in some settings, such as prisons in the former Soviet Union,⁵⁷ TB incidence is more broadly dispersed in most populations. Thus, while congregate and health care settings should be a key focus of TB screening activities, broader and combined approaches are generally required for maximum epidemiological impact.

Beyond the more easily defined risk groups, more broadly focused strategies should target other sub-

populations with increased TB incidence, including slums,⁶⁰ impoverished regions⁶¹ and geographic areas with known high TB incidence than surrounding areas, based on local surveillance data.³⁷ However, access to these settings is unlikely to be straightforward and generally requires careful planning with health officials and key community members. As the sub-populations that contribute most to TB transmission will vary across epidemiologic settings, high-quality surveillance data are of tremendous utility in identifying appropriate target populations;⁸ however, such data are often not available. Mathematical models can also be of utility in assessing the potential population-level impact and/or cost-effectiveness of TB screening strategies, including those that are more narrowly focused⁴⁰ and those that are broader in scope.⁶²

Once target populations are selected for active TB screening, an approach must be determined as to which members of that population will be screened. As with selection of the target population, methods of identifying individuals for screening range from narrow to broad. Narrowly focused approaches, which can be applied even in broad populations, screen only those individuals at highest risk, such as children exposed to active TB,^{63,64} 'sputum depots' that recruit only those individuals who self-identify as symptomatic²⁶ and screening of patients and health care workers on in-patient wards, without including other settings of nosocomial transmission risk such as emergency departments.⁶⁵ Broader approaches might attempt to screen all individuals in a target population, but do so only at one point in time, when the risk of undiagnosed prevalent TB is high, such as at

initiation of antiretroviral therapy for HIV,⁴¹ immigration to a low-incidence country⁶⁶ or treatment of an index case in a household.³⁸ The broadest type of screening approach consists of multiple rounds of screening over time for all members of a target population. One cluster randomized trial has provided evidence that this approach can impact longer-term TB prevalence,¹² but is also much more resource-intensive and less efficient than more targeted approaches. Determining the best screening schedule remains a challenge when considering implementing a screening strategy, with few data available to simplify the decision.

In addition to the target population and screening approach used, implementers should also select a screening tool (or tools). As discussed above, 'triage' tests that function as part of a two-step strategy require high sensitivity, whereas tests used to initiate treatment should result in a high post-test probability of disease—itsself a function of test accuracy—as well as the TB risk in the population being screened, with the risk of false-positives increasing as TB prevalence declines. Furthermore, strategies that employ high-accuracy diagnostics such as TB culture will be more expensive, whereas lower-sensitivity diagnostics, such as sputum smear, may miss a large number of cases. The accuracy (sensitivity and specificity) of the tools may also differ according to risk group (for example, the lower accuracy of sputum smear or CXR in people living with HIV). In choosing between such tools, decision makers should consider such factors as available resources, acceptability to the population being screened and capacity to treat those diagnosed with TB and drug-resistant TB.

SPECTRUM OF OUTCOMES AND IMPACT MEASUREMENTS

Once a screening strategy and the population to be screened have been chosen, the methodology for evaluation should be considered. In doing so, there is a spectrum of available outcomes that can be evaluated during or before and after the TB screening program. As outcomes become more useful in assessing population-level impact, they also become more logistically difficult and resource-intensive to measure (Figure 5). This reality creates an inherent trade-off between utilizing time and resources for actual screening (rather than evaluation) and preserving the ability to demonstrate a meaningful impact. As previously stated in this series,⁶ TB screening ideally confers benefits both of early diagnosis and treatment initiation, leading to reduced immediate morbidity and mortality for individual patients, and of reduced TB transmission, leading to reduced morbidity and mortality over time in populations. For screening to benefit the individual, it must be followed by effective treatment; thus, screening strategies should ensure that newly detected patients achieve high rates of treatment success. Cases detected through screening tend to have less severe disease and lower mortality, but perhaps higher default rates,⁷ emphasizing the importance of linkage between TB screening and treatment. In any case, the ultimate goal of TB screening is not the detection of cases, but the improvement of outcomes at the individual and population levels; while measurement of these outcomes is arguably the most important evaluation of a TB screening program, it is also among the most difficult.

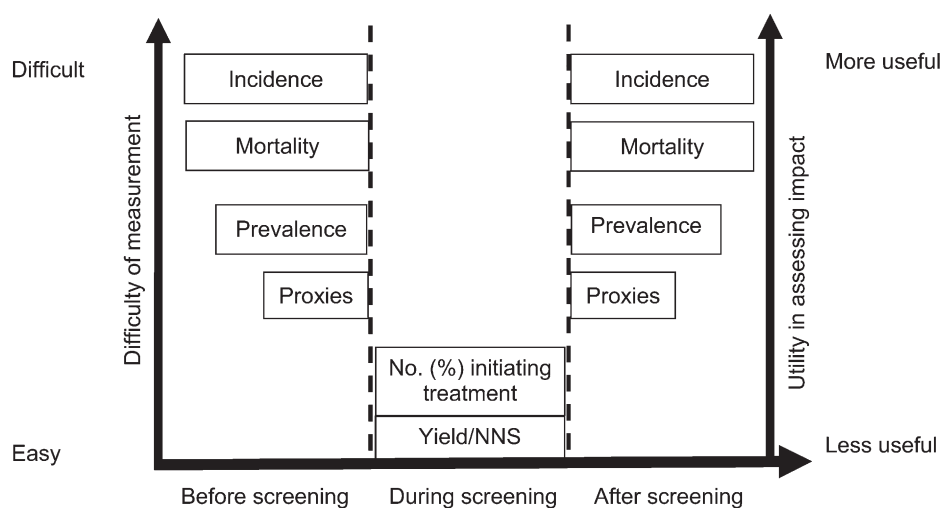


Figure 5 The spectrum of outcomes and impact measurements of screening programs. Outcomes that can be utilized to measure the impact of screening programs on the epidemiology of TB within a population or subpopulation. There is a trade-off between simple outcomes, such as yield and NNS, measured operationally during the screening program and more complex outcomes (e.g., prevalence, incidence) requiring careful comparison of estimates calculated before and after the screening program, and how useful these outcomes are towards understanding the impact of the screening strategy. Proxy measures include screening for latent tuberculosis infection among young children and other markers (e.g., strain clustering) of recent transmission. NNS = number needed to screen; TB = tuberculosis.

Methodological challenges

The first three spectra covered methodological challenges in implementing screening strategies for active TB; however, if such strategies are implemented in such a way that appropriate evaluation is not also allowed for, the effectiveness of those strategies will remain uncertain. The overwhelming majority of TB screening programs report only the yield of the program (i.e., the number of incident and/or prevalent TB cases detected among the number screened [NNS]), an outcome measure that offers little insight into the individual-level effects of the program and virtually no assessment of impact at the population level. While screening programs are unlikely to be successful if they do not increase the total number of people diagnosed and treated for TB, the ultimate aim of TB screening is not to increase diagnoses, but to reduce morbidity and mortality. Moreover, it is not yet clear what proportion of cases detected through screening programs add to the total number of cases notified, or if they would have been diagnosed passively in the near future. The spectrum of TB screening strategies discussed earlier may be seen as a trade-off of efficiency and cost-effectiveness vs. yield and potential impact. Efficiency is commonly conceptualized as the NNS,⁷ but these are the minimal data to strive for in screening programs (Figure 5).

Another metric of efficiency that incorporates resource use is cost-effectiveness, typically measured as the incremental cost-effectiveness ratio.⁶⁶ Cost-effectiveness may be measured as the cost per case detected (or initiated on treatment), or alternatively using more generalizable metrics such as the cost per disability-adjusted life year (DALY) averted or year of life saved.^{40,67} TB screening has been shown in some settings (e.g., South Africans starting antiretroviral therapy⁶⁸) to be cost-effective according to traditional thresholds, and can be compared in cost-per-DALY terms to other TB interventions with demonstrated cost-effectiveness, including smear microscopy and first-line treatment,⁶⁹ expansion of other passive diagnostic modalities including Xpert MTB/RIF²² and TB culture,⁷⁰ diagnosis and treatment of multidrug-resistant TB,⁷¹ and bacille Calmette-Guérin vaccination.⁷²

In contrast to cost-effectiveness, yield is defined as the number of previously undetected cases that are found through a particular screening program, and it is more an intermediate measure of impact than of efficiency. Assuming that the most efficient TB screening strategies are adopted first, further increases in yield should come at the expense of reduced efficiency. While increased yield (and thereby population-level impact on transmission) is the primary goal of any screening strategy, setting-specific constraints, such as resource limitations and political realities, will dictate that only strategies above a certain efficiency threshold will be feasible or appropriate. Determining this

threshold and crafting screening strategies—in terms of target population and the approach for identifying individuals to screen and diagnostic test(s) applied—that fall within this efficiency threshold is arguably the primary challenge faced by implementers. This task requires local epidemiologic knowledge, such as surveillance data, combined with models of impact and cost-effectiveness, to be done with maximum effectiveness.

In addition to reduced efficiency, increasing yield (for example, by screening of lower-risk populations) also usually implies detecting a higher proportion of false-positive diagnoses as the prevalence of true disease declines. As TB chemotherapy is not without risk, increasing the ratio of false-positive to true-positive diagnoses will not only reduce program efficiency, it will also alter the risk-benefit ratio for individuals being screened. As these individuals are not seeking care on their own initiative, a higher ethical standard to avoid treating people with no chance of benefit may apply.⁴⁷ The selection of populations with sufficient TB prevalence to justify screening is thus a question not only of efficiency, but also of individual-level risk-benefit and ethics.

The ideal population-level metrics for TB control programs are changes in incidence and mortality; however, both incidence⁷³ and mortality⁷⁴ are challenging to measure, and assessment of a screening program's effect on either outcome even more so. In most high-burden countries, the TB surveillance infrastructure is weak,⁷⁵ as are vital statistics systems, with few high-burden countries even reporting any cause-of-death data to the WHO.⁷⁶ Furthermore, even in the highest-burden countries, TB is still relatively rare, with an annual TB incidence of 1/200 population (500/100 000) or TB mortality of 1/2000 (50/100 000), which is nearly four times higher than the global average.⁴ Extremely large sample sizes, over long periods of time, are thus needed to accurately calculate incidence or TB-specific mortality at the population level. Finally, while screening programs may have more rapid impact on prevalence by 'mopping up' undiagnosed prevalent cases, such individuals are less likely to be seriously ill, as incidence falls more slowly than prevalence in response to TB control efforts.⁷⁷

TB incidence, prevalence and mortality are challenging to assess and may change gradually over time due to reactivation of old infections, even when ongoing transmission rates have been dramatically reduced. When these broader outcome measures cannot be reliably assessed, proxy measures may capture effects on transmission more rapidly. Transmission proxies include serial screening for latent tuberculous infection (e.g., with tuberculin skin testing) among children, in whom positive tests are more likely to represent recent infection,^{10,26} and molecular epidemiology, evaluating *Mycobacterium tuberculosis* strains before and after screening to determine if

newly diagnosed TB cases are more likely to result from recent transmission, indicated, for example, by clustered strains, although the latter is only feasible if a strong genotyping surveillance system has been established.

The ability to measure epidemiologic outcomes depends on an appropriate study design. Screening programs are conducted at community level and therefore cannot generally be assessed using individually randomized trials. Randomized assessment therefore requires cluster randomization; such trials can either be parallel in design, or incorporate randomly phased roll-out of a screening program, such as a stepped-wedge or phased implementation design.⁷⁸ Parallel designs have less risk of bias from secular trends, but may be seen as ethically inferior when evaluating an intervention that is likely to benefit the population. In either case, random assessment of incidence, prevalence or mortality requires very large sample sizes and resources that could otherwise be used for direct intervention rather than evaluation. Logistically simpler designs, such as before-after experiments, may contain bias due to secular trends and changes to the overall health care system that occur as a result of implementing the screening program. The validity of such assessments also depends on the quality of the existing surveillance systems and the ability to follow longitudinal cohorts, both before and after the implementation of a screening program. When such longitudinal assessment cannot be performed, before-and-after prevalence surveys offer the 'next best' alternative. Prevalence surveys are costly (often \geq US\$20/person screened²⁵), and must be conducted carefully to ensure that the population surveyed is representative of the target population of the screening strategy, whether that population is a high-risk group, such as children or the HIV-infected, or more broadly inclusive. Furthermore, prevalence surveys themselves may act as active TB screening, making the impact of the target program difficult to disentangle from that of the evaluation.

As evidence of the challenges in appropriate impact evaluation, an earlier review in this series reported only five published studies in which epidemiologic impact measures of active TB screening were assessed;⁷ these included TB case notification (i.e., yield),^{79,80} TB incidence⁸¹ and TB prevalence.^{12,82} Without more direct evidence, we are left with several critical questions that are presently answerable only through modeling exercises. These questions include: 1) What is the likely relationship (and range of possible relationships) between detection of previously unknown TB cases (i.e., yield) and impact at the population-level (i.e., incidence and mortality)? 2) What degree of impact must a screening program show to merit replication or scale-up? 3) If a screening program identifies mostly TB cases of mild severity and lower infectiousness (left of the spectrum in

Figure 1), is its likely population-level impact greater or less?

To summarize the spectrum of outcomes and impact measurements, increasing the number of TB diagnoses is a minimal requirement of a successful screening strategy, although even if the screening does not increase case notifications, if it captures TB cases earlier, thus reducing morbidity, mortality and transmission, then benefits at both the individual and the population levels may be gained. However, if the yield, morbidity and mortality associated with the screening program are not greater than the standard passive system, then there is likely no benefit to be gained. If TB screening programs do not increase the number of diagnoses made, then screening is unlikely to augment the TB control strategy for the corresponding population. Instead, resources can be better allocated towards passive diagnosis and treatment of active TB cases. However, yield alone does not guarantee individual- or population-level impact; this can only be assessed through evaluation of other measures, including transmission proxies, prevalence and, in the ideal setting, incidence and TB-specific mortality. To have such an impact, screening programs should ideally not be conducted as one-time interventions, but rather work in conjunction with scaling up diagnostic availability and DOTS implementation as part of a larger TB control strategy. Such a combined approach has resulted in screening yield, followed by long-term success in bringing down incidence rates.⁸³ An active TB screening strategy with high yield, coupled with strong treatment and retention, will likely reveal declines in epidemiological outcomes, but long-term monitoring and evaluation of such outcomes is required to conclusively demonstrate impact.

CONCLUSION

When a decision has been made to implement a screening strategy for active TB in a given setting, careful consideration needs to be given a priori to ensure that the strategy has a strong chance of success. Success can be measured both at the individual and the population levels, although the ultimate objective of active screening for TB is to reduce transmission, leading to population-level reductions in TB burden and mortality. We have described several spectra of methodological challenges that implementers may face when choosing a screening strategy, including feasibility, selection of target populations, resource allocation, outcomes and evaluation. If we are to achieve long-term success in the global fight against TB, we must begin to develop and implement strategies for TB screening that are both efficient and effective; addressing these methodological challenges is a necessary first step in this critical process.

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R É S U M É

Vu que les stratégies de dépistage actif de la tuberculose (TB) continuent à se développer au niveau mondial, l'importance d'envisager les défis méthodologiques que comportent l'élaboration et la mise en œuvre de ces stratégies est croissante. Les défis-clé liés au dépistage de la TB peuvent être résumés en termes de quatre données continues ou de quatre spectres, notamment 1) la mala-

die TB et rendement diagnostique ; 2) le risque de TB et la disponibilité des ressources ; 3) les stratégies de dépistage de la TB ; et 4) les mesures des résultats et l'impact des programmes de dépistage. Dans cette revue, nous analysons ces défis afin d'aider à l'élaboration de directives de stratégies de dépistage de la TB qui soient efficaces dans un contexte épidémiologique déterminé.

R E S U M E N

A medida que aumentan las estrategias de detección sistemática activa de la tuberculosis (TB) en todo el mundo, se hace cada vez más importante considerar las dificultades metodológicas del diseño y la ejecución de las mismas. Los obstáculos que se presentan en la detección de la TB se pueden resumir en cuatro espectros o procesos continuos, a saber: 1) la enfermedad tuberculosa y el rendimiento diagnóstico; 2) el riesgo de con-

traer la TB y la disponibilidad de recursos; 3) las estrategias de detección de la enfermedad; y 4) los resultados y las repercusiones de los programas de detección. En el presente artículo se analizan estos obstáculos con el fin de contribuir a formular las estrategias de detección sistemática de la TB que serán eficaces en un determinado contexto epidemiológico.
