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The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review

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SUMMARY

BACKGROUND: Screening for tuberculosis (TB) disease aims to improve early TB case detection. The ultimate goal is to improve outcomes for people with TB and to reduce *Mycobacterium tuberculosis* transmission in the community through improved case detection, reduction in diagnostic delays and early treatment. Before screening programmes are recommended, evidence is needed of individual and/or community-level benefits.

METHODS: We conducted a systematic review of the literature to assess the evidence that screening for TB disease 1) initially increases the number of TB cases initiated on anti-tuberculosis treatment, 2) identifies cases earlier in the course of disease, 3) reduces mortality and morbidity, and 4) impacts on TB epidemiology.

RESULTS: A total of 28 798 publications were identified by the search strategy: 27 087 were excluded on initial screening and 1749 on full text review, leaving 62 publications that addressed at least one of the study questions. Screening increases the number of cases found in the short term. In many settings, more than half of the prevalent TB cases in the community remain undiagnosed. Screening tends to find cases earlier and with less severe disease, but this may be attributed to case-finding studies using more sensitive diagnostic methods than routine programmes. Treatment outcomes among people identified through screening are similar to outcomes among those identified through passive case finding. Current studies provide insufficient evidence to show that active screening for TB disease impacts on TB epidemiology.

CONCLUSION: Individual and community-level benefits from active screening for TB disease remain uncertain. So far, the benefits of earlier diagnosis on patient outcomes and transmission have not been established.

KEY WORDS: screening; impact evaluation; mortality; transmission

INVESTMENTS in tuberculosis (TB) control on a global scale have resulted in reductions in prevalence and deaths due to TB. However, TB case detection has stagnated in recent years, while estimated TB incidence is declining very slowly. This has resulted in renewed interest in the potential contribution to early case detection from systematic TB screening. TB screening in human immunodeficiency virus (HIV) infected individuals has been recommended by the World Health Organization (WHO) as part of the 'Three I's' policy initiative.[1,2] Although systematic screening of household contacts of infectious TB cases has been recommended,[3–5] population-wide mass screening has been discouraged due to its uncertain impact, high cost and poor sustainability.[6–8] There has recently been a renewed interest in systematic screening for active TB disease among risk groups as well as population-wide screening interventions.

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National TB prevalence surveys have demonstrated that a large pool of undetected prevalent cases exists even in settings with well-functioning TB programmes, and many of these prevalent cases would have been difficult to reach with passive case finding (PCF) approaches.[9–11] Several recently launched screening initiatives have shown promising results.[6,12,13]

The ultimate goal of systematic TB screening is to improve health outcomes among people with TB and reduce *Mycobacterium tuberculosis* transmission in the community through improved TB detection, reduction in diagnostic delays and early treatment.[7] The impact evaluation of TB control interventions, however, is technically difficult and expensive, and is thus rarely included in programmatic or research studies.

Before screening programmes are recommended, evidence is needed of individual or community-level benefits from early diagnosis provided by screening, and that any benefits outweigh any harms incurred. We reviewed the evidence of individual and/or community benefits from active TB screening, focusing on additional TB cases detected, reduction in diagnostic delay, improved treatment outcomes and impact on TB epidemiology.

METHODS

Definitions

We defined screening for active TB as the systematic identification of people with suspected active TB in a predetermined target group by the application of tests, examinations or other procedures. Among those with suspected TB, diagnosis needs to be established through the application of one or several diagnostic tests and clinical assessment. Screening can be done either as an outreach activity in the general community, among TB contacts and in other specific high-risk groups, or among people seeking care, including those who seek care for reasons other than symptoms compatible with TB. The latter category includes, for example, people attending for regular check-up of conditions that are risk factors for TB, such as HIV and diabetes. Passive case finding (PCF) is defined as the detection of active TB disease among symptomatic patients who self-present to medical services for the diagnosis of symptoms, with a specific focus on people with typical TB symptoms, such as chronic cough. Active case finding (ACF) implies screening through outreach activities outside health services. Enhanced case finding (ECF) primarily aims to make a population aware of TB symptoms through publicity and education, and encourages self-presentation to medical services, which may be decentralised as part of the intervention. This in effect means that ECF is PCF combined with intensified health information.[7] However, ECF can also include a screening element, for example as part of a chest/health camp, in which case the intervention is a combined ACF/ECF intervention. In this paper, we will use 'screening' to describe ACF interventions and ECF for interventions that mainly focus on health information.

Specific questions

The review addressed four specific questions:

1 Does screening for TB disease increase the number of TB cases detected compared to PCF?
2 Does screening for TB disease identify cases at an earlier stage of TB disease than PCF?
3 Is there a difference in treatment outcomes between TB cases found by screening and those found through PCF?
4 Does the addition of screening for TB disease to PCF affect TB incidence or prevalence in the community?

The questions were defined in 2011 in the scoping meeting for the development of TB screening guidelines held by the Stop TB Department.[8] A detailed study protocol and a data extraction form were developed.

Inclusion criteria

Inclusion criteria for studies addressing the four questions are outlined below.

Does screening for tuberculosis disease increase case detection?

Studies should ideally be longitudinal, with continuous or repeated rounds of screening in addition to PCF, to report the number of cases detected by screening and PCF over time. This would allow the effects of screening to be assessed beyond the first round, in which a large number of long-term undetected cases may be found. However, due to the paucity of such studies, the inclusion criteria were widened to include cross-sectional studies of one-off screening reporting the number or proportion of TB cases detected by screening and passively, and prevalence surveys reporting the proportion of undiagnosed TB.

Does screening for tuberculosis disease identify cases earlier?

All studies comparing at least one of 1) the length of time between reported onset of symptoms and start of treatment, 2) sputum positivity rate, or 3) chest X-ray (CXR) abnormalities at time of diagnosis in TB cases detected through screening and passively were eligible. Contact tracing studies were eligible if the index cases were representative of all TB cases detected passively (so that they could form the comparison group).

Does screening for tuberculosis disease affect treatment outcome?

Studies should ideally allow direct comparisons of outcomes of patients identified actively or passively in the same area. However, as there were few such

studies, we included all studies reporting on outcomes of TB cases identified actively for comparison with WHO target outcomes.

Does screening for tuberculosis disease affect tuberculosis epidemiology?

All studies comparing TB prevalence, incidence or transmission in communities receiving screening and PCF, and in communities receiving PCF only, were eligible. Studies investigating impact in specific groups (such as prisons, mines or risk groups) that did not investigate the impact on the general population were excluded. Study designs could be before-after comparisons, cluster randomised controlled trials or quasi-experimental designs.

Search strategy

The initial search used papers selected on initial screening by an existing systematic review[14] which had already identified TB case-finding studies published up to 13 October 2010. The review by Shapiro et al. searched online databases PubMed, EMBASE and SCOPUS from 1980 to 2010 to identify titles and abstracts of peer-reviewed papers that met the criteria for initial review. The detailed search strategy is outlined in Appendix Table A.1.*

Titles and abstracts identified by the search terms were entered into a database, duplicates were eliminated and the remaining entries were independently screened by two readers for inclusion in the next stage of review. Discrepancies were resolved by consensus and/or consultation with a third reader. Initial review criteria were very broad, and required only that the publication be original research (i.e., not a review, commentary or author reply letter); titles, abstracts or key words suggest that screening took place. Titles and abstracts were included for further review if a determination could not be made at this stage. Studies that screened only for TB infection and not active TB, such as the annual risk of TB infection, were excluded. Papers and abstracts in English, Spanish, French, Russian and Japanese were included; other languages were excluded. In addition to online databases, abstracts from 2008–2010 of the conferences of the International AIDS Society (AIDS/IAS), the International Union Against Tuberculosis and Lung Disease and the American Thoracic Society were searched to identify the most recent research conducted on screening strategies.

No exclusions were made on the basis of study population, geographical setting or year of publication. This review identified a total of 827 publications and abstracts: 759 were published in English, 20 in Spanish, 25 in Japanese and 23 in Russian. In addition, data from prevalence surveys provided by the WHO were added, together with further papers identified by experts in the field and unpublished data from the recently completed ZAMSTAR (Zambia South Africa TB and HIV Reduction) study. As treatment outcome data might be published separately from the initial screening results, additional searches were undertaken to identify subsequent publications reporting anti-tuberculosis treatment outcomes of all studies with at least 40 TB cases identified through screening and published after 1992 (when DOTS became widely available). Searches used Ovid Medline using the first or the last authors' names combined with 'treatment outcomes' and 'tuberculosis'. In addition, first and last authors of studies published between 2005 and 2011 were contacted directly.

Selection of publications for inclusion

The full texts of all publications identified by Shapiro et al. were screened for relevance for any of the four outcomes. This was done in stages: an initial screen to check for possible eligibility, then a more detailed screening of retained papers, followed by data extraction of eligible publications. The first 120 publications reviewed in the initial screening were done in duplicate to ensure consistency, and all data extraction of included papers was done in duplicate using a standardised data extraction tool. Any discrepancies were resolved by discussion.

Data synthesis and analysis

Settings, populations (e.g., homeless, refugees, general population) and screening approach differed considerably. Due to the heterogeneity of the studies, a narrative approach was adopted for data synthesis. A formal meta-analysis was conducted where appropriate, which was only for the treatment outcome analysis. The relative risk (RR) of successful treatment by case-finding method was calculated and pooled with the DerSimonian-Laird random-effects method, which treats studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. The I^2 statistic was calculated as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity.

Quality assessment

The vast majority of the studies included in this review are observational. Furthermore, while comparisons are often made between actively and passively found groups, details of these groups that would enable an assessment of comparability, such as baseline characteristics, are often absent.

The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) guidelines identify four key limitations that can lead to a risk of bias in observational studies:[15–17] 1) failure to develop

*The Appendix is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00004

and apply appropriate eligibility criteria, 2) flawed measurement of both exposure and outcome, 3) failure to adequately control confounding, and 4) incomplete follow-up. In the context of this review, such limitations were assessed for each of the questions being evaluated.

Thus, for question 1—the yield of TB cases identified from screening—an assessment of quality was based upon 1) the extent to which study findings can be applied to the broader population from which the study sample was drawn, and 2) the standard of diagnosis of active TB for both actively and passively found cases. Specific aspects of each study that were assessed include the sampling method, the sample size, the inclusion/exclusion criteria of participants, the level of non-participation, the method by which active TB was diagnosed and the nature of the quality control of TB diagnosis.

For question 2, which compares disease progression in groups found through screening and passively found groups, quality assessment was based upon 1) details given of prognostic factors in both groups, and 2) the standard of diagnostic measures used to assess the nature and duration of symptoms.

For question 3—assessment of TB outcomes—quality assessment was based on the methods used to ascertain outcomes. Specific measures included the method by which death was notified, efforts made to trace lost to follow-up and defaulting patients, and the methods by which TB cure was established and verified.

For question 4, in which changes in the epidemiology of TB were being assessed, studies could be randomised controlled trials, prevalence surveys or quasi-experimental designs. The quality assessment varied according to the nature of the study, but particular attention was paid to methods for assessing trends in incidence/prevalence (e.g., surveys or routine notification).

RESULTS

Identification of studies

A total of 31 915 publications and 79 abstracts were identified in the previous search. In addition, we reviewed unpublished studies and studies identified through expert opinion, prevalence surveys from Cambodia and Myanmar and conference abstracts and unpublished reports from the ZAMSTAR study, and identified 21 relevant studies; 1811 publications were identified for full-text review after removal of duplicates and screening of the titles and abstracts. Of these, 963 were excluded on an initial screen and 786 subsequently, leaving 62 publications that addressed at least one of the study questions (Appendix Figure).

Studies covered a range of different populations and used a variety of screening algorithms. Details are summarised in Appendix Table A.2. Screening included symptoms, CXR and sputum for smear microscopy and/or culture. A key distinction is whether the methods were used sequentially or together and, in particular, whether only symptomatic cases were screened further or whether the initial screen included bacteriology or X-ray even among asymptomatic cases (thus increasing the sensitivity of the screen).

Does screening for tuberculosis disease increase the number of tuberculosis cases detected?

Studies assessing the contribution of screening over time

One recent study and two historical studies were identified in which the proportion of cases identified through screening could be assessed over time. In Morocco, household contacts were screened for TB.[18] National figures were reported from 1993 to 2004, involving more than one million identified contacts. In this context, with different individuals involved in screening every year, no change in the proportion found due to removal of prevalent cases is expected. The proportion of TB in the population detected through this screening averaged 5.6% and decreased slightly over time; this decrease may be attributed to a fall in the ratio of household contacts screened to index cases over time.

In a district in Czechoslovakia, mass miniature radiography (MMR) surveys with >95% coverage were carried out every 3 years from 1960 (together with bacilli Calmette-Guérin vaccination of newborns and revaccination of adolescents), while screening was also performed during regular check-up of people with previously known CXR lesions.[19] The prevalence of smear- and/or culture-positive TB was 73/100 000 at the beginning of the study and had declined to 56/100 000 by 1972. The total number of smear- and/or culture-positive TB cases was 79 in 1966 and 52 in 1972. The proportion detected through screening declined from 0.86 (95% confidence interval [CI] 0.76–0.93) in 1966 to 0.56 (95%CI 0.41–0.70) in 1972. Over the whole period, the contribution of MMR was 102/379 cases (27%), which was similar to the contribution of other screening approaches (108/379, 28%).

In the Netherlands, MMR surveys were initiated in 1941.[20] A quarter to a third of the adult population was examined each year. In addition, individuals with fibrotic lesions, recent TB contacts and tuberculin skin test (TST) converters were regularly followed. The overall number of smear-positive TB cases declined between 1951 and 1955 (n = 2393) and 1962 and 1967 (n = 1011). The proportion of bacteriologically positive cases found through mass surveys and active surveillance was 0.35 (95%CI 0.33–0.37) at the beginning of the study and 0.47 (95%CI 0.44–0.50) in the latter years.

The studies from Czechoslovakia and the Netherlands were conducted before the DOTS strategy and

standard short-course treatment regimens became available. The screening algorithm applied to individuals with positive CXR was not described, but as cases were disaggregated by both smear and culture status, all patients were most likely investigated with both tests. The Czech study achieved very high coverage at 3-yearly screening intervals, while the Dutch study screened continuously, with lower coverage. Both studies show a reduction in smear- and/or culture-positive TB cases, but this may reflect underlying secular trends and/or the combined effect of screening and PCF. The contribution of ACF to the overall number of cases remained high in the Netherlands, but decreased substantially from very high initial levels in Czechoslovakia. Both studies used both MMR surveys and CXR screening in specific high-risk groups, notably people with CXR lesions identified in previous screenings, and the contribution by the two screening approaches was similar in both countries. Recent community-based screening programmes in high-prevalence countries have mainly relied on symptom screening, sputum smears and culture, partly due to the logistical and operational challenges of mass CXR screening.[6,21] It is difficult to assess how the results from these two historic studies compare with the current situation in high TB prevalence countries. Despite these limitations, these are the only studies evaluating mass screening activities over prolonged periods of time.

Cases identified in trials of screening

Four randomised trials were identified that investigated the effect of screening on TB case finding, all over a short time period (Table 1). They compared TB case notification rates among communities or individuals actively screened or not screened. Different interventions were used, as summarised in the Table. In Brazil, door-to-door screening increased the case yield during the intervention, but not overall during the whole period of the study, so the effect seemed to be on delay rather than on the total number diagnosed.[25] The Ethiopian studies used community health workers in different ways to increase awareness, case finding and diagnosis, and were thus ECF interventions with a screening element. One of the Ethiopian studies used pre-advertised outreach clinics,[22] whereas the other implemented a combination of increased awareness, facilitation of sputum collection and treatment support.[23] Both found higher case rates in the intervention communities. The South African study followed a cohort of infants randomised to screening or PCF, and found that screening increased case finding by 2.6 times.[24]

All of these studies were large cluster randomised trials, except for the trial in infants. All used smear-positive patients diagnosed at the local clinics as the outcome. The Ethiopian study conducted in 2003[22] did not describe the method for choosing which communities received the intervention. Few baseline comparison data are given, but the map suggests a

Table 1 Community randomised trials, comparing cases registered in the intervention and control communities*

Country, year, reference	Setting	Intervention	TB in intervention communities/infants	TB in control communities	Effect of intervention (95% CI)
Ethiopia, 2003[22]	Rural	Community promoters and outreach sputum collection for symptomatics over 1 year (12 intervention vs. 20 control communities)	All: 125/100 000 (159/127 607) Adults: 207/100 000 (153/74 012)	All: 98/100 000 (221/225 284) Adults: 158/100 000 (207/130 665)	Difference 27/100 000 (−19–72) Difference 49/100 000 (−27–123)
Ethiopia, 2006[23]	Rural	Health extension workers advised symptomatics to attend and collected sputum samples at health posts over 20 months; 30 intervention vs. 20 control communities	All: 122/100 000 (230/178 138) Adults: 194/100 000	All: 69/100 000 (88/118 673) Adults: 118/100 000	Difference 52.8/100 000 (39.8–65.4) Difference 76/100 000 (56–96)
South Africa, 2005[24]	Urban (township)	4786 infants were randomised to 3-monthly household visits or passive case finding; suspected TB disease was investigated on in-patient basis	2.2/100 py	0.8/100 py	Rate ratio 2.6 (1.8–4.0)
Brazil, 2000[25]	*Favela* in Rio de Janeiro	Door-to-door screening; 7 vs. 7 communities (paired)	(n = 11 249)	(n = 12 304)	
		During intervention (average 27 days)	934/100 000 py (n = 19)	604/100 000 py (n = 16)	Rate ratio 1.55 (1.10–1.99)
		Intervention +60 days	516/100 000 py (n = 32)	493/100 000 py (n = 41)	Rate ratio 1.05 (0.56–1.54)
		Whole period (283 days)	818/100 000 py (n = 92)	821/100 000 py (n = 101)	

*See Appendix Table A.1 for screening algorithms used; available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00004
TB = tuberculosis; CI = confidence interval; py = person-years at risk.

non-random selection and differences between intervention and control communities. As the communities were contiguous, there could be contamination. The intervention was through community promoters, encouraging presentation and sputum collection at outposts, and not house-to-house screening. The analysis took the clustering into account. There was a small increase in cases found. The other Ethiopian study described the method of randomisation, but few baseline comparison data are given.[23] The areas were contiguous. In intervention communities, health extension workers based at health posts encouraged symptomatic individuals to present and took sputum samples. Although they were called case-detection rate, the results presented appear to be prevalence and difference in prevalence, adjusted for the clustering. There was an increase in cases detected in the intervention communities. The Brazilian study used paired communities, matched by TB case notification rates, and random allocation of intervention between the pairs.[25] Intervention communities were smaller, with a higher proportion of women. The intervention communities received house-to-house visits enquiring about cough and collecting sputum if symptomatic: 71% of identified households were enrolled. The control communities received pamphlets with information on TB and encouraging attendance at health centres. The analysis took pairing and clustering into account. The results showed an increase in case finding during the short period of the intervention, but not overall.

Prevalence surveys

Prevalence surveys provide an estimate of the burden of undiagnosed TB, which could potentially be diagnosed by systematic TB screening. These surveys are summarised in Appendix Table A.3. They vary in scope from small studies in high-prevalence areas to national surveys. The prevalence of TB varied considerably between studies, but the proportion of previously undiagnosed TB was high in all, 35–85% of cases. Recent surveys have calculated the 'patient diagnostic rate' (reported cases/100 000/year divided by prevalence/100 000). Higher numbers imply a faster rate of diagnosis (less undiagnosed TB), but exactly how this relates to the proportion of cases detected depends on the duration of untreated TB.[37] Many of these studies were large, covered randomly selected representative populations and included a high proportion of eligible individuals (although this was not always stated). Screening algorithms varied (Appendix Table A.2) and would have had varying sensitivity. Case definitions also varied, and culture was only available in some settings. As shown by the study in Cambodia, the proportion of cases undiagnosed is crucially dependent on the definition used. The case definitions used for those already on treatment were not usually given. The number on treatment sometimes depended on reports by the individuals, sometimes on verification of registers and sometimes on notifications, but, as illustrated in the Ethiopian studies,[23,29] there could be considerable discrepancy between reports and registers. In all studies, the number on treatment is an underestimate of the period prevalence of diagnosed TB, as only survivors and non-hospitalised patients were included.

Contribution of screening to total number of tuberculosis cases diagnosed

In addition to the longitudinal studies cited above, a total of 14 studies provided data on the contribution of screening to the total TB cases diagnosed (Appendix Table A.4). These included studies of home visits to higher-risk members of the community, outreach screening combined with information activities in the community, contact screening or clinic screening. Community-based studies that covered a high proportion of the total community found a substantial proportion of the total cases. In contrast, studies targeting specific groups contributed relatively few cases. Notably, none of the studies of contacts, even those from low-prevalence areas, contributed >9% of the total cases identified. Screening algorithms varied widely, and the TB case definitions used to estimate the total number of TB cases diagnosed in the region were not clear. It was thus difficult to draw firm conclusions.

As the studies included here addressed different issues, an overall assessment of quality is not really appropriate. Some of the issues discussed above apply: the screening algorithms varied, the definitions used for the estimate of prevalence in the region were not clear. Contact tracing studies were most comparable, although the settings and background incidence of TB varied considerably; therefore, the proportion of total TB in the area that occurs in contacts is not expected to be consistent, whether or not ACF is used.

Does screening for tuberculosis disease identify cases earlier?

Several studies compared delay to treatment or extent of disease at presentation between those identified through screening and PCF (Table 2). All studies found that those who were identified through screening were more likely to be at an earlier stage of disease: they were less likely to be smear-positive, had a lower degree of smear positivity and were less likely to have severe CXR changes such as cavitation. There was less direct evidence of a difference in duration of symptoms, but there was a marked shortening of delay in the only large study to measure it.[44] In addition, in the case-finding intervention trial in Ethiopia,[22] patients from communities with the intervention had shorter delays than those in comparison communities. In the Brazilian trial, at the community level there was little difference in the delay, with the door-to-door intervention group having a mean delay of 57 days (95%CI 33–82) compared to the pamphlet group,

Table 2 Symptom duration, smear status and cavitation in screened and passively found cases*

Country, year, reference	Total cases: Active *n*	Total cases: Passive *n*	Delay from onset of symptoms to start of treatment: Active	Delay from onset of symptoms to start of treatment: Passive	Smear-positive cases among pulmonary cases: Active %	Smear-positive cases among pulmonary cases: Passive %	Smear-positive grade: Active %	Smear-positive grade: Passive %	CXR indicates severe disease: Active %	CXR indicates severe disease: Passive %	Comments
Africa											
Ethiopia, 2003[26]	13	24	54% had symptoms for >90 days	58% had symptoms for >90 days	—	—	—	—	—	—	No information on diagnostic algorithm for passively found cases
South Africa, 2002[52]	27	473	—	—	67	94	17 scanty 28 1+ 22 2+ 33 3+	4 scanty 26 1+ 18 2+ 52 3+	—	—	Passively found cases from 2–3 years later. Passive cases more symptomatic, e.g., weight loss in 92% vs. 44% in active cases. Culture not routinely performed for passively found cases. Smear grade *P* trend = 0.03 No information on diagnostic algorithm for passively found cases
Americas											
Brazil, 2005[25]	9	64	Median time = 56 days (range 28–336)	Median time = 53 days (range 7–336)	—	—	—	—	—	—	Diagnostic algorithm was probably the same in actively and passively found cases
Canada, 1960[20]	90	425	—	—	52	62	—	—	—	—	No information on diagnostic algorithm for passively found cases
Canada, 1967[20]	140	403	—	—	45	70	—	—	—	—	No information on diagnostic algorithm for passively found cases
USA, 2001[53]	39	61	—	—	26	59	—	—	3	21	Screening in arriving immigrants/refugees compared to passive cases in immigrants arrived in last year, $P < 0.01$. Diagnostic algorithm unclear for both actively and passively found cases
Asia											
Cambodia, 2009[54]	405	602	—	—	29	60	9 scanty 48 1+ 26 2+ 17 3+	2 scanty 40 1+ 39 2+ 19 3+	—	—	$P < 0.001$, smear-positive *P* trend = 0.009 smear grade No information on diagnostic algorithm for passively found cases
India, 1999[44]	211	508	37% with cough <3 weeks	18% with cough <3 weeks	45	65	0 scanty 59 1+ 38 2+ 3 3+	3 scanty 28 1+ 27 2+ 42 3+			$P < 0.001$ for all Diagnostic algorithm did not include routine CXR and culture in passively found cases
Taiwan, 1993[55]	284	3903	—	—	—	—	—	—	6	16	No information on diagnostic algorithm for passively found cases
Europe											
Czechoslovakia, 1965[19]	100	119	—	—	29	44	—	—	—	—	No information on diagnostic algorithm for passively found cases
Netherlands, 1951[20]	1682	2209	—	—	38	58	—	—	—	—	No information on diagnostic algorithm for passively found cases
Netherlands, 2008[56]	454	368	Median duration of symptoms: 0 weeks	Median duration of symptoms: 7.5 weeks	38	55	—	—	—	—	Passively found cases were more likely to be admitted to hospital (60%) compared to actively found cases (20%); no information on diagnostic algorithm for passively found cases
UK, 1967[57]	54	71	—	—	58	85	—	—	13	31	$P < 0.01$; no information on diagnostic algorithm for passively found cases
UK, 1968[58]	42	26	—	—	26	58	—	—	—	—	$P < 0.01$; no information on diagnostic algorithm for passively found cases
UK, 2008[59]	35	240	—	Passively found cases had 3 times the diagnostic delay of actively found cases	44	66	—	—	—	—	Adjusted odds ratio for smear positivity comparing active and passive cases was 0.36 ($P < 0.001$); no information on diagnostic algorithm for passively found cases

*Two studies of mass X-ray screening were not included in this table as all data regarding the screening algorithm following a positive CXR were unknown.[19–20] See Appendix Table A.2 for the screening algorithms used; available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00004

CXR = chest X-ray.

which had a mean delay of 53 days (95%CI 38–68).[25] However, the short-term increase in case finding during door-to-door screening, but not subsequently, suggests a reduction in delay for these cases (Table 1).

A difficulty in assessing these studies is to know what diagnostic procedures were applied to passively detected cases. Unfortunately, these data were not available for the majority of the studies (Table 2). The proportion of smear-positive cases was consistently lower among cases identified through screening and ECF than among passively found cases, but this would be expected if smear is the main method of routine diagnosis in PCF, as was the case in South Africa, where culture was not routinely used for those found passively. The degree of smear positivity (routinely graded from +++ to scanty positive) among smear-positive cases may be a better indicator: in three studies presenting these data (conducted in South Africa, Cambodia and India), the degree of smear positivity was higher in passively diagnosed cases. CXR grading was restricted to those with CXR: all three studies reporting this found less extensive disease among screened cases. However, in none of the studies were all cases bacteriologically confirmed, and less severe changes without independent confirmation of TB may have other diagnoses, particularly in actively found patients. Delay is difficult to measure, and some studies were small, but most results were consistent with a reduction in delay.

Overall, only three studies, in India, Taiwan and Cambodia, included large numbers of cases identified through screening. Therefore, although the evidence was largely consistent that screening reduces delay and leads to diagnosis of cases at an earlier stage of disease, inherent biases, such as the use of more sensitive and sometimes less specific diagnostic techniques in screening compared to the routine programme, would tend to give the same result. The strongest evidence comes from a comparison of the degree of smear positivity, which was lower in actively found cases.

Does screening for tuberculosis disease affect treatment outcomes?

Unpublished data from two further studies were included. As well as looking at the outcome for those who started treatment, we recorded the proportion of patients who were identified but who did not register for treatment due to default, death or loss to follow-up ('initial defaulters').

Table 3 summarises the results from studies reporting on outcomes in TB cases identified through screening (restricted to those that presented results for >10 patients). Initial default was not always reported, but was as high as a quarter of cases identified through screening in the South African and Indian studies. Given the range of time periods, settings, treatment regimens, drug resistance and patients, absolute values of treatment outcome are difficult to compare between studies, but many achieved >80% successful outcomes, and the Cambodian studies >90%.

Six studies (2 in Nepal, 1 in Cambodia, 1 in India, 1 in South Africa and 1 in the Netherlands) presented comparable data on cases found through screening and passively. In all six, the outcomes for cases found through screening and PCF within each study were very similar, and this was seen in the meta-analysis: RR 1.01 (95%CI 0.99–1.04), with low heterogeneity (I^2 = 0%; Figure). In India, subsequent studies reported initial default rates for actively and passively found cases.[68,69] Initial default was higher in cases identified through screening (29% in 1999–2001 and 24% in 2001–2002) than in passively found cases (respectively 14% and 15%). There were no deaths among the 57 actively found initial defaulters and 23 (19%) deaths among passively found initial defaulters.[68] The reasons given by the 57 patients identified through screening for initial default included unwillingness to start treatment, symptoms too mild to warrant treatment, too sick, and work-related problems.[68] For all the other settings, initial default rates in passively found cases were not reported, but these can be high, and such patients have poor outcomes.[70–75]

There were many differences between the cases found through screening and passively (Tables 2 and 3), including a tendency for cases identified through screening to have less severe disease (which would tend to give lower mortality but possibly higher default rates) and to be older (which would tend to give worse outcomes). There were large differences between the six studies in the proportions with successful outcomes, but internal comparisons were consistent: treatment success was comparable in TB cases found through PCF and screening.

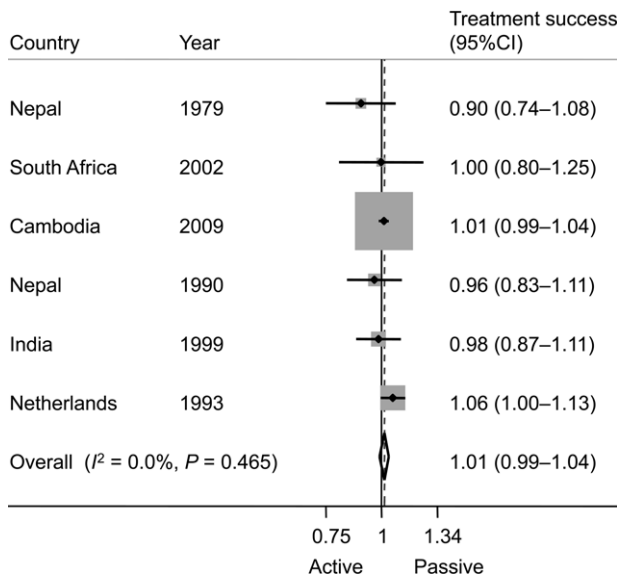

Figure Meta-analysis: risk ratio comparing successful treatment in cases found through screening with passively found cases. CI = confidence interval.

Table 3 Treatment outcomes of cases detected through screening and passively detected cases*

Country, year, reference	Type of TB	Actively found *n*	Initial defaulter	Started treatment		Treatment successful		Died		Defaulted, transferred, failed, missing		Comments
			Active *n* (%)	Active *n* (%)	Passive *n* (%)	Active *n* (%)	Passive *n* (%)	Active *n* (%)	Passive *n* (%)	Active *n* (%)	Passive *n* (%)	
Africa Region												
Botswana, 2004[60]	Pulmonary	43	—	43	—	35 (81)	—	5 (12)	—	3 (7)	—	All HIV+
Ivory Coast, 1990[61]	All	108	—	108	—	80 (74)	—	28 (26)	—	—	—	Prisoners, 30% HIV+
Malawi, 1999[62]	Smear+	318	22 (7)	296	—	181 (61)	—	36 (12)	—	79 (27)	—	Prisoners
South Africa, 2002[52]	Smear or culture+	27	7 (26)	20	473	16 (80)	380 (80)		—	—		Initial defaulter defined as not starting treatment within 2 months of diagnosis
South Africa, 2009[13]	Smear or culture+	56	14 (25)	42	—	34 (81)	—	2 (5)	—	—	—	Mobile HIV testing service, 54% HIV+
Zimbabwe, 2005[36]	Pulmonary	91	4†	80	—	58 (73)	—	9 (11)	—	13 (16)	—	Unpublished results
Zimbabwe, 2005[6]	Smear+	249	15 (6)	234	—	175 (75)	—	26 (11)	—	33 (14)	—	Unpublished results
South-East Asia Region												
India, 1999[44]	Pulmonary	211	58 (27)	153	508	107 (70)	361 (71)	5 (3)	36 (7)	41 (27)	111 (22)	ACF older, more men, poorer backgrounds
Nepal, 1979[63]	Smear+	111	11 (10)	100	159	62 (62)‡	110 (69)	9 (9)	17 (11)	29 (29)	32 (20)	Treatment: 2 months SM, 12–18 months of INH and Th1
Nepal, 1990[45]	New smear+	68	—	68	1306	50 (74)	997 (76)	5 (7)	104 (8)	13 (19)	205 (16)	—
Western Pacific Region												
Cambodia, 2002[64]	Smear or culture+	271	27 (10)	244	—	232 (95)	—	—	—		—	—
Cambodia, 2009[54]	Pulmonary	405	21 (5)	384	602	370 (96)	573 (95)	3 (0.8)	11 (2)	8 (2)	10 (2)	Screening cases older and higher proportion smear-negative
Japan, 2002[65]	Pulmonary	17	—	17	—	12 (71)	—	—	—	5 (29)	—	From homeless shelters
Philippines, 1985[66]	Smear or culture+	158	14 (9)	144	—	91 (63)	—	5 (3)	—	48 (33)	—	Regimen: 1 month HRZE, 7 months HEZ (twice weekly). 82% resistant to at least one drug
Viet Nam, 1992[67]	Smear+	322	—	322	—	265 (82)	—	3 (1)	—	54 (17)	—	34% previously treated
European Region												
Netherlands, 1993[56]	Pulmonary	454	—	454	368	386 (85)	293 (79)	1 (0.2)	12 (3)	69 (15)	63 (17)	Immigrants
Netherlands, 2002[51]	Pulmonary	28	—	28	—	25 (89)	—	—	—	—	—	Homeless and drug users Outcome of other 3 not given

*See Appendix Table A.2 for screening algorithms used; available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00004

[1]Seven started treatment elsewhere, outcomes unknown.

† Outcomes were reported including those who did not start treatment. We assumed they were not among the 62 with 'sputum conversion recorded'.

TB = tuberculosis; HIV = human immunodeficiency virus; + = positive; ACF = active case finding; SM = streptomycin; INH, H = isoniazid; Th1 = thiacetazone; R = rifampicin; Z = pyrazinamide; E = ethambutol.

Length-time bias (through which slowly progressing and less severe cases with potentially higher chance of treatment success are more likely to be detected through screening than PCF) is likely in all studies comparing outcomes between screened vs. not-screened individuals. Controlled trials with comparison of treatment outcomes between the arms are required for firm conclusions. Only two such trials were identified. In the community randomised trial in Ethiopia, the proportion successfully treated was similar in the intervention communities (81%, 128/159) and comparison communities (75%, 165/221), with 3% deaths in each.[22] The South African trial in infants did not find any difference in mortality between infants undergoing ACF and PCF despite an increase in case detection, but overall mortality was low (<3%).[24] These studies are not included in the table or in the meta-analysis, as they used a trial design, but the findings are consistent with studies for which a meta-analysis was performed.

Only one study showed a difference in mortality among TB cases identified through screening compared to TB cases identified through PCF.[76] In this study, among South African miners with high HIV prevalence and before the availability of antiretroviral therapy, all were screened by CXR annually. TB-specific mortality was 15.1 (95%CI 2.1–655) times higher in HIV-negative and 2.6 (0.7–14.9) times higher in HIV-positive TB cases identified through PCF between screens compared to those identified through screening. Length-time bias and residual confounding might explain part of the result.

Does screening for tuberculosis disease affect tuberculosis epidemiology in the community?

Five studies provide evidence for the effect of TB screening on the overall epidemiology of TB in the general population over several years (Table 4). As the interventions, assessment and settings all vary, these are discussed individually.

The community-randomised trial in Zimbabwe (DETECTB) used two different case-finding interventions (mobile vans or door-to-door), with the intervention contributing 37% of all smear-positive cases notified during the intervention period (unpublished data).[6] There was no control group without an intervention, so for the purposes of this question the comparison of interest is the TB prevalence in the communities before and after the intervention, as assessed by prevalence surveys. This showed a 41% reduction over 3 years, after adjusting for differences between the two surveys in HIV prevalence and demography. The reduction was similar in areas covered by the different interventions, although the cumulative yield of cases during the intervention was higher in the mobile van group. The population of the area increased by 10% over the study period, and Zimbabwe experienced a

Table 4 Studies that measured the general population impact of case-finding interventions*

Country, year, reference	Setting	Intervention	Time to assess impact, years	Outcome in control arm	Outcome in intervention arm	Comparison
Cambodia, 2002[64]	2-year follow-up of individuals screened in the national prevalence survey	Household screening with chest X-ray and symptom screen followed by sputum investigations in randomly selected clusters	2	Expected TB notification	Actual TB notification	Standardised TB notification ratio: 0.38 (95%CI 0.27–0.52)
Brazil, 2005[77]	8 urban communities Rio de Janeiro	CRT intensive screening + IPT in household contacts	5	Incidence increased 5% to 358/100 000	Incidence decreased 10% to 305/100 000	$P = 0.04$
Zimbabwe, 2005[6]	High-density suburbs, Harare	CRT mobile van or door-to-door vs. baseline pre-intervention	3	Baseline prevalence: 6.5/1000 (5.1–8.3) ($n = 66$)	Prevalence post-intervention: 3.7/1000 (2.6–5.0) ($n = 41$)	aRR: 0.59 (95%CI 0.40–0.89) $P = 0.01$
Zambia, 2006[21]	Communities in South Africa and Zambia	Factorial CRT 1 ECF vs. no ECF 2 Household intervention vs. no household intervention	3 3	TB prevalence: 711/100 000 Infection incidence: 1.05% TB prevalence: 883/100 000 Infection incidence: 1.71%	TB prevalence: 927/100 000 Infection incidence: 1.41% TB prevalence: 746/100 000 Infection incidence: 0.87%	aRR TB: 1.11 (95%CI 0.87–1.42) aRR infection: 1.36 (95%CI 0.59–3.14) aRR TB: 0.78 (95%CI 0.61–1.00) aRR infection: 0.45 (95%CI 0.20–1.05)
USA, 1985[78]	Oregon, Burnside area	Mandatory screening, prophylaxis and treatment for those wanting to use homeless shelters vs. baseline	10	Annual notifications in area in 1985 227/100000 ($n = 39$)	Annual notifications in area in 1995 29/100000 ($n = 5$)	Decline over the 10-year period in this district much greater than decline in other districts or state-wide

* See Appendix Table A.2 for screening algorithms used; available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000004/art00004
TB = tuberculosis; CI = confidence interval; CRT = community randomised trial; IPT = isoniazid preventive therapy; aRR = adjusted risk ratio; ECF = enhanced case finding.

period of political unrest, factors that may have influenced TB prevalence

The ZAMSTAR study, conducted in communities in Zambia and South Africa, was a 2 × 2 factorial trial comparing ECF, a household intervention, both or neither.[21] The ECF sites received community mobilisation and easy access to sputum collection points either at clinics or mobile outreach activities, aiming to return results within 48 h. In the household intervention sites, households of TB patients were visited three times for education and screening for TB and HIV, and HIV-positive household members without active TB were offered isoniazid (INH) preventive therapy. The household intervention only directly saw 6% of individuals in the community. Outcomes assessed were TB prevalence from surveys, and *M. tuberculosis* infection incidence, assessed from tuberculin conversion in children. As shown in Table 4, the household intervention, but not ECF, was associated with a reduction in TB prevalence. From the preliminary results (Table 4), it seems that only 13% of patients in ECF communities were found directly through the ECF. The ZAMSTAR study has yet to be published. There were 24 communities with very varied characteristics in two countries. Restricted randomisation was used to improve balance between the trial arms.[79] With only preliminary results available, full assessment is not possible.

A follow-up study was conducted in Cambodia 2 years after a TB prevalence survey, to capture incident TB cases in community clusters screened for TB as part of the national survey.[64] The standardised TB notification ratio was 0.38 (95%CI 0.27–0.52) in communities included in the national TB prevalence survey, showing a two thirds reduction in notification in the study areas. Cases identified during the national TB prevalence survey were not included in the calculation of the standardised TB notification ratio. It is thus not clear if screening really reduced the total number of TB notifications or whether it simply diagnosed these cases earlier. The method used to identify all individuals treated for TB who participated in the survey is not described. It is likely that some survey participants were not identified in the TB register, resulting in an underestimation of TB notification among survey participants.

In Brazil, four matched pairs of communities were randomised: intervention communities received intensive household screening of contacts, including TST and INH prophylaxis.[25] Control communities received the standard DOTS package. Although this theoretically included referral of contacts for investigation, this was thought to be rare in practice, and no data on contact tracing were available. Outcomes were assessed from registration data, with the denominator from the national census. Overall, TB notifications decreased by 10% in the intervention communities and increased by 5% in the control communities, but long-term trends in TB incidence are not presented. The pairing of the communities is not clear. Assuming they were paired in the order shown in the table, then communities of very unequal size were paired. It is not clear if the analysis took full account of the pairing of communities and the sizes of communities.

A study in the United States evaluated a programme of mandatory screening and mandatory prophylaxis and treatment as indicated for those wanting to use homeless shelters.[78] Trends in TB in the whole district fell by almost 90% over 10 years. Statewide TB incidence or incidence in other areas shown were much lower, but showed no such fall. The study did not assess the effect of screening alone, and the population of the district was noted to have changed over the period due to gentrification, which may have accounted for some of the fall.

DISCUSSION

This review assessed four potential beneficial effects of screening for TB disease. The increase in TB cases and earlier diagnosis through screening could be considered intermediate outcomes. Reduction in morbidity, mortality and transmission through earlier detection and detection of cases who would otherwise remain undiagnosed are the ultimate outcomes of interest when assessing individual and community-level benefits. Despite extensive implementation of systematic TB screening during the last century, very few studies have primarily addressed mortality or transmission, and only one (ZAMSTAR) has had a cluster-randomised design that directly evaluated impact on TB epidemiology. The available evidence base is thus weak and shows little evidence of benefit of systematic TB screening for individuals and communities.

There is moderate evidence to suggest that screening increases the number of cases found in the short term. The extent depends on the setting and the methods used. In many settings, more than half the prevalent TB cases in the community are undiagnosed. Targeting of some high-risk groups, or a combination of risk groups, can contribute a high proportion of cases, but targeting contacts did not contribute more than 9% of cases. It is possible that part of the impact on case detection is due to the detection of additional false-positive TB diagnoses. The proportion of false-positive cases out of all cases detected is inversely correlated with TB prevalence, and target groups for screening typically have much lower TB prevalence than people tested through PCF. A high proportion of false-positives is particularly likely when the specificity of the final diagnostic test is suboptimal. The specificity of sputum smear microscopy ranges between 93% and 100%.[80–82]

There is moderate evidence to suggest that screening tended to find cases earlier and with less severe

disease. This may partly be attributed to screening studies using more sensitive diagnostic methods than routine programmes, rather than screening per se. A recent study conducted in miners in South Africa compared 6-monthly vs. 12-monthly CXR screening (not included in this review, as it did not have a 'no screening intervention' arm). TB cases detected in the 6-monthly screening arm had less extensive disease and a lower TB-specific mortality compared to TB cases detected in the 12-monthly screening arm.[83] However, South African mines are a special setting, with high prevalence of both HIV and silicosis and a high risk of rapid progression to TB disease, as well as a background of ACF programmes with yearly CXR screening. It is therefore difficult to extrapolate these findings to other settings.

Treatment outcomes for those identified through screening or passively were very similar in all studies. This is surprising, as patient characteristics were different and length-time bias is likely in all studies, but the results were consistent in varied settings with different proportions of successful treatment. However, only two studies reported initial default rates in actively and passively found cases.[68,69] It is well documented that a high proportion of passively found cases die before initiating anti-tuberculosis treatment.[68,74,75] 'On treatment' mortality in passively found cases might thus underestimate overall mortality due to survival bias. The reasons for initial default in cases identified through screening might be different: they are less symptomatic and less likely to use health care.[13,44] The overall mortality in cases diagnosed through screening might therefore be lower than in cases diagnosed through PCF, but only one study identified in this review provided data on overall mortality in adults. The South African trial in infants[24] and the community randomised trial in Ethiopia[22] both showed similar outcomes in intervention and control arms.

The evidence that screening in addition to PCF impacts on TB epidemiology remains weak, but with an insufficient body of evidence to allow firm conclusions to be drawn about absence of effect. The ZAMSTAR study provides the most thorough assessment, in challenging circumstances of high HIV prevalence. The study evaluated two different interventions (respectively TB household visits and community-wide ECF) using a factorial design, and reported a significant reduction in undiagnosed TB at community level from the household intervention but not the ECF intervention. The household intervention went beyond the usual remit of TB contact tracing, with multiple visits and a strong focus on HIV as well as TB prevention, but had direct contact with only 6% of the population. Possible explanations include that the household intervention might have had extended benefit beyond the household, through heightened awareness. ECF interventions detected only a small proportion of cases directly, and did not provide community TB screening as such, instead promoting early diagnosis through facility-based services; negative trial outcomes are therefore not necessarily generalisable to interventions using more intensive TB screening approaches. The study from Cambodia provides some evidence of reduced TB notifications among individuals who underwent intensive screening for TB, but the follow-up time in this study was short (2 years).[64] The study from Zimbabwe showed increased case-notification rates during the study period, with a 41% reduction in TB prevalence following 3 years of implementation of community-based TB case finding; however, this was based on a before-after comparison with no non-intervention group to control for secular trends.[6]

The main limitations of this review include a search strategy starting from a previously conducted review and high heterogeneity in screening algorithms, study setting and population. We supplemented the search strategy by contacting experts in the field and authors and by conducting additional, more targeted searches. We adopted a narrative approach to account for the heterogeneity of study designs and settings, and only conducted a meta-analysis to calculate pooled risk ratios for treatment outcome. Studies showing negative or no effect of screening are less likely to be published. This is especially true for studies assessing the additional yield of screening and/or comparing treatment outcomes in actively found cases, and therefore publication bias might have influenced the results.

In conclusion, the evidence of individual and community-level benefits of systematic screening is remarkably limited, given the high public health significance, long history and scale on which this approach has been implemented in the past. Large cluster randomised trials, such as the ZAMSTAR study, with long-term follow-up, would be needed to provide more evidence for such a benefit if indeed it exists, ideally including studies that evaluate a range of interventions with different screening intensities in different epidemiological settings. In the meantime, more rigorous and consistent reporting of TB notification and mortality rates over prolonged periods of time in settings where large-scale screening programmes have been implemented should be encouraged, together with the capture of the mode of detection and other variables to support TB impact assessment. Furthermore, a better understanding of the magnitude of initial defaulting within national TB programmes is needed. This could be facilitated by including initial defaulters in the routine TB notification registers.

Conflict of interest: none declared.

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APPENDIX

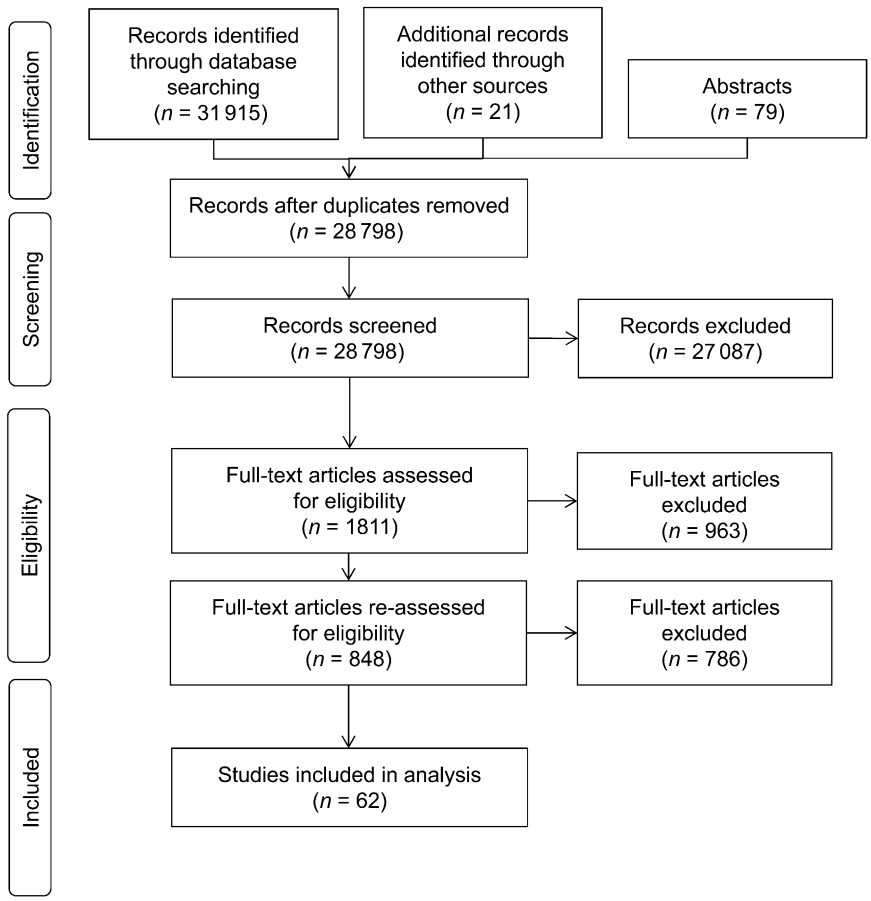

Figure A PRISMA flow chart for derivation of studies included in the analysis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table A.1 A Database search terms

Database	Terms
PubMed/ Medline	((("Mass Screening"[MeSH Terms] OR "Mass Chest X-Ray"[MeSH Terms] OR "contact tracing"[MeSH Terms] OR "health surveys"[MeSH Terms] OR "Cross-Sectional Studies"[MeSH Terms] OR "Epidemiologic Studies"[MeSH Terms]) OR ("Mass Chest X Ray" OR "Mass Chest X-Rays" OR "Mass Screenings" OR "Mass screening" OR "Screenings" OR "screening" OR "health survey" OR "Cross-Sectional Studies" OR "Case-detection" OR "case finding" OR "active case finding" OR "contact tracing" OR "intensified case-finding" OR "intensified case finding" OR "contact screening" OR "survey" OR "cross-sectional studies" OR "tuberculosis case-finding" OR "population screening" OR "prevalence studies")) AND (("tuberculosis"[MeSH Terms] OR "tuberculosis" OR "Pulmonary Consumption" OR "Consumption, Pulmonary" OR "Pulmonary Phthisis" OR "Tuberculoses") OR ("Mycobacterium tuberculosis"[MeSH terms]))) NOT ("animals"[MeSH Terms] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms]))
EMBASE	'tuberculosis'/exp OR 'lung tuberculosis'/exp OR 'lung tuberculosis' OR 'tuberculosis' OR 'pulmonary consumption' OR 'consumption, pulmonary' OR 'pulmonary phthisis' OR 'tuberculoses' AND ('tuberculosis control'/exp OR 'case finding'/exp OR 'mass radiography'/exp OR 'mass screening'/exp OR 'contact examination'/exp OR 'screening'/exp OR 'mass radiography' OR 'mass screening' OR 'contact examination' OR 'population screening' OR 'mass roentgenologic screening' OR 'mass chest X ray' OR 'mass chest X-rays' OR 'mass screenings' OR 'screenings' OR 'screening' OR 'health survey' OR 'cross-sectional studies' OR 'case-detection' OR 'case finding' OR 'active case finding' OR 'contact tracing' OR 'intensified case-finding' OR 'intensified case finding' OR 'contact screening' OR 'cross-sectional' OR 'tuberculosis case-finding' OR 'prevalence studies') NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp))
SCOPUS	((KEY(tuberculosis OR phthisis OR (pulmonary consumption))) OR (TITLE(tuberculosis OR phthisis OR (pulmonary consumption)))) AND (TITLE-ABS-KEY((("Mass Chest X Ray") OR ("Mass Chest X-Rays") OR ("Mass Screenings") OR ("Mass screening") OR (screenings) OR (screening) OR ("health survey") OR ("Cross-Sectional Studies") OR ("Case-detection") OR ("case finding") OR ("active case finding") OR ("contact tracing") OR ("intensified case-finding") OR ("intensified case finding") OR ("contact screening") OR ("prevalence survey") OR ("cross-sectional studies") OR ("population screening") OR ("prevalence study"))))

B Conference abstract search terms

Conference	Search terms
IAS/AIDS	Tuberculosis; TB Note: this search retrieved nearly 3500 fewer hits than a search that also included words attempting to limit to active case-finding.
The Union	Case-finding; contact tracing; active
ATS	Tuberculosis

IAS/AIDS = International AIDS Society/International AIDS Conference; The Union = International Union Against Tuberculosis and Lung Disease World Conference of Lung Health; ATS = American Thoracic Society International Conference.

Table A.2 Studies included in the review

Country, year, reference	Year of study	Rural or urban	Setting	How was screening performed?	Order of screening*						
					Symptom screen	Clinical	Smear	Culture	CXR	Anti-biotics†	TST
African Region											
Ethiopia, 2003[26]	2003	Rural	Community	Home visits, TB suspects identified by head of household	1 (cough for >2 weeks)	—	2 (MMS)	—	—	—	—
Ethiopia, 2003[22]	2003–2004	Rural	Community	Outreach teams (once per month), advertised by local lay health care worker	1	—	2 (MSS)	—	—	—	—
Ethiopia, 2006[23]	2006–2008	Rural	Community	Lay health care workers identified TB suspects in the community and facilitated sample transport	1 (cough for >2 weeks)	—	2 (MSS)	—	—	—	—
Ethiopia, 2008[27]	2008	Urban/rural	Community	Home visits, TB suspects identified by head of household	1 (cough for >2 weeks)	—	2 (MS)	—	—	—	—
Ethiopia, 2009[28]	2009	Rural	Community	Home visits	1 (cough for >2 weeks)	—	2 (MS)	2 (MS)	—	—	—
Ethiopia, 2010[29]	2010	Rural	Community	Home visits	1 (cough for >2 weeks)	—	2,5 (MS)	—	4	3	—
Botswana, 2004[60]	2004–2006	Urban	HIV Clinics	IPT programme	—	2	2	2	1	—	—
Guinea-Bissau, 2006[30]	2006–2007	Urban	Community	Home visits	1 (cough)	—	2	—	2	3	—
Ivory Coast, 1990[61]	1990–1992	Urban	Prison camp	—	—	1	2	—	2	—	—
Kenya, 2006[31]	2006–2007	Rural	Community	Home visits	1	—	1 (MS)	2	1	—	—
Malawi, 1999[62]	1999–2001	—	Prison	At time of entry into prison	1 (cough for >2 week)	—	2 (UUU)	—	—	—	—
South Africa, 1993[76]	1993–1997	—	Mines	Workplaces screening programme	—	—	2	2	1	—	—
South Africa, 2002[52]	2002	Urban	Community (township)	Home visits	—	—	1	1	1	—	—
South Africa, 2005[24]	2005–2008	Urban	Community (township), infants	Home visits, TB register checks to identify adult smear positive cases	1 (cough for >2 weeks)	2	2	2	2	—	2
South Africa, 2005[32]	2005	Urban	Community (township)	Home visits and referral to clinic	—	—	1 (MS)	1 (MS)	—	—	—
South Africa, 2008[84]	2008	Urban	Community (township)	Home visits and referral to clinic	—	—	1 (MS)	1 (MS)	—	—	—
South Africa, 2009[13]	2009–2011	Urban	Community (township)	Mobile HIV testing unit	1 (cough for >2 weeks) (if HIV–)	—	2: HIV– (S) 1: HIV+ (S)	2: HIV– (S) 1: HIV+ (S)	—	—	—
Uganda, 2001[34]	2001–2002	Urban	Community	Home visits and referral to clinic	1 (cough for >2 weeks)	—	2	2	2	—	—
Uganda, 2005[35]	2005	Urban	Slum	Home visits	1 (cough)	—	2 (MS)	—	—	—	—
Zambia, 2006[21]	2006–2011	Urban/rural	Communities in Zambia and South Africa	Household, clinic, sputum collection points	—	—	—	—	—	—	—
Zimbabwe, 2005[36]	2005	Urban	Community	Home visits	—	—	1 (MS)	1 (MS)	—	—	—
Zimbabwe, 2005[6]	2005–2008	Urban	Community	Home visits and mobile van	1 (cough for >2 weeks)	—	2 (MS)	—	—	—	—

(*continued*)

Table A.2 (*Continued*)

Country, year, reference	Year of study	Rural or urban	Setting	How was screening performed?	Order of screening*						
					Symptom screen	Clinical	Smear	Culture	CXR	Anti-biotics†	TST
Eastern Mediterranean Region											
Morocco, 1993[18]	1993–2004	Urban/rural	Household contacts of index cases	Active follow-up of contacts at home/by phone and referral to clinic	1	1	2 (MS)	—	1	—	—
Region of the Americas											
Brazil, 2005[25]	2005–2006	Urban	Community	Home visits	1 (cough for >3 weeks)	—	2 (MS)	—	—	—	—
Brazil, 2000[77]	2000–2004	Urban	Household contacts of index cases	Home visits	—	1	2	2	1		1
Canada, 1960[20]	1960–1969	Rural	Community, 1960–1963 > 20 years of age, 1964–1969 >30 years of age	MMR in communities where a case of active TB was discovered in the previous year	—	—	—	—	1	—	—
Canada, 1967[20]	1967–1968	Mixed	Hospital, workplace, community	CXR survey at admission to hospital, jail, industrial and community surveys	—	—	—	—	1	—	—
Cuba, 2003[41]	2003–2005	Urban/rural	Community	Home visits by family physicians performed for reasons other than TB	1 (cough for >2 weeks)	—	2	2	—	—	—
Mexico, 1995[42]	1995–1996	Rural	Households, shelters, jails, orphanages, support for alcoholics, diabetics, intravenous drug users	Health promoters identified TB suspects and referred them to clinics	1 (cough for >2 weeks)	—	2 (MSS)	—	—	—	—
USA, 1985[78]	1985–1995	Urban	Homeless, shelters, jails	—	—	—	—	—	—	—	—
USA, 1999[49]	1999	National	—	—	—	—	—	—	—	—	—
USA, 2001[53]	2001–2003	Part of immigration process	Refugees and immigrants	TB suspects identified in the country of departure and screening repeated at entry	—	1	2	2	1	—	1
South-East Asia Region											
India, 1981[43]	1981–1982	Rural	Community	Lay health care workers identified TB suspects in the community, prepared microscopy slides and facilitated transport	1	—	1	—	—	—	—
India, 1999[44, 69]	1999–2000	Rural/urban	Community	Home visits	1	—	2 (UU)	2 (UU)	1	—	—
India, 1999[68,85]	2001–2003	Rural/urban	Community	Home visits	1	—	2 (UU)	2 (UU)	1	—	—
India, 2003[50]	2003–2004	Urban	VCT centres at hospitals	—	1 (cough for >3 weeks)	2	2	—	—	—	—
Myanmar, 2009[39]	2009–2010	National	National prevalence survey	Home visits	1 (cough for >3 weeks)	—	2 (MS)	2 (MS)	1	—	—
Nepal, 1979[63]	1979–1980	Rural	Community	Home visits	1 (cough for >3 weeks)	—	2 (MMM)	—	—	—	—
Nepal, 1990[45]	1990–1993	Rural	Community	Temporary microscopy camps with pre-camp publicity	1 (cough for >3 weeks)	—	2	—	—	—	—

(*continued*)

Table A.2 (*Continued*)

Country, year, reference	Year of study	Rural or urban	Setting	How was screening performed?	Order of screening*						
					Symptom screen	Clinical	Smear	Culture	CXR	Anti-biotics†	TST
Western Pacific Region											
Cambodia, 2002[9]	2002	National	National prevalence survey	Home visits	1 (cough for >3 weeks)	—	2 (MS)	2 (MS)	1	—	—
Cambodia, 2002[64]	2002–2004	National	Follow-up of national prevalence survey	Home visits	1 (cough for >3 weeks)	—	2 (MS)	2 (MS)	1	—	—
Cambodia, 2009[54]	2009–2010	National	Household contacts and neighbours of index cases	Home visits and referral to clinic	1	—	2 (UUU)	—	2	—	—
China, 2000[37]	2000	National	National prevalence survey	—	1 (cough for >2 weeks)	—	2 (UUU)	2 (UUU)	1	—	—
Hong Kong, 2000[46]	2000	Urban	Contact of TB cases	—	—	—	—	—	—	—	—
Japan, 2002[65]	2002–2004	Urban	Tertiary hospital	—	—	—	2	2	1	—	—
Korea, 1995[86]	1995	National	National prevalence survey	Home visits	2	—	2 (SSS)	2 (SSS)	1	—	—
Papua New Guinea, 2010[40]	Unknown	Rural	Community	Home visits	1 (cough)	—	2	—	—	—	—
Philippines, 1985[66]	1985	Urban	Community	Health promoters identified TB suspects in the community and took them to a temporary clinic	1	—	2	—	—	—	—
Philippines, 1997[11]	1997	National	National prevalence survey	Home visits	—	—	2 (UUU)	2 (UUU)	1	—	—
Taiwan, 1993[55]	1993–1996	Urban	Household contacts	Home visits and referral to clinic	1	1	2	2	1	—	—
Viet Nam, 1992[67]	1992–1993	Mixed	Individuals applying for departure	Hospital	—	1	2 (MMM)	—	1	—	—
Viet Nam, 2006[10]	2006–2007	National	National prevalence survey	Home visits	1	—	2 (UUU)	2 (U)	1	—	—
European Region											
Netherlands, 1951[20]	1951–1967	National	Community	MMR screening and surveillance of risk groups (contact tracing, recent TST converters, person with fibrotic lesions)	—	—	—	—	1	—	—
Netherlands, 1993[56]	1993–1996	National	Immigrants	Obligatory entry screening	—	—	2	2	1	—	—
Netherlands, 2002[51]	2002–2005	Urban	Methadone centres, night care facilities, street prostitution zones	Mobile X-ray unit	—	—	—	—	1	—	—
Czechoslovakia, 1965[19]	1965–1972	Mixed	Community	MMR survey, surveillance of people with fibrotic lesion	—	—	2	2	1	—	—
UK, 1967[57]	1967–1975	Urban	Hostels	Mobile X-ray unit	—	—	—	—	1	—	—
UK, 1968[58]	1968–1982	Urban	Homeless and hostel dwellers	Mobile X-ray unit	—	2	3	3	1	—	—
UK, 1977[47]	1977–1981	Urban	Contacts of TB cases	—	—	—	—	—	1	—	1
UK, 1982[48]	1982–1990	Urban	Contact of TB cases	—	—	—	—	—	—	—	—
UK, 2008[59]	Unknown	Urban	Hard to reach groups (homeless, drug users, prisoners)	Mobile X-ray unit	—	—	—	—	1	—	—

*Numbers indicate the order in which investigational screening tools were used in the screening process. For example, the prison study by Aerts et al. performed symptom screening first, indicated by a '1' in the symptom column. Individuals with symptoms had a CXR and sputum smears, indicated by a '2' in these columns. All positive sputum smears were cultured, indicated by a '3'.

†Antibiotics implies that non-response to antibiotics was part of the diagnostic algorithm.

CXR = chest X-ray; TST = tuberculin skin test; TB = tuberculosis; M = morning sputum; S = spot sputum; U = unknown if morning or spot sputum; no letter in parentheses indicates that the number of sputum samples was not stated; IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; − = negative; + = positive; MMR = mass miniature radiography; VCT = voluntary counselling and testing.

Table A.3 Prevalence surveys in general populations: extent of undiagnosed TB in house-to-house surveys in the general population*

Country, year, reference	Setting	Population *n*	Proportion included %	Type of TB	Number of previously undiagnosed TB cases (diagnosed in the survey)	Number of TB cases on treatment at the time of the survey	Undiagnosed TB as a proportion of the total number of TB cases	Patient diagnostic rate (smear-positive) (95% CI)
Africa								
Ethiopia, 2003[26]	Rural	16 697, adults	Not stated	Smear-positive	13	24	0.35	—
Ethiopia, 2008[27]	Rural and urban	47 478, adults	Not stated	Smear-positive	38	15†	0.72	—
Ethiopia, 2009[28]	Rural area	29 257, adults	Not stated	Smear-positive	22	4	0.85	—
Ethiopia, 2010[29]	Rural and urban	23 590, adults	Not stated	Smear-positive,	41	22‡	0.65	—
				all pulmonary	58		0.73	
Guinea-Bissau, 2006[30]	Urban	3 714, adults	80	Pulmonary	2	2	0.50	—
Kenya, 2006[31]	Rural	30 416, adults	68	Pulmonary	117	86	0.58‡	0.93
South Africa, 2005[32]	Urban high density	971, adults	78	Pulmonary	12	11	0.52	—
South Africa, 2008[33]	Urban high density	1 383, adults	90	Pulmonary	8	12	0.40	—
Uganda, 2001[34]	Urban	1 142, all ages	Not stated	All	10	9	0.53	—
Uganda, 2005[35]	Urban	1 000, adults	88	Pulmonary	33	9	0.79	—
Zimbabwe, 2005[36]	Urban	12 426, adults	82	Pulmonary	82	74	0.53	—
Asia								
Cambodia, 2002[9]	National	23 084, age >10 years	96	Smear-positive	74		0.64§	0.63
				Smear- or culture-positive	260	42	0.86	
				All pulmonary	552		0.93	
China, 2000[37]	National							0.24
Korea, 1995[37,38]	National	~73 000, age >5 years	88	Smear or culture	106			0.43
Myanmar, 2009[39]	National	57 607 adults	89	Pulmonary	280	79	0.78‡	0.47 (0.36–0.62)§
Papua New Guinea, 2010[40]	Rural	7 211	Not stated	Smear-positive?	19	29 (estimated)	0.40	
Philippines, 1997[11,37]	National	15 905, age >10 years	81	Smear- or culture-positive	127	—	—	0.51
Viet Nam, 2006[10]	National	114 389 adults	82	Pulmonary	263	—	—	0.60 (0.49–0.78)

* See Appendix Table A.2 for the screening algorithms used.
† 33 reported being on treatment; 15 found in registers.
‡ 150 reported being on treatment; 22 found in registers.
§ Not adjusted for cluster sampling.
TB = tuberculosis; CI = confidence interval.

Table A.4 Contribution of screening to total notified cases*

Country, year, reference	Screening programme	Total number of TB cases diagnosed by screening	Total number of diagnosed TB cases through PCF in same area	Proportion of TB cases diagnosed by screening of all TB cases
Community-based				
Canada, 1960[20]	MMR and TST surveys had been carried out since 1941; from 1960 to 1963, TST− individuals aged <20 years were not surveyed, and from 1964 to 1969 TST− individuals aged <30 years were not surveyed; 18% of the total population was examined annually; the screening procedure following an abnormal CXR was not described	47 (smear-positive) 43 (culture-positive)	354 (smear-positive) 202 (culture-positive)	0.12 (smear-positive) 0.18 (culture-positive)
Canada, 1967[20]	Mass CXR surveys on community and industrial bases were performed from 1948 to 1968; from 1968, a hospital admission CXR programme was added; contact tracing and CXR screening, pre-employment and in jails, were also conducted. The screening procedure following an abnormal radiograph was not described	145 (smear-positive) 136 (culture-positive)	420 (smear-positive) 183 (culture-positive)†	0.26 (smear-positive) 0.43 (culture-positive)
Cuba, 2003[41]	Home visits to risk groups (elderly, heavy alcohol users, ex-prisoners, HIV-positive, socio-economically vulnerable)	24	19	0.56
Mexico, 1995[42]	Health promoters (each promoter serving 3000 individuals) were trained to identify individuals with cough. They sought out individuals at their houses, jails, shelters, orphanages, alcohol support groups and other risk groups. TB suspects were asked to attend the clinic to submit sputum samples	92	15	0.86
India, 1981[43]	Lay health care workers identified TB suspects in the community, prepared microscopy slides and facilitated transport to microscopy centres.	26	13	0.67
India, 1999[44]	Door-to-door in approximately one third of the population	211	508	0.25
Nepal, 1990[45]	Temporary microscopy camps were put up in remote villages (at an average walking time from the nearest health post of 4.25 h). Pre-camp publicity included theatre shows and house-to-house visits. The camps lasted for 2–4 days	71	1 175 (estimate)	0.06
Contact tracing				
Hong Kong, 2000[46]	Contacts of TB cases were screened	31	1 635	0.02
Morocco, 1993[18]	Contacts of TB cases were screened	?–20 000	?	0.048 (age ⩾10 years) 0.19 (age <10 years)
UK, 1977[47]	Contacts of pulmonary TB cases were screened	78	816	0.09
UK, 1982[48]	Contacts of TB cases were screened	50	649	0.07
USA, 1999[49]	Contacts of smear- or culture-positive cases were screened	561	9 199	0.06
High-risk settings				
India, 2003[50]	TB suspects were identified among VCT clients (both HIV-positive and HIV-negative). A total of 5 VCT centres in the district participated: 2 at medical schools, 1 at a tertiary hospital, 2 at district hospitals	83	15 835	0.01
Netherlands, 2002[51]	Drug users and homeless in Rotterdam	28	562 (estimate)	0.05

*See Appendix Table A.2 for the screening algorithms used.
†136 additional cases (67 smear-positive TB cases and 69 culture-positive TB cases) were found through routine chest X-rays.
TB = tuberculosis; PCF = passive case finding; MMR = mass miniature radiography; TST− = tuberculin skin test negative; CXR = chest X-ray; HIV = human immunodeficiency virus; VCT = voluntary counselling and testing.

RÉSUMÉ

CONTEXTE : Le dépistage de la tuberculose (TB) a pour objet d'améliorer la précocité de la détection des cas de TB. Le but ultime est d'améliorer les résultats chez les personnes atteintes de TB et de limiter la transmission de *Mycobacterium tuberculosis* dans la collectivité grâce à une amélioration de la détection des cas, à la réduction du délai de diagnostic et à la précocité du traitement. Avant de recommander des programmes de dépistage, on a besoin de preuves au sujet de leurs bénéfices à la fois au niveau individuel et au niveau de la collectivité.

MÉTHODES : Nous avons mené une revue systématique de la littérature pour évaluer les preuves que le dépistage actif de la maladie TB 1) augmente initialement le nombre de cas de TB mis sous traitement antituberculeux, 2) identifie les cas plus précocement dans le décours de la maladie, 3) réduit la mortalité et la morbidité, et 4) a un impact sur l'épidémiologie de la TB.

RÉSULTATS : Notre stratégie de recherche a permis d'identifier au total 28 798 publications. On en a éliminé 27 087 lors de la sélection initiale et 1749 lors de la revue du texte complet, avec persistance de 62 publications abordant au moins une des questions de l'étude. Le dépistage augmente le nombre de cas trouvés à court terme. Dans beaucoup de contextes, plus de la moitié des cas de TB prévalents dans la collectivité ne sont pas diagnostiqués. Le dépistage a tendance à trouver les cas plus précocement à un stade où la maladie est moins grave, mais ceci pourrait être attribué au fait que les études de dépistage des cas utilisent des méthodes de diagnostic plus sensibles que les programmes de routine. Les résultats du traitement chez les personnes identifiées grâce à un dépistage actif sont similaires aux résultats du traitement chez ceux identifiés par un dépistage passif. Les études actuelles ne donnent pas suffisamment de preuves pour démontrer qu'un dépistage actif de la maladie TB a un impact sur l'épidémiologie de la TB.

CONCLUSION : Les bénéfices à la fois aux niveaux individuel et de la collectivité provenant d'un dépistage actif de la maladie TB restent incertains. Jusqu'ici, les bénéfices d'un diagnostic plus précoce n'ont pas été démontrés tant pour les résultats pour le patient que pour la transmission dans la collectivité.

RESUMEN

MARCO DE REFERENCIA: La detección sistemática de la tuberculosis (TB) busca optimizar la detección temprana de los casos. La meta fundamental consiste en lograr desenlaces clínicos más favorables en las personas que sufren de TB y disminuir la transmisión de *Mycobacterium tuberculosis* en la comunidad, mediante la detección más eficaz de los casos, la disminución de los retrasos en el diagnóstico y el comienzo oportuno del tratamiento. Antes de recomendar programas de detección sistemática es preciso obtener datos sobre la utilidad que estos pueden ofrecer a escala individual y comunitaria.

MÉTODOS: Se llevó a cabo un análisis sistemático de las publicaciones científicas con el fin de buscar datos probatorios que indiquen que la detección sistemática de la enfermedad tuberculosa contribuye a: 1) aumentar inicialmente el número de casos de TB que comienzan el tratamiento; 2) detectar los casos en una etapa más temprana de la enfermedad; 3) disminuir la mortalidad y la morbilidad; y 4) modificar las características epidemiológicas de la TB.

RESULTADOS: La estrategia de búsqueda puso en evidencia 28 798 publicaciones. En el examen inicial se excluyeron 27 087 artículos y en el análisis del texto completo se eliminaron 1749, lo cual dejó un total de 62 publicaciones que trataban como mínimo una de las preguntas analizadas. A corto plazo, la detección sistemática aumenta el número de casos diagnosticados. En muchos entornos, más de la mitad de los casos prevalentes en la comunidad pasan desapercibidos. Con la detección sistemática se observa una tendencia a diagnosticar los casos en etapas más tempranas y con enfermedad menos grave, pero estas ventajas se pueden atribuir a los estudios de búsqueda de casos que aplican medios diagnósticos más sensibles que los utilizados en los programas corrientes. Los desenlaces terapéuticos de los casos reconocidos mediante la detección sistemática fueron equivalentes a los desenlaces de los pacientes diagnosticados mediante la búsqueda pasiva de casos. Hasta el presente, los estudios no aportan datos suficientes que permitan afirmar que una detección sistemática activa de la TB tiene repercusiones en las características epidemiológicas de la enfermedad.

CONCLUSIÓN: No se han demostrado aún las ventajas individuales ni comunitarias de la detección activa de casos de TB. Hasta el momento no se ha establecido la utilidad del diagnóstico en una etapa más temprana, con respecto al desenlace clínico del paciente ni la transmisión de la enfermedad.