

# Screening strategies for active tuberculosis: focus on cost-effectiveness

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**Abstract:** In recent years, there has been renewed interest in screening for active tuberculosis (TB), also called active case-finding (ACF), as a possible means to achieve control of the global TB epidemic. ACF aims to increase the detection of TB, in order to diagnose and treat patients with TB earlier than if they had been diagnosed and treated only at the time when they sought health care because of symptoms. This will reduce or avoid secondary transmission of TB to other people, with the long-term goal of reducing the incidence of TB. Here, the history of screening for active TB, current screening practices, and the role of TB-diagnostic tools are summarized and the literature on cost-effectiveness of screening for active TB reviewed. Cost-effectiveness analyses indicate that community-wide ACF can be cost-effective in settings with a high incidence of TB. ACF among close TB contacts is cost-effective in settings with a low as well as a high incidence of TB. The evidence for cost-effectiveness of screening among HIV-infected persons is not as strong as for TB contacts, but the reviewed studies suggest that the intervention can be cost-effective depending on the background prevalence of TB and test volume. None of the cost-effectiveness analyses were informed by data from randomized controlled trials. As the results of randomized controlled trials evaluating different ACF strategies will become available in future, we will hopefully gain a better understanding of the role that ACF can play in achieving global TB control.

**Keywords:** disease elimination, epidemic, active case-finding, review

## Epidemiology of tuberculosis and role of screening

Tuberculosis (TB) remains a leading cause of morbidity and mortality globally, predominantly affecting low- and middle-income countries. In 2013, an estimated 9 million people developed TB, and 1.5 million died from the disease.<sup>1</sup> In 2014, the World Health Organization (WHO) developed a post-2015 global TB strategy with a vision to progress toward TB elimination.<sup>2</sup> The goals are a 95% reduction in TB deaths and a 90% reduction in TB-incidence rate (fewer than ten TB cases per 100,000 population) from 2015 to 2035, and full elimination of TB (defined as under one case per million people per year) by 2050. While the worldwide TB incidence decreased at an average rate of ~1.5% per year between 2000 and 2013, TB-control efforts must be accelerated if the post-2015 targets are to be met.<sup>1</sup>

Strategies to improve TB control include: 1) treating every person in the population diagnosed with active TB with short-course directly observed treatment, a strategy strongly recommended by the WHO;<sup>3</sup> 2) reducing time to treatment; 3) increasing treatment success; 4) increasing the TB case-detection rate through passive case-finding

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(PCF), which requires that patients are aware of their symptoms, have access to health facilities, and are evaluated by health workers or volunteers who recognize the symptoms of TB and who have access to a reliable laboratory; 5) TB screening/active CF (ACF) among target populations; and 6) preventive treatment among TB contacts and other high-risk groups, especially in countries with a low TB incidence. Screening for active TB, also called ACF, aims to increase the detection of TB cases among a specific population, in order to diagnose and treat patients with active TB earlier than if they had been diagnosed and treated only at the time when they sought health care (if at all) because of symptoms (PCF). Therefore, screening for active TB will reduce or avoid secondary transmission of TB to other people, with the long-term goal of reducing the incidence of TB in a specific setting. ACF entails screening through an outreach program outside established health-service facilities. Enhanced CF includes activities that raise awareness about TB symptoms among a population and promote self-presentation to medical services.

In recent years, there has been renewed interest in ACF as a possible means to achieve control of the global TB epidemic, as traditional TB-control strategies (increasing case-detection rate by PCF and using short-course directly observed treatment to increase treatment success) failed to reduce the long-term incidence of TB significantly.<sup>4</sup> A modeling study found that in areas where a target case-detection rate of 70% and a treatment-success rate of 85% have already been achieved, maintaining stable case-detection levels may not meaningfully reduce TB incidence further.<sup>5</sup> The study results suggested that case-detection targets above 70% must be pursued, in order to achieve TB elimination with existing tools. This paper summarizes strategies for ACF for TB, examining the evidence for TB screening among different target groups based on cost-effectiveness analyses (CEAs).

## Overview of different screening strategies for detection of active TB

### Historical perspective

Screening for active TB can either include the whole population (mass screening) or it can focus on selected high-risk groups (targeted screening). In the mid-20th century, mass-screening campaigns were conducted in Europe and North America. Screening was performed using mass miniature radiography (MMR), first developed in 1936, using a miniature (50–100 mm) photograph from a chest X-ray displayed on a fluorescent screen. MMR costs less than a large chest X-ray, and radiation exposure for patient and operator is less compared to standard chest X-rays. MMR played an

important role during the Second World War (1939–1945) for screening of military personnel and civilians,<sup>6–8</sup> and was subsequently scaled up when mobile MMR using “TB vans” became available, taking the screening out into the community, and thus greatly increasing the capacity for targeted and whole-community screening.<sup>9</sup> While MMR has been successful in detecting previously unknown TB cases and diagnosing TB cases earlier, it remains unclear how much of the major reduction in TB incidence in North America and Europe in the 20th century can be attributed to this intervention, as TB incidence was already decreasing in developed countries in the first half of the 20th century because of better nutrition and housing conditions. Additionally, the introduction of effective anti-TB medication in the 1940s–1960s led to a steep decline in TB-related mortality and an accelerated drop in incidence of TB.

The financial cost and logistics associated with mass screening using MMR made it difficult to implement in resource-poor countries.<sup>10</sup> In the 1960s, new CF strategies, relying more on the detection of symptomatic patients, were trialed in developing countries.<sup>11</sup> A seminal Indian study published in 1963 concluded that TB-control programs should primarily be based on PCF, as the majority of patients with bacteriologically confirmed TB had at least one major TB-related symptom.<sup>12</sup> ACF strategies were proposed as an additional measure only, once the health care system was satisfactorily developed to take care of patients who sought medical attention for TB-related symptoms. Several studies suggested that focusing screening on people with a history of cough as a determining symptom was sufficient, and extensive history-taking was not required.<sup>13–15</sup>

Emphasis was thus put on developing a strong health system infrastructure with high-quality diagnostic services and increasing awareness of TB in health care workers. Large-scale studies from Europe, Canada, and Japan in the 1960s and early 1970s found that most cases of TB were detected through PCF and not periodic MMR screening.<sup>16–19</sup> Based on these findings, the ninth report of the WHO Expert Committee on Tuberculosis in 1974 recommended that MMR be abandoned.<sup>20</sup> The principles of the current WHO strategy of TB control were established, focusing on PCF and delivery of TB case-management activities through the general health infrastructure.<sup>10</sup>

## Community-wide screening in more recent times

Despite the focus on PCF promoted by the WHO since 1974, there have been more recent studies that have evaluated ACF strategies in the whole population of a community

or district. Screening algorithms and diagnostic tools used have varied, with sputum-smear microscopy in patients with a history of cough being a common screening tool. A systematic review that included studies published between 1980 and 2010 assessed the evidence that screening for TB: 1) increases the number of TB cases detected and initiated on anti-TB medication, 2) identifies cases at an earlier stage of disease, 3) reduces TB-related mortality and morbidity, and 4) impacts on TB epidemiology (incidence and prevalence of TB in the community) compared to PCF alone.<sup>21,22</sup> The review identified four randomized trials<sup>23–26</sup> and 14 prevalence studies that investigated the effect of screening on TB CF. An additional 14 studies provided data on the contribution of screening to the total TB cases diagnosed. The review found moderate evidence to suggest that screening increases the number of TB cases found in the short term. In many settings, more than half the prevalent TB cases in the community were undiagnosed. The risk of false-positive TB diagnosis, however, which is higher in populations undergoing ACF compared to PCF (due to the inverse relationship between false-positive diagnosis and TB prevalence) needs to be considered. There was moderate evidence that screening identifies TB cases earlier and with less severe disease, based on 15 studies from both high and low-TB-incidence settings. No significant impact of screening on TB-treatment outcomes was found based on a review of 17 studies, with similar treatment success in TB cases found through screening and PCF in varied settings with different proportions of successful treatment. Evidence that screening (in addition to PCF) impacts on TB epidemiology (incidence and prevalence of TB in the community) was weak, based on five studies.<sup>27–31</sup> There were some significant study limitations, including lack of a control group without an intervention,<sup>27</sup> methodological concerns about the calculation of the standardized TB-notification ratio,<sup>28</sup> lack of long-term trends in TB incidence and unclear pairing of communities for randomization,<sup>29</sup> and study assessment not limited to the effect of screening alone.<sup>30</sup> ZAMSTAR was the only study with a cluster-randomized design that directly evaluated the impact of screening on TB epidemiology. It was published in 2013, and preliminary results only were available at the time of the systematic review.<sup>31</sup> The study, conducted in Zambia and South Africa, used a 2×2 factorial design comparing enhanced CF, a household intervention (combined TB–HIV activities based on the activities included in the WHO guidelines for collaborative TB–HIV care in clinics),

both, or neither. Neither intervention led to a statistically significant reduction in TB. In summary, the evidence to support community-wide ACF in high-incidence settings is insufficient. Current WHO guidelines include a conditional recommendation for community-wide systematic screening for active TB, suggesting that screening “may be considered for geographically defined subpopulations with extremely high levels of undetected TB (1% prevalence or higher)”.<sup>32</sup> Additionally, the guidelines propose that subpopulations with limited access to health services may be considered for TB screening. This includes people living in urban slums or remote areas, homeless people and other vulnerable or disadvantaged groups such as some indigenous populations, migrants and refugees.

A cluster-randomized controlled trial is under way in Vietnam that will evaluate the effect of yearly community-wide TB screening for 3 years compared to no screening on the prevalence of microbiologically confirmed pulmonary TB (measured in the intervention and control clusters in the fourth year). Residents are visited in their home, asked about symptoms of TB, and asked to produce a single spontaneous sputum specimen for testing. The collected sputum specimen will be tested for *Mycobacterium tuberculosis* using a fully automated polymerase chain reaction test (Xpert MTB/RIF; Cepheid Inc, Sunnyvale, CA, USA).

## Screening for active TB in high-risk groups

The WHO’s 2013 guidelines on systematic screening for active TB include strong recommendations for screening of: 1) household contacts and other close contacts of patients with active TB, 2) people living with HIV, and 3) current and former workers in workplaces with silica exposure.<sup>32</sup> It is however worth noting that the guidelines state that direct evidence underlying these strong recommendations was poor, and the recommendations were mainly influenced by the views of the members of the guideline development group.

A strong recommendation in these guidelines was defined as one “for which the desirable effects of adhering to the recommendation are judged to clearly outweigh the undesirable effects (and for which) screening is judged to be feasible, acceptable, and affordable in all settings”.

A Cochrane review published in 2011 examined whether ACF among contacts of people with confirmed TB increased case detection compared to usual practice.<sup>33</sup> The review identified only one randomized controlled trial that tested

the effect of ACF in contacts, but the intervention in that trial also included screening for and treatment of latent TB infection (LTBI) in contacts, and the separate effect of ACF could not be estimated.<sup>29</sup> The ZAMSTAR study did not find a significant benefit of household screening in a cluster-randomized trial.<sup>31</sup> The results of a pragmatic stepped-wedge cluster-randomized trial of ACF among household contacts of sputum smear-positive TB cases in Lima, Peru are pending.<sup>34</sup> Also pending are the results of a cluster-randomized trial of ACF among household contacts of sputum smear-positive TB cases in Vietnam.<sup>35</sup>

The evidence for screening people living with HIV and current and former workers in workplaces with silica exposure is weak (despite strong recommendations by the WHO for screening), due to a lack of randomized controlled trials comparing ACF versus PCF in these high-risk groups. The WHO additionally outlines conditional screening recommendations for prisoners, people with an untreated fibrotic chest X-ray lesion, and people who are seeking health care or who are in health care if they belong to selected high-risk groups, such as patients with diabetes mellitus or patients with chronic renal failure or on hemodialysis.<sup>32</sup>

## Practical considerations

A good screening test is characterized by high performance (sensitivity, specificity, and reproducibility) and favorable operational characteristics, including the time taken to perform the test, its technical simplicity or ease of use, user acceptability, and the stability of the test under the expected conditions of use.<sup>36</sup> The ease of use will depend on how easy it is to acquire and maintain the equipment required to perform the test, how difficult it is to train staff to use the test and to interpret the results of the test correctly, and the stability of the test under the expected conditions of use. Until recently, the lack of rapid and accurate diagnostic tools for TB has been a major obstacle to achieving global TB control.<sup>37</sup> TB diagnosis, even today, is still reliant on older diagnostic tools, such as direct smear microscopy and culture, tests which often perform poorly and for which the infrastructure is frequently unavailable in the periphery of the health system. Sputum-smear microscopy has been the primary method for diagnosis of pulmonary TB in low- and middle-income countries, but it has some significant limitations. Its sensitivity is highly variable, ranging between 20% and 80%,<sup>38</sup> with the lowest sensitivity in children<sup>39</sup> and HIV-infected patients.<sup>40</sup> Serial sputum examinations are required to increase sensitivity, but some patients do not return for repeated sputum examinations and become “diagnostic defaulters”, ie, patients who do not

complete the diagnostic process.<sup>41</sup> Most of the diagnostic defaulters are unaware that they have a positive sputum smear and are thus infectious. Additionally, smear microscopy relies on well-trained microscopists: sensitivities can vary up to 28% between readings in the field and reference laboratories.<sup>42</sup> The sensitivity of smear microscopy for extrapulmonary specimens is very low, because the specimens usually contain only a few irregularly distributed organisms that tend to clump together.<sup>43</sup>

In the last few years, new TB diagnostics have been introduced. The most significant shift in the TB-diagnostics landscape has been the worldwide rollout of Xpert MTB/RIF.<sup>44</sup> The Xpert MTB/RIF is a cartridge-based automated diagnostic test that can identify *M. tuberculosis* DNA and resistance to rifampicin by polymerase chain reaction. The Xpert technology has significantly increased sensitivity for detection of TB compared to sputum-smear microscopy, and can also rapidly detect rifampicin resistance with high accuracy.<sup>45</sup> Rifampicin resistance is highly indicative of multidrug-resistant (MDR) TB, although formal confirmation of isoniazid resistance is required. The WHO endorsed Xpert MTB/RIF in 2010 for use in TB-endemic countries, and declared it a major milestone for global TB diagnosis. According to the WHO, as of December 31, 2014, 3,763 GeneXpert instruments (comprising 17,883 modules) and >10 million Xpert MTB/RIF cartridges had been procured by the public sector in 116 of 145 countries eligible for concessional pricing.<sup>46</sup> The worldwide success and rollout of MTB/RIF has contributed to considerable interest in new TB diagnostics. A significant expansion of molecular technologies that could potentially replace smear microscopy can be expected.<sup>47</sup> Unmet needs in TB diagnostics relevant to TB screening include: 1) a simple triage test to identify individuals with presumed TB who need confirmatory testing (currently used tools are symptom check, eg, cough for 2 weeks, which lacks sensitivity and specificity, and chest X-ray, which has low specificity for TB), 2) a sputum-based replacement test for smear microscopy (for diagnosis of active pulmonary TB); and 3) a nonsputum-based biomarker test for all forms of extrapulmonary TB, ideally suitable for use at levels below microscopy centers (for diagnosis of extrapulmonary and childhood TB).<sup>48</sup>

It is important to distinguish tests to detect active TB from tests to detect latent (dormant) TB infection. In most infected persons, TB remains clinically asymptomatic and microbiologically inactive (latent). Approximately 5% of infected persons will progress from infection to primary TB disease, and another estimated 5% of people with LTBI

will develop active TB through endogenous reactivation of LTBI at some point in their life (postprimary TB), sometimes many years after the initial infection.<sup>49</sup> There are two available investigations for identification of LTBI: the tuberculin skin test (TST), also called the Mantoux test, and IFN $\gamma$ -release assays (IGRAs). If a patient has a positive TST or IGRA, active TB needs to be ruled out (by asking about TB symptoms, performing chest X-ray and sputum smear if indicated) before preventive TB treatment can be started. A positive TST or IGRA result does not discriminate between LTBI and active TB disease. There is some concern that TSTs and IGRAs are being misused in some high-TB-incidence settings, such as India, to diagnose active TB.<sup>50</sup> This will lead to significant overdiagnosis of active TB, as LTBI is highly prevalent in India.<sup>51</sup>

## Cost-effectiveness of screening strategies for active TB

CEA is increasingly used to inform decisions on allocation of health care resources, including resources in TB care. It compares the costs and outcomes (effects) of two or more courses of action to assess the extent to which an intervention can be regarded as providing value for money. Cost-utility analysis is a form of CEA where effectiveness is expressed in terms of utility (quality-adjusted life years [QALYs]). In order to calculate QALYs, health-state utility scores need to be incorporated into a model. A utility score, obtained through preference-measurement techniques, reflects the “value” people place on a health state on a scale from 0 (equal to death) to 1 (equal to perfect health). Expressing effectiveness in terms of utility allows comparison across different health programs and policies by using a common unit of measure (cost/QALY gained). As an alternative to QALYs, disability-adjusted LYs (DALYs) can be used in cost-utility analyses (cost/DALY avoided). DALYs are a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death. For DALYs, the scale used to measure health state is inverted to a “severity scale”, whereby 0 equates to perfect health and 1 equates to death. The weight factors are age-adjusted, and they are discounted with time, thus favoring immediate over future health benefits.<sup>52</sup> While QALYs and DALYs both allow for comparison of interventions across health sectors, they are not interchangeable. The WHO recommends that DALYs are used to express health-outcome effectiveness, but states that QALYs can be used alternatively.<sup>53</sup> If the effectiveness measure is disease-specific (eg, cost per case of TB detected or per case of TB cured), comparison is only possible across interventions for

this particular disease, and there is no standardized measure of what constitutes good value for money.

When (mutually exclusive) choices have to be made between interventions (or an intervention and no intervention) for the same health issue, eg, different screening strategies to detect active TB, the question that needs to be addressed is: What are the additional benefits to be gained from a new intervention, and at how much additional cost? The use of incremental cost-effectiveness ratios (ICERs) answers these questions. These are calculated by dividing the difference in costs (between interventions) by the difference in health effects (between interventions). In order to determine whether an intervention represents good value for a national health care system, the Commission on Macroeconomics and Health has proposed thresholds based on the per capita gross domestic product (GDP).<sup>54</sup> Using this approach, promoted by the CHOosing Interventions that are Cost-Effective (WHO-CHOICE) project, an intervention that costs less than three times the national annual GDP per capita per DALY avoided is considered cost-effective, whereas one that costs less than once the national annual GDP per capita is considered highly cost-effective.<sup>55</sup>

To examine the available evidence on cost-effectiveness of screening for active TB, the author performed an electronic search on PubMed/Medline on March 6, 2016. I searched using the terms (screening OR case finding OR case-finding) AND (tuberculosis OR TB) AND (cost OR value). I included every study that assessed the cost-effectiveness of a screening intervention for active TB, compared with “doing nothing”, ie, PCF, or compared with other screening interventions for active TB. I excluded: 1) studies that focused on screening for LTBI or tests used primarily to detect LTBI (TST, IGRAs); 2) studies that included LTBI treatment for patients with abnormal chest X-rays, but no active disease, in the overall cost-effectiveness assessment; 3) studies that compared only screening for active TB with screening for LTBI, but not to “no screening”; and 4) reviews or opinion pieces (editorials, letters, etc). Screening for LTBI with the intention to offer preventive TB treatment always incorporates screening for active TB, as active TB needs to be excluded before preventive TB treatment is initiated.

The search strategy identified 86 publications, of which 14 met the inclusion and exclusion criteria; one additional study was identified from the reference list of a paper (Table 1).<sup>56-71</sup> The 15 identified studies contained 17 analyses of target groups for screening. Thirteen analyzes used ICERs, thus evaluating the difference in cost between two possible interventions (or an intervention and no intervention) divided by the difference in their effect. Four studies reported only the



Table 1 Characteristics of CE analyses included in the review

Study	Study type	Setting	Population screened	Intervention	Outcome measures	Results	Interpretation
<b>Community-wide screening</b>							
Sekandi et al <sup>56</sup>	Decision analysis, data from ACF study 2008–2009	Kampala, Uganda	People in the community	ACF in addition to PCF using door-to-door cough surveys, sputum samples collected if cough $\geq 2$ weeks	ICER expressed as cost in 2013 US\$ per additional true TB case detected	ICER (cost per additional TB case detected): US\$1,492.95	ACF (in addition to PCF) was not cost-effective using the authors' definition of an ICER less than twofold GDP per capita for CE. The ICER was, however, less than threefold GDP per capita. Discrete campaigns were all highly cost-effective (cost per DALY averted less than per capita GDP). Prolonged integration of ACF was even more effective and cost-effective.
Azman et al <sup>57</sup>	Mathematical model using published data	India, PRC, South Africa	People in the community	1) Discrete ACF campaigns lasting 2 years; 2) programmatic changes incorporating ACF into routine TB-control activities for the duration of the analysis period (10 years)	ICER: cost per DALY, measured in relationship to the cost per additional TB case detected by ACF and started on treatment	Cost per additional TB case detected by ACF and started on treatment: India \$1,200, PRC \$3,800, South Africa \$9,400	
Mupere et al <sup>58</sup>	Decision analysis with Markov model	Kampala, Uganda	Ugandan residents of Kampala aged $\geq 10$ years	ACF in addition to PCF using door-to-door screening; persons with a cough lasting $\geq 2$ weeks referred to health facilities for evaluation	ICER: addition cost per QALY gained	ICER: US\$109 per additional QALY (compared to PCF only); program was most cost-effective in the 45–54-year age-group (US\$51/QALY)	ACF was an effective strategy for TB control and improving quality of life, and was highly cost-effective (cost $< US$350/\text{QALY} = \text{GDP per capita}$ ).
Harper et al <sup>59</sup>	Cohort study 1990–1993	Nepal, remote areas	People in the community	Outreach TB-diagnostic service (microscopy camps lasting 2–4 days) with precamp publicity; those who had a cough $> 3$ weeks had sputum-smear examination; if smears were positive, they were started on anti-TB treatment	Additional cost per detected sputum smear-positive patient	Additional cost to the program of detecting a smear-positive patient through microscopy camps was US\$37.50/case diagnosed	For an international NGO, to run 15 camps a year adds only an additional 0.35% to the overall running costs. However, for a government program, it would be prohibitively expensive (Nepalese health expenses were US\$1.30/person/year).
<b>TB contacts</b>							
Sekandi et al <sup>56</sup>	Decision analysis, data from ACF study 2008–2009	Kampala, Uganda	Household contacts of patients with active TB	Screening of all household members (independently of symptoms) of an index TB case with sputum examinations or chest X-ray, if no sputum could be produced	ICER: additional cost per additional true TB case detected	ICER (cost per additional TB case detected): US\$443.62	Screening of household contacts in addition to PCF was cost-effective for detecting TB cases.
Yadav et al <sup>60</sup>	ACF intervention in the community in 2012 and decision analysis with Markov model	Cambodia	35,000 household and neighborhood contacts	Smear-positive patients registered for treatment in previous 2 years with ongoing TB symptoms, their household contacts irrespective of symptoms, and neighborhood contacts if they had any TB symptoms were motivated during household visits to come to health centers for screening; those attending the sessions screened for symptoms and chest X-ray taken; persons with clinical symptoms and/or chest X-ray findings consistent with TB tested by using the Xpert MTB/RIF assay	ICER: cost per DALY averted and cost per death averted (for ACF in addition to PCF)	CE of program compared with scenario of PCF alone estimated to be \$330 per DALY averted, or \$5,300 per death averted	The ACF program in Cambodia was highly cost-effective and had an ICER that was well below the GDP per capita. The incremental benefit of ACF was driven by the modeled excess mortality in the absence of the ACF program.

Study	Study type	Setting	Population screened	Intervention	Outcome measures	Results	Interpretation
Dasgupta et al <sup>61</sup>	Decision analysis, data from cohort-screening studies	Montreal, Canada	Close contacts of patients with active contagious TB	Chest X-ray in close contacts with a TST >4 mm	ICER: incremental cost for each additional case of prevalent active TB treated	ICER: net savings of \$815 per case of prevalent active TB treated (compared to PCF)	Investigation of close contacts was highly cost-effective and resulted in net savings. CE can be further increased by including treatment for LTBI.
<b>Persons with HIV infection</b>							
Zwerling et al <sup>62</sup>	Decision analysis using costs and operational data from an ongoing cluster-randomized trial of Xpert versus LED microscopy for TB screening in 12 rural clinics	Rural Malawi (low-income countries in sub-Saharan Africa)	People newly diagnosed with HIV	Xpert and LED microscopy screening: all patients newly diagnosed with HIV and at least one TB symptom screened. Compared to standard of care: screening done at the discretion of the treating physician with standard smear microscopy.  Patients diagnosed by smear, LED microscopy, or Xpert with a negative test for rifampicin resistance put on first-line therapy; those diagnosed with rifampicin-resistant TB by Xpert would initiate second-line therapy	ICER: incremental cost per DALY averted (compared to standard of care)	LED microscopy: ICER \$1,808/DALY averted for low patient volume, ICER \$699 for high patient volume.  Xpert: ICER \$2,809/DALY averted for low patient volume, ICER \$564 for high patient volume	Compared to the standard of care, both LED microscopy and Xpert had an ICER of over \$1,800 per DALY averted, above the per capita GDP of most low-income countries in sub-Saharan Africa. However, if higher patient volume could be achieved, the ICER improved to \$500–\$700 per DALY averted, and Xpert became more cost-effective than LED microscopy. Using a CE threshold of threefold GDP per capita for Malawi (\$1,080), the ICER was higher than the threshold; however, screening for TB would be considered cost-effective in most countries (eg, neighboring Tanzania, where per capita GDP was \$525 in 2010).
Andrews et al <sup>63</sup>	Monte Carlo microsimulation model	South Africa	HIV-infected individuals initiating ART	Eight TB-screening strategies: sputum-smear microscopy (two samples), smear and culture (two samples), and either one or two samples of sputum tested by Xpert MTB/RIF; strategies involving two samples deemed positive if either test positive; each diagnostic strategy evaluated for use in TB-symptomatic patients only or in all patients irrespective of TB-related symptoms	ICER: additional cost per years of life saved (\$/YLS) compared to no screening	Two smears in symptomatic patients: ICER \$2,600/YLS compared with no screening. Two smears in all patients: ICER \$2,800/YLS compared with no screening. Two smears and cultures in all patients: ICER \$5,100/YLS compared with two smears and cultures in all patients. This approach had greater effectiveness with a lower ICER than two smears and cultures in symptomatic patients, one Xpert test, or two Xpert tests in symptomatic patients.	Screening all individuals initiating ART with Xpert MTB/RIF was very cost-effective (< per capita yearly GDP of South Africa of \$7,100 in 2010).

(Continued)

Table 1 (Continued)

Study	Study type	Setting	Population screened	Intervention	Outcome measures	Results	Interpretation
<b>Immigrants to low-incidence settings</b>							
Wingate et al <sup>64</sup>	Decision analysis	USA	Student-visa applicants from India, PRC, and Germany going to the US	Overseas screening (and treatment where necessary) for active TB by "panel physicians" according to the most recent directly observed therapy technical instructions for testing and treating TB, or culture and directly observed therapy tuberculosis technical instructions (CDOT TB TI)	ICER: additional cost per case of TB prevented from being imported into the US (from a societal perspective, combining both overseas and US costs)	ICER: for PRC \$22,187 per case prevented from being imported; for India \$22,187 per case prevented from being imported; for Germany ICER could not be calculated (no TB cases)	When both overseas and US costs were included, each TB case prevented from being imported into the US from Chinese and Indian students would cost an additional \$22,187 and \$15,063, respectively. Implementing screening programs for German students would prevent no cases in most years, and would result in increased costs both overseas and in the US.
Dasgupta et al <sup>61</sup>	Decision analysis, data from cohort-screening studies 1996–1997	Montreal, Canada	Individuals coming to Canada on visas for longer than 6 months	Premigration screening: chest X-ray screening and further investigation if abnormal postarrival surveillance for newly arrived immigrants with inactive TB	ICER: incremental cost for each additional case of prevalent TB treated, compared to PCF	Immigrant screening ICER CA\$20,328 per case of prevalent active TB treated; immigrant surveillance CA\$24,225 per case of prevalent active TB treated	Immigrant screening and surveillance did not appear to be very cost-effective.
<b>Patients attending medical services</b>							
Feingold <sup>65</sup>	Cohort study 1969–1971	Hospital, Atlanta, USA	Patients attending a hospital's outpatient clinic who had not had a chest X-ray within a year	Chest X-ray microfilm and further investigation or surveillance if abnormal	Cost per case of active TB detected	Cost of \$8,000 per case of active TB detected	Chest X-ray screening was not cost-effective.
Kranzer et al <sup>66</sup>	Cohort study 2009–2011	Cape Town, South Africa	HIV-negative adults with symptoms suggestive of TB and adults with HIV infection or diabetes regardless of symptoms	HIV testing and chronic disease screening, including TB-symptom screening, performed at a mobile HIV-testing service; identified individuals asked to provide one sputum sample	Additional cost per case of active TB detected and additional cost per TB case cured	US\$1,117 per TB case detected and US\$2,458 per TB case with a positive treatment outcome (cured or treatment completed)	The cost of US\$2,458 per case successfully treated was threefold higher than the cost per case treated under PCF. CE needs to be further assessed.
<b>Prisoners and jail inmates</b>							
Winetsky et al <sup>67</sup>	Dynamic transmission model of TB and MDR-TB	Former Soviet Union	Prisoners	Eight strategies for TB screening and diagnosis, involving alone or in combination: self-referral, symptom screening, MMR, and sputum examination with Xpert MTB/RIF	Primary outcome: ICER expressed as cost per QALY gained Secondary outcomes: total dollars spent, total QALYs gained, and prevalence of TB (all forms) and MDR-TB	Using sputum Xpert MTB/RIF as an annual primary screening tool among the prison population most effectively reduced overall TB prevalence (from 2.78% to 2.31%) and MDR-TB prevalence (from 0.74% to 0.63%), and cost US\$543/QALY gained compared to MMR screening with sputum PCR reserved for rapid detection of MDR-TB	Annual screening of the general inmate population with sputum Xpert MTB/RIF was cost-effective compared to MMR. The current strategy of annual MMR was both more effective and less expensive than strategies using self-referral (no screening) or symptom screening alone.



Study	Study type	Setting	Population screened	Intervention	Outcome measures	Results	Interpretation
Jones and Schaffner <sup>68</sup>	Decision analysis, estimates from the literature	USA	People admitted to jail	Several methods of screening for active TB evaluated: routine miniature chest X-ray, TST, symptom screening	Cost per case of active TB detected	Miniature chest radiography: cost of \$9,600 per case of active TB detected TST: \$32, 100 per case detected Symptom screening: \$54,100 per case detected	Screening for active TB with miniature chest radiography was cost-effective under even a wide range of assumptions regarding risk factors and prevalence of disease.
<b>Elderly population</b>							
Kowada et al <sup>70</sup>	Decision analysis with Markov model	Japan	BCG-vaccinated elderly population (≥65 years old)	Chest X-ray at age 65 years, treatment for TB if chest X-ray suggestive of TB	ICER: cost per QALY gained	ICER for chest X-ray screening: US\$729,905.25 per QALY (incremental cost/incremental utility) compared to no screening	Chest X-ray screening was not cost-effective.
<b>Employees</b>							
Kowada <sup>71</sup>	Decision analysis with Markov model	Japan	Immunocompetent 40-year-old employees	Chest X-ray, treatment for TB if chest X-ray suggestive of TB	Cost per QALY gained (ICER)	ICER for chest X-ray screening: US\$95,12/0.00001 QALYs = US\$9,512,000 per QALY (incremental cost/incremental utility) compared to no screening	Chest X-ray screening was not cost-effective.

**Abbreviations:** ART, antiretroviral therapy; ACF, active case-finding; BCG, bacillus Calmette–Guérin; CE, cost-effectiveness; DALY, disability-adjusted life-year; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; LED, light-emitting diode; LTBI, latent tuberculosis infection; MDR, multidrug-resistant; MMR, mass miniature radiography; NGO, nongovernmental organization; PCF, passive CF; PCR, polymerase chain reaction; PRC, People's Republic of China; QALY, quality-adjusted LY; TB, tuberculosis; TST, tuberculin skin test.

additional cost per TB case detected via screening without outlining the estimated difference in the effect compared to no screening or another screening method (PCF).<sup>59,65,66,68</sup> Comparison with the effect of “no screening” is important, because it cannot be assumed that every TB case diagnosed through a screening intervention for active TB is an additional case detected compared to “no screening”/PCF. It is likely that some of these cases would eventually have been diagnosed with PCF when patients sought health care.

## Community-wide screening

Of four studies evaluating costs for community-wide ACF, three performed a true CEA<sup>56–58</sup> and one evaluated the incremental cost per TB case detected without estimating the incremental effect compared to PCF.<sup>59</sup> Two studies examining ACF in Kampala, Uganda came to different conclusions regarding the cost-effectiveness of door-to-door screening with sputum collection in people who had had cough for 2 weeks or longer.<sup>56,58</sup> This difference was despite the fact that both used data from the same pilot ACF survey in Kampala.<sup>72</sup>

Mupere et al calculated an ICER expressing cost per additional QALY, which was US\$109 and as such below the amount of GDP per capita (\$350) and highly cost-effective.<sup>58</sup> Sekandi et al calculated an ICER expressing cost per additional TB case detected, which was US\$1,493.<sup>56</sup> As the study authors defined the cost-effectiveness threshold for this study at below twice Uganda’s GDP per capita for the study period (\$1,102), the cost did not fall below the threshold. The cost would, however, have been less than three times the national annual GDP per capita (\$1,653), the cost-effectiveness threshold promoted by WHO-CHOICE. It needs to be noted that the cost-effectiveness threshold recommendations by WHO-CHOICE are based on cost per DALY averted, and cannot simply be adapted for nonstandardized effect measures, such as cost per TB case detected.

A mathematical modeling study estimated the cost-effectiveness of discrete ACF campaigns lasting 2 years and of programmatic changes incorporating ACF into routine TB-control activities in the long term (study period 10 years) in India, the People’s Republic of China, and South Africa.<sup>57</sup> Discrete campaigns were all highly cost-effective (cost per DALY averted less than per capita GDP); prolonged integration of ACF was even more cost-effective. A study from Nepal evaluated the cost of ACF in the community using an outreach TB-diagnostic service (microscopy camps lasting 2–4 days) with precamp publicity.<sup>59</sup> The cost was US\$37.50 per smear-positive diagnosed TB case, which was prohibitively expensive for the national health program when the entire ministry of

health expenditure on health for the people of Nepal per annum was only ~\$1.30 per person per year during the study period. The additional estimated cost for an international nongovernmental organization to run 15 camps a year, however, was only an estimated 0.35% of the overall running costs.

## Targeted screening of high-risk groups

Three studies from Cambodia, Uganda, and Canada found that ACF among contacts of patients with contagious TB was cost-effective or even highly cost-effective.<sup>56,60,61</sup> The ICER in the studies from Uganda and Canada was expressed as cost/savings for each additional case of active TB detected and each additional case of active TB treated, respectively. The ICER in the Cambodian study was expressed as cost per DALY averted (US\$330) and cost per death averted (\$5,300), and was consistent with high cost-effectiveness (cost/DALY averted well below the GDP per capita). The Cambodian study used data from a large ACF program initiated in 2012 targeting household and symptomatic neighborhood contacts of known TB cases, covering more than a third of the population.

Two studies evaluated the cost-effectiveness of ACF among people with HIV infection in Africa.<sup>62,63</sup> A CEA by Zwerling et al was based on data from a cluster-randomized trial of point-of-care screening for TB among people receiving a new HIV diagnosis in rural Malawi.<sup>62</sup> It evaluated TB screening in all patients diagnosed with HIV and at least one TB symptom with Xpert MTB/RIF or light-emitting diode microscopy versus standard care (screening performed at the discretion of the treating physician with standard smear microscopy). Based on low patient volume, the ICER was US\$1,808/DALY averted for light-emitting diode microscopy and US\$699/DALY averted for Xpert MTB/RIF. Using a cost-effectiveness threshold of three times the GDP per capita for Malawi (\$1,080), the ICER was higher than the cost-effectiveness threshold; however, screening for TB with Xpert MTB/RIF would have been cost-effective in most other sub-Saharan low-income countries. A South African study found that screening all HIV-infected individuals initiating antiretroviral therapy with two Xpert MTB/RIF tests was highly cost-effective.<sup>63</sup> Both African studies found that the prevalence of active TB was a key driver of cost-effectiveness when considering TB screening for people with newly diagnosed HIV, with the study in Malawi additionally identifying test volume as a key driver of cost-effectiveness.

A Canadian study found that TB screening and surveillance in immigrants was not very cost-effective, with an ICER of CA\$20,328 per case of prevalent active TB treated

for the screening program and an ICER of \$24,225 per case of prevalent active TB treated for the surveillance program (both compared to PCF).<sup>61</sup> The study authors explained the lack of cost-effectiveness mainly with operational problems of the screening/surveillance program. Another study pointed out that premigration screening can save the destination country significant amounts of money if screening overseas is performed at the expense of the visa applicants.<sup>64</sup>

The value of screening patients attending medical services for active TB was assessed in two studies, but neither calculated an ICER.<sup>65,66</sup> A study conducted in the US from 1969 to 1971 found that chest X-ray screening of patients attending outpatient clinics in a US hospital was not cost-effective. A South African study evaluated the cost of screening HIV-negative adults with symptoms suggestive of TB and all adults with HIV infection or diabetes regardless of symptoms who attended a mobile HIV-testing service.<sup>66</sup> The cost of US\$2,458 per case treated successfully was threefold higher than the cost per case treated under PCF in this study, suggesting that ACF may not be cost-effective.

A study using a dynamic transmission model for TB and MDR-TB found that annual screening with Xpert MTB/RIF of prisoners in the former Soviet Union most effectively reduced TB and MDR-TB and was cost-effective.<sup>67</sup> The current strategy of annual MMR was both more effective and less expensive than strategies using self-referral or symptom screening alone. Another study found that miniature chest X-ray screening of jail inmates in the US was more cost-effective than TST and symptom screening, but the cost-effectiveness of miniature chest X-ray screening compared to no screening was not assessed.<sup>68</sup>

A Japanese study found that chest X-ray screening for active TB among the elderly (65-year-old bacillus Calmette–Guérin-vaccinated persons) was not cost-effective (ICER of US\$729,905.25 per QALY compared to no screening).<sup>70</sup> Another Japanese study found that chest X-ray screening among immunocompetent 40-year-old employees was not cost-effective (ICER of US\$9,512,000 per QALY compared to no screening).<sup>71</sup>

## Conclusion

There are a number of relatively recent CEAs that have focused on screening and diagnostic tests for LTBI, but there are few studies that have evaluated the cost-effectiveness of screening for active TB. CEAs of community-wide ACF suggest that this intervention can be cost-effective or even highly cost-effective in settings with a high incidence of TB. ACF among (close) TB contacts was found to be

(highly) cost-effective in settings with a low as well as a high incidence of TB. The evidence for cost-effectiveness of screening among HIV-infected persons is not as strong as for TB contacts, but the reviewed studies suggest that the intervention can be (highly) cost-effective depending on the background prevalence of TB and test volume. Screening of prisoners and jail inmates was cost-effective in studies from the US and the former Soviet Union. Screening and surveillance programs for TB among migrants funded by destination countries with a low incidence of TB were not cost-effective.

The evidence from all analyzed CEAs is severely limited by the fact that none of the estimates for incremental effectiveness (compared to PCF) was based on randomized controlled trials. Randomized controlled trials that compare ACF with PCF in different populations are thus urgently needed to inform CEAs. New TB-diagnostic tests impact on the cost-effectiveness of screening, and integrating these tools into trials on ACF strategies is essential. As the results of randomized controlled trials evaluating different ACF strategies will become available in future, we will hopefully gain a better understanding of the role that ACF can play in achieving global TB control.

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