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Interventions to increase tuberculosis case detection at primary healthcare or community-level services (Review)

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Interventions to increase tuberculosis case detection at primary healthcare or community-level services.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD011432.
DOI: 10.1002/14651858.CD011432.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Francis A Mhimbira[1,2,3], Luis E. Cuevas[4], Russell Dacombe[5], Abdallah Mkopi[6], David Sinclair[4]

[1]Bagamoyo Research and Training Center (BRTC), Ifakara Health Institute (IHI), Bagamoyo, Tanzania. [2]Swiss Tropical and Public Health Institute, Basel, Switzerland. [3]University of Basel, Basel, Switzerland. [4]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [5]Department of International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK. [6]Impact Evaluation, Health Systems Interventions & Policy Translation, Ifakara Health Institute (IHI), Dar es Salaam, Tanzania

Contact address: Francis A Mhimbira, Bagamoyo Research and Training Center (BRTC), Ifakara Health Institute (IHI), PO Box 74, Bagamoyo, Tanzania. fmhimbira@ihi.or.tz.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New, published in Issue 11, 2017.

Citation: Mhimbira FA, Cuevas LE, Dacombe R, Mkopi A, Sinclair D. Interventions to increase tuberculosis case detection at primary healthcare or community-level services. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD011432. DOI: 10.1002/14651858.CD011432.pub2.

ABSTRACT

Background

Pulmonary tuberculosis is usually diagnosed when symptomatic individuals seek care at healthcare facilities, and healthcare workers have a minimal role in promoting the health-seeking behaviour. However, some policy specialists believe the healthcare system could be more active in tuberculosis diagnosis to increase tuberculosis case detection.

Objectives

To evaluate the effectiveness of different strategies to increase tuberculosis case detection through improving access (geographical, financial, educational) to tuberculosis diagnosis at primary healthcare or community-level services.

Search methods

We searched the following databases for relevant studies up to 19 December 2016: the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library, Issue 12, 2016; MEDLINE; Embase; Science Citation Index Expanded, Social Sciences Citation Index; BIOSIS Previews; and Scopus. We also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and the metaRegister of Controlled Trials (mRCT) for ongoing trials.

Selection criteria

Randomized and non-randomized controlled studies comparing any intervention that aims to improve access to a tuberculosis diagnosis, with no intervention or an alternative intervention.

Data collection and analysis

Two review authors independently assessed trials for eligibility and risk of bias, and extracted data. We compared interventions using risk ratios (RR) and 95% confidence intervals (CI). We assessed the certainty of the evidence using the GRADE approach.

Main results

We included nine cluster-randomized trials, one individual randomized trial, and seven non-randomized controlled studies. Nine studies were conducted in sub-Saharan Africa (Ethiopia, Nigeria, South Africa, Zambia, and Zimbabwe), six in Asia (Bangladesh, Cambodia, India, Nepal, and Pakistan), and two in South America (Brazil and Colombia); which are all high tuberculosis prevalence areas.

Tuberculosis outreach screening, using house-to-house visits, sometimes combined with printed information about going to clinic, may increase tuberculosis case detection (RR 1.24, 95% CI 0.86 to 1.79; 4 trials, 6,458,591 participants in 297 clusters, *low-certainty evidence*); and probably increases case detection in areas with tuberculosis prevalence of 5% or more (RR 1.52, 95% CI 1.10 to 2.09; 3 trials, 155,918 participants, *moderate-certainty evidence*; prespecified stratified analysis*).* These interventions may lower the early default (prior to starting treatment) or default during treatment (RR 0.67, 95% CI 0.47 to 0.96; 3 trials, 849 participants, *low-certainty evidence*). However, this intervention may have may have little or no effect on treatment success (RR 1.07, 95% CI 1.00 to 1.15; 3 trials, 849 participants, *low-certainty evidence*), and we do not know if there is an effect on treatment failure or mortality. One study investigated long-term prevalence in the community, but with no clear effect due to imprecision and differences in care between the two groups (RR 1.14, 95% CI 0.65 to 2.00; 1 trial, 556,836 participants, *very low-certainty evidence*).

Four studies examined health promotion activities to encourage people to attend for screening, including mass media strategies and more locally organized activities. There was some increase, but this could have been related to temporal trends, with no corresponding increase in case notifications, and no evidence of an effect on long-term tuberculosis prevalence. Two studies examined the effects of two to six nurse practitioner educational sessions in tuberculosis diagnosis, with no clear effect on tuberculosis cases detected. One trial compared mobile clinics every five days with house-to-house screening every six months, and showed an increase in tuberculosis cases.

There was also insufficient evidence to determine if sustained improvements in case detection impact on long-term tuberculosis prevalence; this was evaluated in one study, which indicated little or no effect after four years of either contact tracing, extensive health promotion activities, or both (RR 1.31, 95% CI 0.75 to 2.30; 1 study, 405,788 participants in 12 clusters, *very low-certainty evidence*).

Authors' conclusions

The available evidence demonstrates that when used in appropriate settings, active case-finding approaches may result in increase in tuberculosis case detection in the short term. The effect of active case finding on treatment outcome needs to be further evaluated in sufficiently powered studies.

PLAIN LANGUAGE SUMMARY

Interventions to increase the number of tuberculosis cases being diagnosed

This review summarized trials evaluating the effects of interventions aiming to increase the diagnosis of tuberculosis and reduce the number of undiagnosed tuberculosis cases in communities. After searching for relevant trials up to 19 December 2016, we included 17 studies conducted in sub-Saharan Africa (nine studies), Asia (six studies), and South America (two studies).

Why does tuberculosis go undiagnosed and how might programmes improve this?

Tuberculosis is a chronic infectious disease that affects over 10 million people worldwide, with an estimated four million tuberculosis patients remaining undiagnosed each year. Interventions such as outreach tuberculosis screening with or without health promotion that actively screen for tuberculosis among individuals presenting with symptoms of tuberculosis, may increase detection of microbiologically confirmed tuberculosis cases. These interventions may improve treatment outcomes by increasing the number of tuberculosis patients who are cured and complete treatment. However, we do not know if these interventions reduce either tuberculosis treatment failure, or tuberculosis-associated death or long-term tuberculosis burden in moderate- and high-tuberculosis settings.

What the research says

House-to-house screening for active tuberculosis, and organizing tuberculosis diagnostic clinics nearer to where people live and work, may increase tuberculosis case detection in settings where the prevalence of undiagnosed disease is high (*low-certainty evidence*). These people may have higher levels of treatment success and lower levels of default from treatment (*low-certainty evidence*).

There was insufficient evidence to determine if health promotion activities alone increase tuberculosis case detection (*very low-certainty evidence*).

There was also insufficient evidence to determine if sustained improvements in case detection impact on long-term tuberculosis prevalence, as the only study to evaluate this found no effect after four years (*very low-certainty evidence*).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Tuberculosis outreach screening (with or without health promotion) to encourage presumptive tuberculosis patients to attend health services

Patient or population: all age groups
Settings: countries with moderate or high tuberculosis prevalence (> 10 tuberculosis cases per 100,000 population per year)
Intervention: tuberculosis outreach screening with and without health promotion activities
Comparison: no screening
Trial design: cluster-RCTs only (non-randomized studies are commented on in the footnotes)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Tuberculosis outreach screening ± health promotion				
Tuberculosis cases detected (microbiologically confirmed)	90 per 100,000	112 per 100,000 (77 to 161)	RR 1.24 (0.86 to 1.79)	163,043 participants in 297 clusters (4 studies)	low[1,2,3,4] due to imprecision and inconsistency	Screening with health promotion may increase the number of microbiologically confirmed people with tuberculosis
Default within first 2 months	16 per 100	12 per 100 (8 to 15)	RR 0.67 (0.47 to 0.96)	849 patients (3 cluster-RCTs)	low[1,2,5] due to imprecision	Screening with health promotion may reduce default prior to and at the first 2 months of tuberculosis treatment
Treatment success	78 per 100	83 per 100 (78 to 90)	RR 1.07 (1.00 to 1.15)	849 patients (3 cluster-RCTs)	low[1,6,7] due to imprecision and indirectness	Screening with health promotion may have little or no effect on treatment success

Treatment failure	1.3 per 100	2.0 per 100 (0.3 to 6.4)	RR 1.57 (0.50 to 4.92)	849 patients (3 cluster-RCTs)	very low[1,2,5,8] due to imprecision and indirectness	We do not know if screening with health promotion influences treatment failure
Tuberculosis mortality	3 per 100	3 per 100 (1.3 to 6.75)	RR 0.99 (0.43 to 2.25)	849 patients (3 cluster-RCTs)	low[1,2,3,5] due to imprecision	Screening with health promotion may have little or no effect on mortality
Long-term tuberculosis prevalence	773 per 100,000	881 per 100,000 (502 to 1546)	RR 1.14 (0.65 to 2.00)	556,836 participants in 12 clusters (1 cluster-RCT)	very low[1,2,7,8] due to imprecision and indirectness	We do not know if screening with health promotion influences treatment failure

The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]No serious risk of bias: the studies were generally at low risk of bias. Not downgraded.
[2]No serious indirectness. The studies were done in high-prevalent tuberculosis settings in Africa (3) and Asia (1). The results could be generalized to other countries with similar tuberculosis burden and socioeconomic profile.
[3]Downgraded once for serious inconsistency. One study done in South Africa showed that the intervention detected fewer tuberculosis cases compared to no intervention. This cluster-RCT had fewer participants recruited from the farmers, who may have a different risk profile compared to the general population and different from the other three cluster-RCTs. However, in a prespecified subgroup analysis by background tuberculosis endemicity in studies conducted in areas with a prevalence of 5% or more, heterogeneity was explained and the estimate became more precise (RR 1.52, 95% CI 1.10 to 2.09, 3 trials, 155,918 participants, *moderate-certainty evidence*).
[4]Downgraded once for serious imprecision. The 95% CI includes both clinically important effects and no difference for the effect of the intervention compared to control.
[5]Downgraded twice for serious imprecision. The 95% CI is wide and includes both clinically important effects and no difference for the effect of the intervention compared to control. The imprecision of the results could be due to small numbers of

tuberculosis patients and number of tuberculosis patients with the outcome of interest. The studies were not powered enough to detect a difference between groups for the tuberculosis treatment outcomes.

[6]Downgraded once for serious imprecision. The 95% CI includes no difference for the effect of the intervention compared to the control group. The imprecision of the results could be due to small numbers of tuberculosis patients and number of tuberculosis patients with the outcome of interest.

[7]Downgraded twice for serious imprecision.

[8]Downgraded once for serious indirectness. The intervention arms had additional staff and procedures for following up patients on treatment. This may have a paradoxical effect of detecting more people who have treatment failure.

BACKGROUND

Description of the condition

Tuberculosis is caused by infection with the bacterium *Mycobacterium tuberculosis.* In 2015, the World Health Organization (WHO) reported 10.4 million new cases globally, causing 1.8 million deaths (WHO 2016). Africa and Asia are most heavily affected. India, Indonesia, and China contribute over 40% of the world's tuberculosis cases, and populations in some African countries have the highest rates per capita (WHO 2016).

Pulmonary tuberculosis (infection of the lungs) is the most common form of tuberculosis, as well as the most infectious, as transmission occurs from person-to-person via inhalation of respiratory droplets expelled when coughing or sneezing (Glickman 2001). However, most people who are infected with *M. tuberculosis* initially develop latent tuberculosis, where the infection is contained by the immune system and the person remains well (Sharma 2012). Active tuberculosis, with the development of symptoms, can occur at any time and is strongly associated with immune system impairment due to illnesses such as HIV, malnutrition, and diabetes (Lönnroth 2009).

The gold-standard test for pulmonary tuberculosis is sputum culture, but as this can take up to eight weeks due to the slow growth of the bacterium, treatment is usually started based on other test results (Parsons 2011). Sputum smear microscopy and Xpert MTB/RIF (a DNA amplification test) are the most commonly used initial tests and may be combined with a chest X-ray (Steingart 2014; WHO 2009). Treatment of drug-sensitive pulmonary tuberculosis requires patients to take a combination of medicines for six to nine months (WHO 2015a), while drug-resistant forms typically require much longer courses.

Guidelines in high-burden countries advise health workers to consider pulmonary tuberculosis in all people with a cough lasting more than two weeks (WHO 2015a). However, most people diagnosed with tuberculosis have been coughing for much longer than this by the time they are tested (Corbett 2009; Hinderaker 2011). People may delay seeking care due to the stigma associated with tuberculosis, uncertainty about the severity of their illness, the distance to health services, the affordability of health services, or poor perceptions of the local quality of care (Mfinanga 2008). Similarly, health workers may delay diagnosis due to a lack of awareness or training in tuberculosis diagnosis, or the unavailability of appropriate tests (Storla 2008).

Description of the intervention

Pulmonary tuberculosis is usually diagnosed when symptomatic individuals present to healthcare services. This is termed 'passive case detection', as the health system doesn't play a role in the health-seeking behaviour of the individual. Concerns about delayed diagnosis increasing transmission, and a growing desire to tackle the global epidemic head-on have led to the promotion of more 'active' approaches to seek out early or undiagnosed tuberculosis cases amongst communities (WHO 2011).

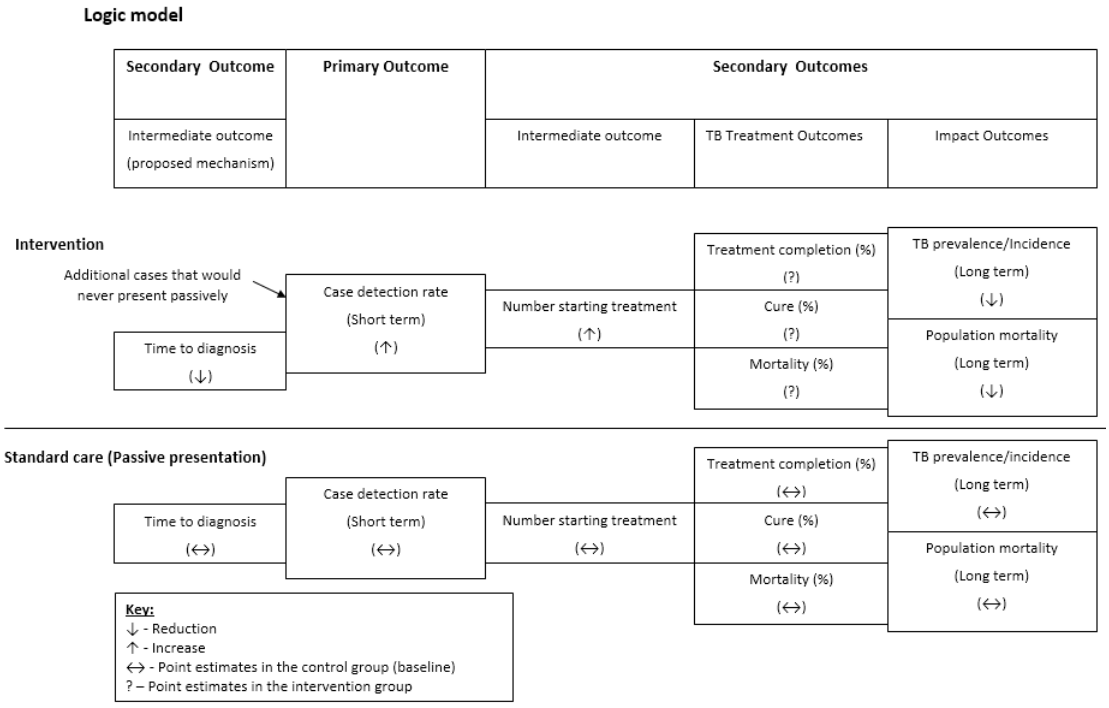
Two terms are now used commonly in the literature: 'active case-finding', which is typically interpreted as systematic screening of populations, and 'enhanced case-finding', which is harder to define but typically involves a lower degree of effort (Golub 2005). The interventions included under these terms are highly variable, and often multifaceted, containing elements that reduce multiple barriers to accessing care. For example, programmes that systematically screen households for tuberculosis will typically improve tuberculosis diagnostic skills among health workers (through training), reduce the financial costs of attending health care (by providing the initial screening test at the patient's home), as well as reduce barriers related to patient awareness of their illness and stigma related to the disease. As the barriers to accessing a tuberculosis diagnosis vary considerably between settings, successful programmes will need to both be aware of the local problems and be designed specifically to overcome them.

For the purposes of this Cochrane Review, we considered any intervention aimed at increasing confirmed tuberculosis cases by providing either improved diagnostic services or health promotion activities at primary health care or the community level.

How the intervention might work

Community-based interventions may initially increase tuberculosis case detection by: 1) identifying people with early tuberculosis who are not yet sufficiently unwell to seek care; or 2) identifying people with advanced tuberculosis who would not have presented to health services of their own accord (Figure 1).

Figure 1. Logic model showing the additional cases that would never present passively and long-term impact on lowering tuberculosis prevalence and incidence.



People who present late to health services, when the disease is severe, tend to have poorer health outcomes (Greenaway 2002). Decreasing the time to diagnosis could therefore translate into improved health outcomes for people with tuberculosis. These may be disease-related outcomes, such as cure or death, but could also be socioeconomic outcomes, such as reduced time off work or reduced loss of earnings. Although diagnosing patients early could reduce transmission, there are also concerns that diagnosing people early may lead to higher levels of default from treatment, with subsequent increased spread of resistance.

Although the aim of these interventions is to increase tuberculosis case detection in the short term, the long-term aim is a reduction in community transmission of tuberculosis, and a consequent fall in tuberculosis incidence and case detection (Golub 2005).

Why it is important to do this review

Early diagnosis is one of the key components of the WHO End TB Strategy published in 2015 (WHO 2015b). It is therefore important to know which interventions work, and under what circumstances.

OBJECTIVES

To evaluate the effectiveness of different strategies to increase tuberculosis case detection through improved access (geographical, financial, educational) to tuberculosis diagnosis at primary healthcare or community-level services.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) for which the unit of randomization is the individual or cluster, and non-randomized studies with parallel control groups.

Types of participants

People living in areas with moderate to high tuberculosis prevalence (tuberculosis notification rate of greater than 10 tuberculosis cases per 100,000 population per year).

Types of interventions

Intervention

Any intervention that aims to improve access to a tuberculosis diagnosis by providing diagnostic services at primary health care or community level. This included educational or health promotion activities, and outreach services using formal and informal health staff through clinics, mobile clinics, and house-to-house screening.

Control

No intervention (standard care) or an alternative intervention for improving access to a tuberculosis diagnosis.

Types of outcome measures

Primary outcomes

- Tuberculosis cases detected (microbiologically confirmed) refers to tuberculosis patients with a positive result of either acid-fast bacilli (AFB) sputum smear microscopy or GeneXpert MTB/RIF and/or mycobacterial culture (solid or liquid culture).

Secondary outcomes

- Tuberculosis cases starting treatment are all forms tuberculosis patients (either microbiologically confirmed or not) who are started on tuberculosis treatment as reported by individual study.
- Time to diagnosis refers to time the presumptive tuberculosis patient presents at the health facility until the tuberculosis diagnosis is made.
- False-positive results with the initial tuberculosis screening test refers to a positive test result and the individual is erroneously classified as positive for tuberculosis due to imperfect testing methods or procedures.
- Default within the first two months is classified as early default (prior to commencing tuberculosis treatment or during the intensive phase of treatment).
- Treatment completion refers to a tuberculosis patient who completed treatment without evidence of failure BUT there is no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because they were not done or because results were not available.
- Tuberculosis cured refers to pulmonary tuberculosis patient who was initially microbiologically confirmed at the beginning of treatment and who had either a negative sputum smear or culture result at the last month of treatment and on at least one previous occasion.
- Tuberculosis mortality refers to tuberculosis patients who die for any reason before starting or during the course of tuberculosis treatment.
- Population tuberculosis mortality refers to any cause of death at the population level during the active case-finding implementation.
- Programme cost refers to the cost per diagnosed case of tuberculosis.
- Long-term tuberculosis prevalence refers to the reduction in tuberculosis prevalence (either microbiologically confirmed or not) in a study population.

Search methods for identification of studies

We identified all relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

We searched the following databases: the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL, published in the Cochrane Library, Issue 12, 2016); MEDLINE (PubMed, 1966 to 19 December 2016); Embase (OVID, 1980 to 19 December 2016); Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation Index (SSCI; Web of Science, 1900 to 19 December 2016); BIOSIS Previews (Web of Science, 1926 to 19 December 2016); and Scopus (1970 to 19 December 2016), using the search terms detailed in Appendix 1. We also searched the metaRegister of Controlled Trials (mRCT), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/trialsearch), and ClinicalTrials.gov (clinicaltrials.gov/) (all accessed on 19 December 2016), using 'tuberculosis' and 'case detection' or 'case finding' or 'active screening' as search terms.

Searching other resources

We checked the reference lists of all studies identified by the above methods for other potentially relevant studies.

Data collection and analysis

Selection of studies

Two review authors (FM and AM) each independently screened all the citations and abstracts to identify potential eligible studies using a study selection form. We obtained the full reports of potentially eligible studies. FM and AM assessed these for inclusion in the review using a predesigned eligibility form based on the

inclusion criteria. Any discrepancies were resolved through discussion or, if required, by consulting a third review author (RD, DS, or LC). Where necessary we contacted the study authors for clarification of study methods. We listed the reasons for excluding studies in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (FM and AM) independently extracted data from the studies using a tailored data extraction form. Any differences in data extraction were resolved through discussion or, if necessary, by consulting a third review author (DS). We extracted the following study information.

- Study details: start and end dates, study location, study design, funding, tuberculosis prevalence (as stated by the study authors).
- Participant details: who was recruited for tuberculosis diagnostic testing? Where were they recruited? What were the eligibility criteria for a person to have a tuberculosis test?
- Details of the intervention: what was the initial screening test? What was the diagnostic test? Who conducted the screening? What training did they have? How long were they trained for? What were they trained to do? How were they supervised? Who trained them?
- Details of any co-interventions: were there any additional health promotion activities? Was tuberculosis testing free? Were there any financial/material incentives/enablers?
- Details of the control: what diagnostic services were available to the control groups? What were the local barriers to care? Distance to health services? Cost of attending health facilities?

For dichotomous outcomes (for example, additional tuberculosis cases starting treatment), we extracted the number experiencing the event (numerator) and the total number of people diagnosed with tuberculosis (denominator). For continuous outcomes, we extracted the mean, the standard deviation, and the number of people observed.

Cluster-RCTs

For cluster-RCTs, we recorded the number of clusters, the average size of the clusters, and the method used to adjust for clustering. If the trial authors adjusted for clustering appropriately, we extracted the cluster-adjusted measure of effect and a measure of variance. For dichotomous outcomes, we extracted the number of participants experiencing the event and the number randomized to each group if the authors did not adjust for clustering. For continuous outcomes, we extracted the summary effect (mean or median) and the measure of variance (standard deviation or range). We extracted the adjusted effect estimate and the standard error for studies that had adjusted for clustering.

Non-RCTs

For non-RCTs, we extracted details of any method used to control confounding, the chosen confounder variables, any reported treatment effects adjusted for one or more baseline characteristics, or any other treatment effect estimate that took confounding into account, for example the overall treatment effects estimate obtained by combining treatment effects from different strata of a study, or an estimate that allows for matching. We contacted the authors for unclear or missing data.

After data extraction, FM entered the data into Review Manager 5 (RevMan 5) (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (FM and AM) independently assessed the risk of bias of each included study using the Cochrane 'Risk of bias' tool (RevMan 2014), and discussed any differences of opinion. In the case of missing or unclear information, we contacted the trial authors for clarification. Review authors who had been involved in any of the included trials were excluded from the 'Risk of bias' assessment,

The Cochrane approach assesses risk of bias across six domains: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential biases. For each domain, we recorded the methods used by the study authors to reduce the risk of bias and assigned a judgement of 'low risk of bias', 'high risk of bias', or 'unclear'.

For cluster-RCTs, we also considered recruitment bias, baseline imbalance in the appraisal of selection bias, loss of clusters in the appraisal of attrition bias, incorrect analysis, comparability with RCTs, and further considered the risk of contamination bias (where people living in the control areas also benefit from the intervention).

Similarly, for non-RCTs we used the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) to assess the risk of bias for non-randomized trials (Sterne 2016). We considered the seven bias domains grouped into pre-intervention (bias due to confounding and selection of participants into study), at intervention (bias in classification of interventions), and post-intervention (bias due to deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results). We summarized the results for the assessment of risk of bias using the 'Risk of bias' summary and the 'Risk of bias' graph in addition to the 'Risk of bias' tables.

Measures of treatment effect

For dichotomous data, we used risk ratios as the primary measure of effect. Where study authors have presented data as odds ratios we recalculated the effect. Count data are expressed as rate ratios.

For continuous data, we compared arithmetic means using mean differences. We presented all measures with 95% confidence intervals (CIs). Medians and ranges are reported in table format only.

Unit of analysis issues

Where cluster-RCTs have not adjusted their results for the effect of the cluster design, we adjusted the sample sizes using the methods described in Section 16.3.4 or 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing an estimate of the intracluster correlation coefficient (ICC). Where possible, we derived the ICC from the trial itself, or from a similar trial. If an appropriate ICC was not available, we conducted sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.
When a multi-arm study contributed multiple comparisons to a particular meta-analysis, we either combined treatment groups or split the 'shared' group as appropriate to avoid double counting.

Dealing with missing data

We applied no imputation for missing data. We attempted to contact trial authors to obtain missing or unclear data.

Assessment of heterogeneity

We assessed for statistical heterogeneity between trials by visually inspecting the forest plots to detect overlapping CIs, and applying the Chi^2 test and I^2 statistic. We considered a Chi^2 test P value less than 0.10 as statistically significant. An I^2 statistic value of 0% to 30% might not be important; 30% to 60% may represent moderate heterogeneity; and more than 60% may indicate substantial or considerable heterogeneity.

Assessment of reporting biases

We planned to assess the likelihood of reporting bias using funnel plots, but there were too few studies.

Data synthesis

We analysed the data using RevMan 5 (RevMan 2014). The primary analysis was stratified by study design, and we did not perform meta-analysis across different trial designs.
We also stratified outcomes by the time point of outcome measurement. Where appropriate, we grouped similar time points together and performed a meta-analysis (for example, tuberculosis case detection at six to 12 months). When interpreting data at different time points, we kept in mind that the desired outcome of the intervention may change with time. For example, a successful intervention may increase tuberculosis case detection in the short term, but if it influences transmission it may result in a fall in tuberculosis case detection in the long term.
We tabulated results from cluster-RCTs that could be adjusted for clustering. We used a random-effects model in the presence of moderate statistical heterogeneity and a fixed-effect model in the absence of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We investigated potential causes of heterogeneity by performing subgroup analyses by tuberculosis prevalence.

Sensitivity analysis

We planned to perform sensitivity analyses to evaluate the robustness of the results to the risk of bias components, but there were too few studies to make this meaningful.

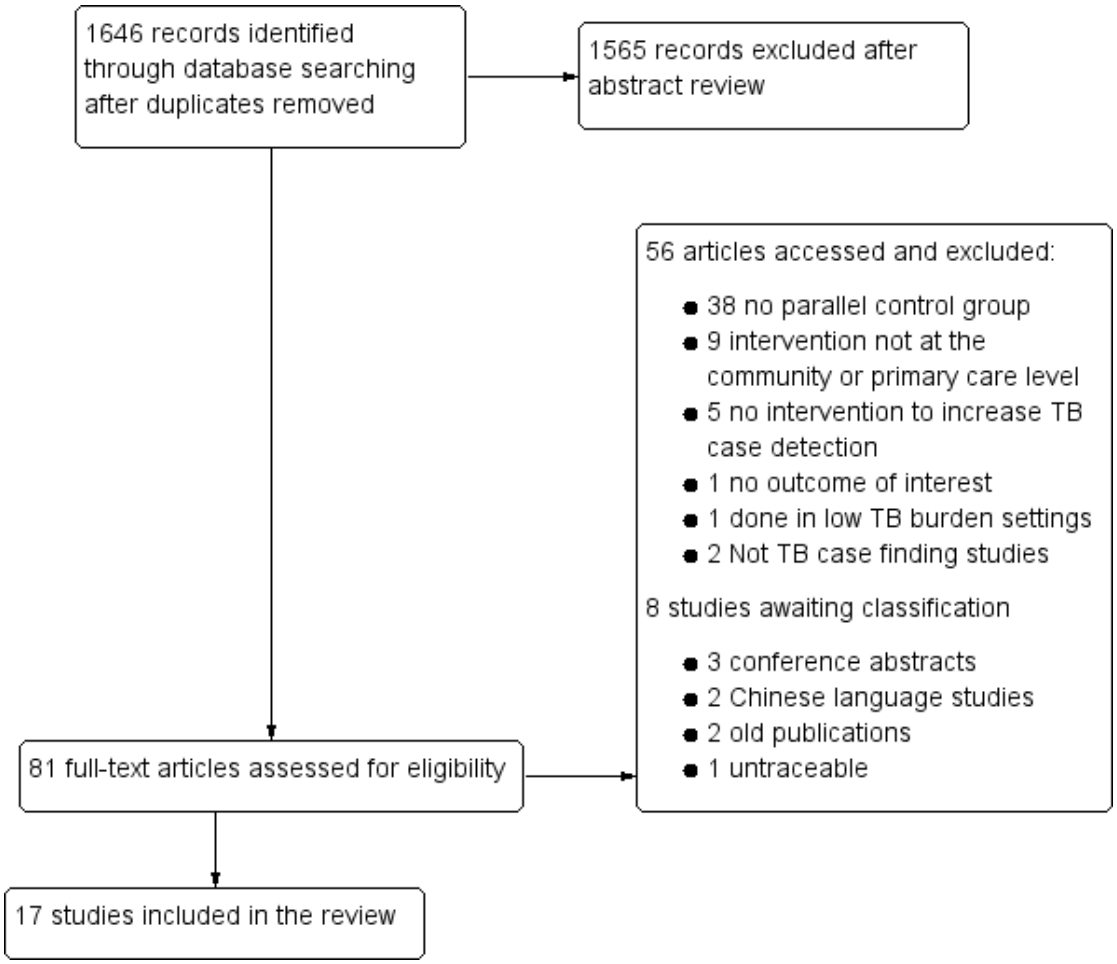
RESULTS

Description of studies

Results of the search

The study flow diagram is shown in Figure 2. The initial searches identified 1646 studies, of which 81 were deemed potentially relevant to this review after the initial abstract screening.

Figure 2. Study flow diagram.



Included studies

We included 17 studies: nine cluster-randomized trials (Ayles 2013 ZMB AND ZAF; Clarke 2005 ZAF; Corbett 2010 ZWE; Datiko 2009 ETH; Fairall 2005 ZAF; Miller 2010 BRA; Shargie 2006 ETH; Talukder 2012 BGD), one individual randomized trial (Moyo 2012 ZAF), and seven non-RCTs (Jaramillo 2001 COL; Joshi 2015 NPL; Khan 2012 PAK; Khan 2016 PAK; Oshi 2016 NGA; Reddy 2015 IND; Yassin 2013 ETH).

Nine studies were conducted in sub-Saharan Africa (Ethiopia, Nigeria, South Africa, Zambia, and Zimbabwe), six in Asia (Bangladesh, Cambodia, India, Nepal, and Pakistan), and two in South America (Brazil and Colombia).

Most of the studies evaluated interventions with multiple components. In 10 studies health workers actively looked for tuberculosis cases outside of conventional health facilities (contact tracing: Ayles 2013 ZMB AND ZAF; Joshi 2015 NPL; Oshi 2016 NGA; outreach clinics: Corbett 2010 ZWE; Joshi 2015 NPL; Shargie 2006 ETH; house-to-house screening: Clarke 2005 ZAF; Corbett 2010 ZWE; Datiko 2009 ETH; Joshi 2015 NPL; Miller 2010 BRA; Morishita 2016 KHM; Reddy 2015 IND; Yassin 2013 ETH), 13 studies included some form of health promotion activities to encourage people to attend health facilities for tuberculosis screening and testing (Ayles 2013 ZMB AND ZAF; Corbett 2010 ZWE; Datiko 2009 ETH; Jaramillo 2001 COL; Joshi 2015 NPL; Khan 2012 PAK; Miller 2010 BRA; Oshi 2016 NGA; Reddy 2015 IND; Shargie 2006 ETH; Talukder 2012 BGD; Yassin 2013 ETH), and most studies included training activities to improve the diagnostic skills available at health facilities (see Table 1).

Sixteen studies evaluated case-finding interventions compared to standard passive case finding at health facilities, while three studies provided direct head-to-head comparisons of different case-find-

ing interventions (Ayles 2013 ZMB AND ZAF; Corbett 2010 ZWE; Miller 2010 BRA).

Most studies presented the raw data for the number of tuberculosis cases detected (microbiologically confirmed) in a defined population, but only three presented an estimate of effect appropriately adjusted for the cluster design. Only one study attempted to evaluate the effects of interventions on long-term tuberculosis prevalence (Ayles 2013 ZMB AND ZAF), and this study measured prevalence at 3.5 to 4.5 years after the intervention had begun.

Thirteen studies used a symptom questionnaire as an entry point for microbiological testing. Sputum microscopy was used to diagnose tuberculosis in 17 studies. In addition, three studies conducted mycobacterial culture and chest X-ray (Ayles 2013 ZMB AND ZAF; Corbett 2010 ZWE; Fairall 2005 ZAF); one study added chest X-ray to symptoms screening to screen presumptive tuberculosis patients (Morishita 2016 KHM); two studies used a tuberculin skin test (Joshi 2015 NPL; Moyo 2012 ZAF); and two studies used GeneXpert MTB/RIF (Khan 2012 PAK; Morishita 2016 KHM).

Excluded studies

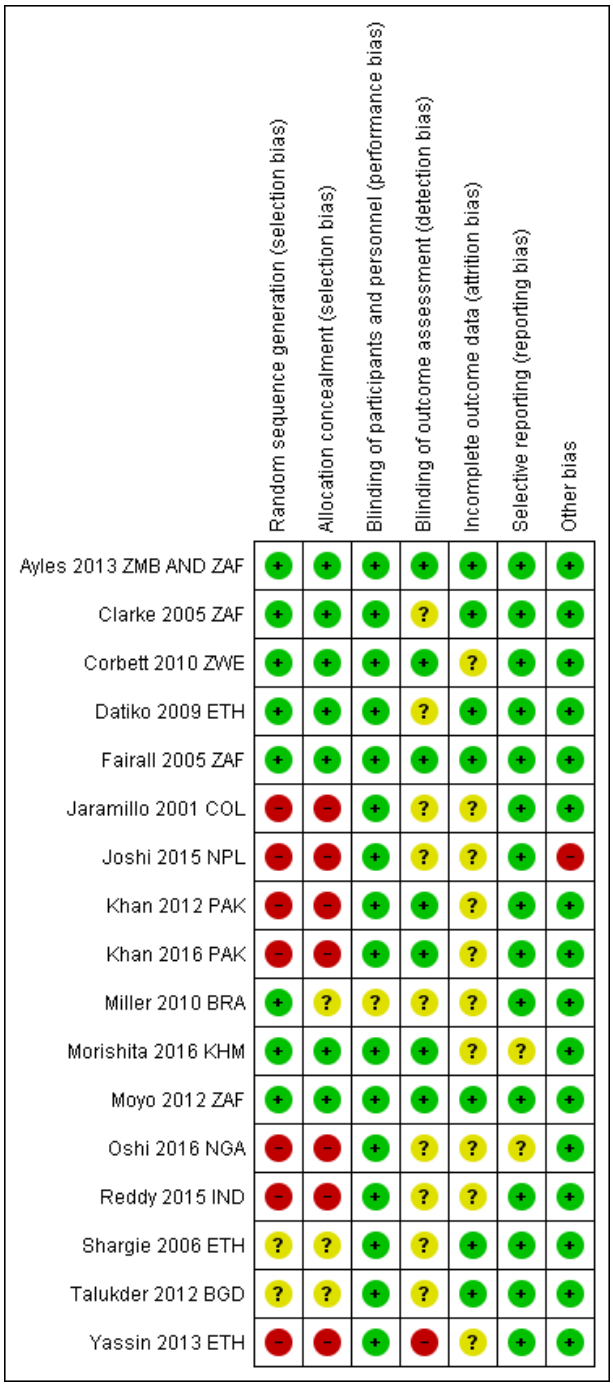
We excluded 56 studies because they did not meet the inclusion criteria. The reasons for their exclusion are presented in the Characteristics of excluded studies section.

Eight references remain unclassified as we have been unable to access full-text copies: three conference abstracts (Gadala 2015; Jensen 2015; Poliakova 2015), two Chinese language studies (Chen 1990; Duanmu 2005), two old publications (Grzybowski 1965; Ursov 1970), and one reference that we have been unable to trace (Nadu 2004).

Risk of bias in included studies

For a summary of the 'Risk of bias' assessments see Figure 3.

Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.



Allocation

Five out of nine cluster-randomized studies adequately described a suitable method for generating the random sequence and were judged to be at low risk of selection bias (Ayles 2013 ZMB AND ZAF; Clarke 2005 ZAF; Corbett 2010 ZWE; Datiko 2009 ETH; Fairall 2005 ZAF); in the other four the description was unclear. Although allocation concealment was not described for most of the cluster-randomized studies, cluster-randomized studies are normally considered to be at low risk of selection bias as the allocation of all clusters is usually done in a single step.

We judged the non-randomized trials to be at high risk of selection bias.

Blinding

None of the trials described blinding of health workers or populations (and this would have been impossible to do), but this is unlikely to bias the measured effects of the intervention.

Five of the randomized studies blinded microscopists or outcome assessors to the treatment allocation and were judged to be at low risk of detection bias (Ayles 2013 ZMB AND ZAF; Corbett 2010 ZWE; Fairall 2005 ZAF; Moyo 2012 ZAF).

Incomplete outcome data

Seven studies were at low risk of attrition bias (Ayles 2013 ZMB AND ZAF; Clarke 2005 ZAF; Datiko 2009 ETH; Fairall 2005 ZAF; Morishita 2016 KHM; Shargie 2006 ETH; Talukder 2012 BGD), and the other 10 studies were at unclear risk of attrition bias (Corbett 2010 ZWE; Jaramillo 2001 COL; Joshi 2015 NPL; Khan 2012 PAK; Miller 2010 BRA; Moyo 2012 ZAF; Oshi 2016 NGA; Reddy 2015 IND; Yassin 2013 ETH)

Selective reporting

We identified one study with unclear risk of selective reporting bias (Oshi 2016 NGA).

Other potential sources of bias

We identified no other sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Tuberculosis outreach screening versus no intervention; **Summary of findings 2** Health promotion activities versus no intervention; **Summary of findings 3** Training interventions compared to no intervention; **Summary of findings 4** Outreach tuberculosis screening versus health promotion; **Summary of findings 5** Outreach clinic versus house-to-house screening

Comparison 1: Outreach tuberculosis screening with or without health promotion activities versus no intervention

See Summary of findings for the main comparison.

Four cluster-RCTs and four controlled before-and-after studies evaluated the effects of tuberculosis diagnostic outreach services into the community. All but one of these interventions also included extensive health promotion activities. For details see Table 1 and Table 2.

Of the cluster-RCTs, Ayles 2013 ZMB AND ZAF screened all household contacts of people with active tuberculosis; Shargie 2006 ETH conducted monthly diagnostic outreach clinics in each cluster; Datiko 2009 ETH used health extension workers who visited every household every two weeks to screen for tuberculosis; and Morishita 2016 KHM used healthcare workers and community volunteers who screened households for a period of one year. Clarke 2005 ZAF was a much smaller trial in which lay health workers screened all farm workers for tuberculosis every month.

Of the non-randomized studies, Yassin 2013 ETH and Reddy 2015 IND screened for active tuberculosis in people's homes; Joshi 2015 NPL used volunteers to conduct contact tracing, set up mobile clinics, and screen at homes and schools; and Oshi 2016 NGA conducted contact tracing plus screening at outpatient clinics and antiretroviral therapy clinics.

Tuberculosis cases detected (microbiologically confirmed)

Among the cluster-RCTs, only Shargie 2006 ETH and Datiko 2009 ETH presented estimates of the effect of the intervention on tuberculosis case detection (microbiologically confirmed) that were appropriately adjusted for the cluster design (see Table 3). However, as both studies used different measures of effect, we have presented an alternative analysis approximately adjusted for the cluster design using the most conservative ICC (from Datiko 2009 ETH).

Analysis 1.1 presents the findings of four studies (Clarke 2005 ZAF; Datiko 2009 ETH; Morishita 2016 KHM; Shargie 2006 ETH), the number of tuberculosis cases detected (microbiologically confirmed) may increase in the intervention groups (risk ratio (RR) 1.24, 95% CI 0.86 to 1.79; 4 trials, 163,043 participants in 297 clusters, *low-certainty evidence*). We further analysed by tuberculosis prevalence and presented in Analysis 1.2. Analysis 1.2 presents the findings of four studies (Clarke 2005 ZAF; Datiko 2009 ETH; Morishita 2016 KHM; Shargie 2006 ETH), which we subgrouped by tuberculosis prevalence of less than 5% (Clarke 2005 ZAF) and 5% or more (Datiko 2009 ETH;

Morishita 2016 KHM; Shargie 2006 ETH). The study among farm workers in South Africa found with calculate prevalence of less than 5% showed no obvious effect of the intervention (RR 0.85, 95% CI 0.60 to 1.19; 1 trial, 8887 participants, Analysis 1.2). In the studies by Datiko 2009 ETH, Morishita 2016 KHM, and Shargie 2006 ETH, the number of tuberculosis cases detected was higher in the intervention areas (RR 1.52, 95% CI 1.10 to 2.09; 3 trials, 155,918 participants in 51 clusters, Analysis 1.2, *low-certainty evidence*).

Analysis 1.3 presents the tuberculosis cases detected microbiologically confirmed by intervention. Overall, the point estimates were similar the overall combined interventions as presented in Analysis 1.1. Tuberculosis outreach clinics plus health promotion (Shargie 2006 ETH) may increase tuberculosis cases detected (RR 1.28, 95% CI 0.76 to 2.17, Analysis 1.3.1). Similarly, the house-to-house screening plus health promotion for three cluster-RCTs (Clarke 2005 ZAF; Datiko 2009 ETH; Morishita 2016 KHM) may increase tuberculosis cases detected (RR 1.25, 95% CI 0.75 to 2.08, Analysis 1.3.2).

The cluster-RCT by Morishita 2016 KHM reported "TB cases detected (all forms)", and the results were consistent with the effects seen in studies that reported microbiologically confirmed tuberculosis cases detected with RR 1.28 (95% CI 0.83 to 1.98, Analysis 1.4).

Of the non-randomized studies, Yassin 2013 ETH and Joshi 2015 NPL reported increases in tuberculosis case notification per 100,000 in the intervention areas compared to control areas (see Table 3); Oshi 2016 NGA and Reddy 2015 IND only reported the number of tuberculosis cases detected without clear denominators, but both reported increased numbers in the intervention areas compared to the pre-intervention period (+31% and +8%, respectively).

Tuberculosis treatment outcomes

None of the studies included in this review adjusted for clustering for the treatment outcomes that they reported. We therefore used a conservative ICC of 0.001 for all the treatment outcomes.

Treatment default was substantially lower in those diagnosed through outreach services compared to standard health facilities (mean treatment default across studies: 10% versus 16%; RR 0.67, 95% CI 0.47 to 0.96; Analysis 1.5, *low-certainty evidence*). In all three randomized trials reporting tuberculosis treatment outcomes, treatment success was slightly higher in the intervention groups compared to the control group (mean treatment success across studies: 84% versus 78%). Although the direction of the effect was towards the intervention, there was very little difference indicated by the point estimate (RR 1.07, 95% CI 1.00 to 1.15; Analysis 1.6, *low-certainty evidence*). The number of treatment failures and deaths was low in all three randomized trials, so the analysis of differences was underpowered (treatment failures: RR 1.57, 95% CI 0.50 to 4.92; Analysis 1.7; tuberculosis mortality: RR 0.99, 95% CI 0.43 to 2.25, Analysis 1.8, 849 patients, very *low-certainty evidence*). Only one of the non-randomized studies reported treatment outcomes (Yassin 2013 ETH).

People diagnosed in intervention areas had higher treatment success (85% versus 77%), and lower default (3% versus 11%) during the implementation period compared to the pre-intervention period (Yassin 2013 ETH).

Long-term tuberculosis prevalence

Only Ayles 2013 ZMB AND ZAF evaluated the effects on long-term prevalence of tuberculosis. In a cross-sectional prevalence study, 3.5 to 4.5 years after the intervention started, there was no effect demonstrated (881 per 100,000 intervention areas versus 773 per 100,000 control areas; RR 1.14, 95% CI 0.65 to 2.00; 1 study, 556,836 participants in 12 clusters, Analysis 1.9, *very low-certainty evidence*). The authors also presented an additional analysis adjusted for multiple confounders such as tuberculosis and HIV prevalence, household socioeconomic status, age, sex, and smoking history, with no obvious effect detected (RR 0.89, 95% CI 0.62 to 1.29).

Comparison 2: Health promotion activities versus no intervention

See Summary of findings 2.

Two cluster-RCTs, Ayles 2013 ZMB AND ZAF and Talukder 2012 BGD, and two non-randomized studies, Khan 2012 PAK and Jaramillo 2001 COL, evaluated health promotion activities that encourage attendance at health services for tuberculosis screening.

These health promotion activities ranged from extensive mass media strategies (television/radio/newspapers) to more local, community-based activities (leafleting, community meetings, school-based drama). For details see Table 1.

Tuberculosis cases detected (microbiologically confirmed)

Neither of the two cluster-RCTs presented an estimate of the effect of the intervention on tuberculosis case detection (see Table 4). Ayles 2013 ZMB AND ZAF used long-term tuberculosis prevalence as the primary outcome, and Talukder 2012 BGD only reported the number of people referred for testing in intervention areas without a population-level denominator. However, Talukder 2012 BGD reported that the number of cases detected was higher in the intervention areas (P = 0.001; author's own figures).

Of the two non-randomized studies, Khan 2012 PAK reported that tuberculosis case detection doubled during the intervention period (343 per 100,000 during intervention versus 176 per 100,000 pre-intervention), but remained stable in the parallel control area (46 per 100,000 during intervention versus 41 per 100,000 pre-intervention). Jaramillo 2001 COL only presented quarterly data on the number of smears conducted, the number of

people tested, and the number of tuberculosis cases notified. These data suggest a temporal association between the intervention period and an increase in the number of smears and people tested. However, there was not a convincing corresponding increase in the number of tuberculosis case notifications.

Long-term tuberculosis prevalence

Ayles 2013 ZMB AND ZAF conducted a cross-sectional prevalence study 3.5 to 4.5 years after the intervention started. There was no effect demonstrated on tuberculosis prevalence at this time point (1012 per 100,000 intervention areas versus 773 per 100,000 control areas; RR 1.31, 95% CI 0.75 to 2.29; 1 trial, 405,788 participants in 12 clusters, Analysis 2.1, *very low-certainty evidence*). The authors presented an additional analysis adjusted for multiple confounders such as tuberculosis and HIV prevalence, household socioeconomic status, age, sex, and smoking history, but did not demonstrate a difference (RR 1.04, 95% CI 0.72 to 1.51).

Tuberculosis treatment outcomes

None of the studies reported comparisons of tuberculosis treatment outcomes between intervention and control areas, or between pre- and post-intervention periods.

Comparison 3: Staff training compared to none

See Summary of findings 3

One cluster-RCT evaluated health worker education compared to no intervention (Fairall 2005 ZAF). In South Africa, nurse practitioners working in primary care clinics were given between two and six educational sessions. One quasi-experimental study evaluated nurses who were trained on case management and monitoring tools in participating health facilities (Khan 2016 PAK). A summary of the tuberculosis case-finding outcomes for the two studies is shown in Table 5.

Tuberculosis cases detected (microbiologically confirmed)

In South Africa, Fairall 2005 ZAF reported an increase in the number of tuberculosis cases diagnosed per 1000 patient consults (RR 1.68, 95% CI 1.03 to 2.72; 1 trial, 1999 participants, Analysis 3.1, *low-certainty evidence*). One non-randomized study, Khan 2016 PAK, reported that tuberculosis case detection more than tripled in the intervention group (511 tuberculosis cases per 100,000 in the intervention group versus 135 tuberculosis cases per 100,000 in the control group).

Other outcomes, including tuberculosis treatment outcomes and long-term tuberculosis prevalence, were not reported.

Comparison 4: Outreach tuberculosis screening versus health promotion

See Summary of findings 4

Two cluster-RCTs directly compared outreach tuberculosis screening with health promotion activities. Ayles 2013 ZMB AND ZAF compared tuberculosis contact tracing with extensive health promotion activities encouraging health service attendance, and Miller 2010 BRA compared house-to-house screening with the distribution of informational leaflets to all households (see Table 6).

Tuberculosis cases detected (microbiologically confirmed)

Only Miller 2010 BRA reported the effect on tuberculosis case detection. During the study period, tuberculosis case detection was higher with house-to-house screening than with health promotion (9.34 per 1000 person years versus 6.04 per 1000 person years; rate ratio 1.55, 95% CI 1.10 to 1.99, 1 trial, 23,553 participants in 14 clusters, Analysis 4.1). However, a second analysis including the intervention period plus 60 days postintervention attenuated this apparent effect (RR 1.05, 95% CI 0.56 to 1.54). See Table 7.

Long-term prevalence

The cluster-RCT from Zambia and South Africa was a cross-sectional prevalence study 3.5 to 4.5 years after the intervention started (Ayles 2013 ZMB AND ZAF). The study had four arms: control arm, health promotion activities, contact tracing, and contact tracing plus health promotion. None of the interventions were shown to reduce prevalence compared to control.

Tuberculosis treatment outcomes

Miller 2010 BRA reported that time to diagnosis and treatment completion were not significantly different between the two groups.

Comparison 5: Outreach clinic versus house-to-house screening

See Summary of findings 5

One cluster-RCT directly compared the effects of a six-monthly outreach tuberculosis clinic (a mobile van) versus six-monthly house-to-house screening (see Table 6) (Corbett 2010 ZWE).

Tuberculosis cases detected (microbiologically confirmed)

The number of tuberculosis cases detected was higher with the outreach clinic in each of the six rounds of the interventions, and the cumulative case detection over the three years of the trial was 48% higher (RR 1.48, 95% CI 1.11 to 1.97; 1 trial, 405,819 participants, Analysis 5.1, *very low-certainty evidence*). The authors

note that this was unexpected, as the mobile clinic is a less intensive method of case finding, and required self presentation at a public clinic specializing in the diagnosis of a disease associated with poverty and HIV. The authors acknowledge this and suggest that the mobile clinic may have been more convenient, and allowed people to encourage those with symptoms to attend. The home visits were conducted between 9 am and 4 pm, when many people may have been absent, but repeated visits (up to three) including at least one weekend visit attempted to mitigate this.

Long-term tuberculosis prevalence

Corbett 2010 ZWE reported that overall tuberculosis prevalence declined by around 44% over the three years of the intervention (95% CI 17% to 62%; author's own figures), with no difference detected between the two interventions; however, this is an uncontrolled observation that could be part of a wider temporal trend unassociated with the intervention.

Tuberculosis treatment outcomes

Not described.

Comparison 6: Active case-finding interventions versus no intervention

In this comparison we evaluated any interventions that had any component of active case finding versus no intervention. We included five studies (Clarke 2005 ZAF; Datiko 2009 ETH; Fairall 2005 ZAF; Morishita 2016 KHM; Shargie 2006 ETH). The results did not differ from comparison one to four (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4; Analysis 6.5; Analysis 6.6; Analysis 6.7; Analysis 6.8; Analysis 6.9).

Comparison 7: Outreach tuberculosis services versus no intervention (sensitivity analyses)

In this comparison we included studies that did not present ICC for the tuberculosis treatment outcome (tuberculosis treatment default, tuberculosis treatment success, tuberculosis treatment failure, and tuberculosis mortality). This comparison demonstrates the results for conservative ICC of 0.001 and the ICC as given by Datiko 2009 ETH. The results did not differ when adjusting for each of the ICCs considered (Analysis 7.5; Analysis 7.6; Analysis 7.7; Analysis 7.8).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Health promotion activities to encourage people with symptoms of tuberculosis to attend health services

Patient or population: all age groups
Settings: areas with moderate or high tuberculosis prevalence
Intervention: health promotion activities alone
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Health promotion				
Long-term tuberculosis prevalence (assessed at 4 years)	773 per 100,000	1012 per 100,000 (580 to 1778)	RR 1.31 (0.75 to 2.30	405,788 in 12 clusters (1 cluster-RCT)	very low[1,2,3,4]	We do not know if health promotion reduces long-term tuberculosis prevalence
Treatment success	-	-	-	-	(0 studies)	-
Tuberculosis mortality	-	-	-	-	(0 studies)	-
Long-term tuberculosis prevalence	-	-	-	-	(0 studies)	-

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]No serious risk of bias: only one study is included and it warrants no downgrading.
[2]No serious inconsistency; it is the only cluster-randomized trial.
[3]Downgraded twice for serious indirectness: this is a single study from Zambia and South Africa, with prevalence measured at four years. It does not exclude the possibility of effects in different settings, or at later time points.
[4]Downgraded once for serious imprecision: the 95% CI is wide and includes both clinically important effects and no difference.

Health staff training in tuberculosis diagnosis

Patient or population: all age groups
Settings: areas with moderate or high tuberculosis prevalence
Intervention: health staff training activities
Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Health promotion				
Tuberculosis cases detected (microbiologically confirmed)	3360 per 100,000	5644 per 100,000 (3461 to 9139)	RR 1.68 (1.03 to 2.72)	1999 participants in 2 clusters (1 study)	low[1,2,3,4]	Training of health staff may increase the number of microbiologically confirmed people with tuberculosis
Treatment success	-	-	-	(0 studies)	-	-
Tuberculosis mortality	-	-	-	(0 studies)	-	-
Long-term tuberculosis prevalence	-	-	-	(0 studies)	-	-

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]No serious risk of bias: only one study is included and it warrants no downgrading.
[2]No serious inconsistency; it is the only cluster-randomized trial.
[3]Downgraded twice for serious indirectness: this is a single study from South Africa.
[4]No serious imprecision.

Outreach tuberculosis screening versus health promotion

Patient or population: adults
Settings: areas with moderate or high tuberculosis prevalence
Intervention 1: mobile clinic situated in each cluster for 5 days every 6 months with associated leafleting and loudspeaker
Intervention 2: house-to-house screening every 6 months

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Mobile clinic	House-to-house				
Tuberculosis cases detected (microbiologically confirmed)	250 per 100,000	406 per 100,000 (317 to 578)	RR 1.71 (1.27 to 2.31)	110,162 (1 study)	very low[1,2,3,4]	We do not know if outreach tuberculosis screening activities increase the number of microbiologically confirmed people with tuberculosis
Treatment success	-	-	-	(0 studies)	-	-
Tuberculosis mortality	-	-	-	(0 studies)	-	-
Long-term tuberculosis prevalence	-	-	-	(0 studies)	-	-

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]No serious risk of bias: only one study is included and it warrants no downgrading.
[2]No serious inconsistency; it is the only cluster-randomized trial.
[3]Downgraded twice for serious indirectness: this is a single study from Brazil.
[4]No serious imprecision.

Outreach clinic compared with house-to-house screening for presumptive tuberculosis patients to test for tuberculosis

Patient or population: adults
Settings: high tuberculosis burden setting
Intervention: outreach clinic
Comparison: house-to-house

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	House-to-house	Outreach clinic				
Tuberculosis cases detected (microbiologically confirmed)	238 per 1000	352 per 1000 (264 to 469)	RR 1.48 (1.11 to 1.97)	405,819 participants in 46 clusters (1 study)	very low[1,2,3,4]	We do not know if outreach clinic activities increase tuberculosis cases detected
Treatment success	-	-	-	(0 studies)	-	-
Tuberculosis mortality	-	-	-	(0 studies)	-	-
Long-term tuberculosis prevalence	-	-	-	(0 studies)	-	-

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1]No serious risk of bias: only one study is included and it warrants no downgrading.

[2]No serious inconsistency; it is only cluster-randomized trial.

[3]Downgraded twice for serious indirectness: this is a single study from Zimbabwe. It does not exclude the possibility of effects in different settings, or at later time points.

[4]No serious imprecision.

DISCUSSION

Summary of main results

Tuberculosis outreach screening (with and without health promotion) to encourage presumptive tuberculosis patients to attend healthcare services may increase tuberculosis case detection in settings where the prevalence of undiagnosed tuberculosis disease is high. This was shown in four cluster-RCTs (*low-certainty evidence*). Regular tuberculosis diagnostic outreach clinics may also increase tuberculosis case detection (*low-certainty evidence*).

There is insufficient evidence to determine if sustained improvements in case detection impact on long-term tuberculosis prevalence, as the only controlled study to evaluate this found no effect after four years of contact tracing plus intensive health promotion intervention (*very low-certainty evidence*).

In all of these trials, there were modest effects on treatment success and default from treatment in participants diagnosed through outreach/screening services (*moderate-certainty evidence*).

Overall completeness and applicability of evidence

We included 17 studies in this review, which have implemented various interventions with contradictory results. Some of the interventions may have a large effect on increasing tuberculosis case detection (microbiologically confirmed), whereas other interventions showed no evidence of being effective. This is perhaps not unexpected, as the efficacy of any tuberculosis case-finding intervention is likely to be dependent on multiple factors such as the prevalence of undiagnosed tuberculosis, local barriers to accessing care, and the practical details of implementation, which may include tuberculosis diagnostic tool used. While we will discuss some of the potential reasons for the presence or absence of demonstrable effects, the limited number of studies for each intervention, and the very limited number of settings in which these interventions have been implemented, limit our ability to make broad generalizations.

The study by Corbett 2010 ZWE from Zimbabwe is particularly interesting as it brings up as many questions as it answers. For those considering periodic tuberculosis diagnostic outreach clinics as the most feasible and affordable option in their setting, this study provides some reassurance that these clinics can be effective. Indeed, the lack of demonstrable effect of monthly clinics in Shargie 2006 ETH may simply be due to the statistical imprecision of the trial (that is, the intervention was effective but a bigger trial was needed to demonstrate this), or may reflect suboptimal implementation of the clinics (that is, they were conducted in the wrong place at the wrong time or were inadequately publicized).

However, the finding that six-monthly outreach clinics were actually more effective than house-to-house visits needs to be interpreted with caution, as it is counterintuitive. The explanation offered by the study authors was that the monthly clinics were somehow more acceptable or accessible to the population. This explanation is reasonable, but again demonstrates how reliant the effects of any intervention are on the practical details of implementation, such as the timing of visits. The intervention effect might disappear or even reverse with different cultural norms, different attitudes towards tuberculosis, or different timing or settings for the clinics or home visits.

Corbett 2010 ZWE also presented evidence of a declining prevalence in tuberculosis over the three years of the study, which was notably absent in the trial by Ayles 2013 ZMB AND ZAF. The interventions in the two trials are obviously different, and one interpretation for the results might be that contact tracing and health promotion alone are not sufficient to reduce tuberculosis prevalence, whereas outreach clinics and household screening are. However, the evidence from Corbett 2010 ZWE is observational in nature, and highly susceptible to confounding. It is also surprising that the same decline was seen in both study arms despite a clear difference in tuberculosis case detection between the two arms. The decline may therefore be due to other temporal trends or activities, rather than the case-finding intervention itself.

The overall limitations of the studies included in this review are as follows.

- Small sample sizes that were not powered to detect a clinical difference in tuberculosis treatment outcomes such as mortality and default rate.
- The likelihood of false-positive results from sputum smear acid-fast bacilli (AFB) microscopy, especially in low tuberculosis prevalence settings, with implications for the overestimation of notification rates and favourable treatment outcomes (treatment success).
- Considerable heterogeneity of interventions that reduced the certainty of the evidence of each reviewed outcome.
- Considerable heterogeneity of the health systems in which the interventions were implemented.

Quality of the evidence

We assessed the certainty of the evidence in this review using the GRADE approach and presented the evidence in five 'Summary of findings' tables.

We generally downgraded the certainty of evidence for the primary outcome of tuberculosis case detected (microbiologically confirmed) to 'low' despite most trials being well conducted. One of the main reasons for this downgrading was indirectness, as the findings of single trials are not easily generalized to other settings. As discussed above, effects will vary widely in line with local tuberculosis prevalence and local implementation.

We considered the certainty of evidence for the secondary outcome of long-term tuberculosis prevalence to be 'very low'. Again, this does not represent inadequacies in the conduct of the trial, but rather reflects the ongoing uncertainty about whether tuberculo-

sis case-finding interventions could reduce prevalence. We downgraded the single study for indirectness (as the findings are not easily generalized to other settings) and imprecision (as the level of statistical certainty does not exclude the possibility of important effects).

Potential biases in the review process

We minimized potential biases during the review process by adhering to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the *Methodological Expectations of Cochrane Intervention Reviews* (MECIR) (Higgins 2016). We conducted a comprehensive search of all languages for both peer-reviewed and grey literature. Two review authors independently assessed study eligibility, extracted data, and assessed the risk of bias in each included trial.

The findings of this review are based on the extensive and updated search of the studies done in high-burden tuberculosis countries. The extensive risk of bias assessment was applied for both randomized and non-randomized trials which helped to critically interpret the findings. The strength of the review is that it enables an assessment of various interventions applied either at the community or the primary healthcare setting to increase tuberculosis case detection. The limitations of the study include the following.

- The diversity of interventions and low number of studies to make a good comparison and asses the level of evidence.
- There is also diversity of diagnostic tools with varying sensitivity such as smear microscopy and more sensitive molecular test like Gene Xpert MTB/RIF.
- The effect of the interventions on tuberculosis treatment outcome was limited because of the low number of tuberculosis patients.

Agreements and disagreements with other studies or reviews

A previous systematic review by Kranzer and colleagues concentrated on the yield of tuberculosis cases achieved with various active case-finding strategies (Kranzer 2012). As such, they included both controlled studies (included here) and uncontrolled studies (which we excluded). The use of 'yield' as an outcome, especially without a control group, has limitations, as it can be unclear whether these cases would have presented passively anyway. However, Kranzer and colleagues also note that people with tuberculosis identified through screening tended to be less sick, and have had the illness for less time, which is consistent with successfully identifying more cases.

Kranzer 2012 also had a wider scope, and included interventions within high-risk communities such as prisons and clinics for people with HIV. They found that generally the yield was lowest with population screening, which may make population screening less attractive and affordable in many settings.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence demonstrates that when interventions are used in high-burden settings, active case-finding approaches may increase tuberculosis case detection in the short term in moderate- to high-tuberculosis prevalence settings. However, it is unclear from the available evidence if active case-finding interventions may improve treatment success and reduce tuberculosis treatment failure, mortality, and default.

Implications for research

For the purposes of this review, we chose to only include controlled trials, as these most reliably demonstrate the true effects of any intervention, and will be most useful to decision-makers designing local interventions. However, it is likely that many national or local decisions will be based upon uncontrolled pilot studies demonstrating an acceptable yield of tuberculosis cases (microbiologically confirmed) with an intervention that is deemed affordable, and that the implementation of the intervention will be periodically modified through monitoring and audit. This pragmatic approach is a perfectly reasonable form of evidence-based decision-making, and we hope that this summary of the global evidence base assists in those decisions. Further studies are being conducted to utilize GeneXpert Ultra (a more sensitive version of the Xpert MTB/RIF cartridge) as the first test for screening populations using active case finding. It is therefore likely that the pool of studies will increase in the near future.

In the future there is a need to design and conduct trials employing appropriate case detection methods for children, in whom tuberculosis is an important cause of illness. The trials could include scoring systems for children using chest X-rays, signs and symptoms, and results of tuberculin skin tests.

ACKNOWLEDGEMENTS

FM was supported by a fellowship offered by Cochrane South Africa, South African Medical Research Council, funded by the Effective Health Care Research Consortium. David Sinclair was supported as an author and editor with the Cochrane Infectious Diseases Group by the Effective Health Care Research Consortium. This Consortium and the editorial base of the Cochrane Infectious Diseases Group are funded by UK aid from the UK Government for the benefit of low-income countries (Grant: 5242).

The views expressed in this review do not necessarily reflect UK government policy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ayles 2013 ZMB AND ZAF

Methods	Trial design: A 2 X 2 factorial design cluster-RCT Unit of randomization: Community - average size 40110 Number of clusters per study arm: 6 Length of follow-up: 54 months Adjusted for cluster design: Yes
Participants	Target group: adults 18 years of age or older. Total population of intervention areas: 962,655 Total number of people screened for tuberculosis: 64643 Exclusions: none Tuberculosis screening test: Symptoms in contact tracing, sputum smear in health promotion Tuberculosis diagnostic test: Sputum smear microscopy and mycobacterial culture
Interventions	**Intervention area 1: Strengthened tuberculosis-HIV programme plus health promotion** • Did they look for TB cases outside of health facilities? No • Did they use health promotion strategies to encourage people to attend diagnostic services? Yes, through extensive promotion activities people were encouraged to drop sputum samples at central collection points. • Did they train health workers in TB diagnosis? Yes, the TB-HIV programme was strengthened at all clinics. **Intervention area 2: Strengthened tuberculosis-HIV programme plus contact tracing** • Did they look for TB cases outside of health facilities? Yes, household contacts of people diagnosed with TB were screened. • Did they use health promotion strategies to encourage people to attend diagnostic services? No. • Did they train health workers in TB diagnosis? Yes, the TB-HIV programme was strengthened at all clinics. **Intervention area 3: A combination of 1 + 2** • Did they look for TB cases outside of health facilities? Yes, household contacts of people diagnosed with TB were screened. • Did they use health promotion strategies to encourage people to attend diagnostic services? Yes, through extensive promotion activities people were encouraged to drop sputum samples at central collection points. • Did they train health workers in TB diagnosis? Yes, the TB-HIV programme was strengthened at all clinics. **Control: Strengthened tuberculosis-HIV programme at the clinics only**
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected • Community tuberculosis prevalence at 3.5 to 4.5 years postintervention

Notes	Countries: Zambia and South Africa Setting: Rural and urban Zambia and Western Cape in South Africa Tuberculosis prevalence: 832 per 100,000 population HIV prevalence: Zambia: 15.9% to 18.0%, South Africa: 16.9% to 19.2% Study dates: 1 August 2006 to 31 July 2009 Study sponsor: Bill & Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization of intervention was stratified by country and the prevalence of tuberculous infection. Additionally randomization was restricted to ensure balance of prevalence of tuberculosis infection, HIV prevalence, urban and rural location, social context and geographical location. A list of 1000 possible allocations of communities to four groups was drawn as a random sample from a total of about 7 million allocations that met restriction criteria."
Allocation concealment (selection bias)	Low risk	Quote: "A two stage public randomization ceremony was done, first to select one of the 1000 possible allocations of the 24 communities into four groups, and second to allocate each of the four trial groups to one of the letters A, B, C, D"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Neither participants nor study personnel were blinded to the intervention group, but this is unlikely to bias the result separately from the effect of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Analysis of sputum samples collected in the prevalence survey was done blinded to group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss of clusters occurred. A large number of samples were either missing (2330), failed to meet predefined quality standards (18,101), or were contaminated (5707). However, the proportions were reasonably balanced across groups

Ayles 2013 ZMB AND ZAF (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: Low risk Incorrect analysis: Primary outcome adjusted for clustering. Comparability with RCTs randomizing individuals: Unclear risk

Clarke 2005 ZAF

Methods	Trial design: cluster-RCT Unit of randomization: farm - median size 44 adult farm workers Number of clusters per study arm: 106 intervention vs 105 control Length of follow-up: 6 months Adjusted for cluster design: yes
Participants	Target population: adults aged > 15 years Total population of intervention areas: 4438 (adults) Total number of people screened for tuberculosis in intervention areas: not stated Exclusion criteria: multidrug-resistant tuberculosis patients Tuberculosis screening test: symptom screen - criteria not defined Tuberculosis diagnostic test: sputum smear microscopy x 2
Interventions	**Intervention areas** • Did health workers look for tuberculosis cases outside of health facilities? Yes, lay health workers screened all farm dwellers monthly and referred to tuberculosis centres. • Were there health promotion activities to encourage people to attend diagnostic services? No. • Were health workers trained in tuberculosis diagnosis? Yes, lay health workers had 5 weeks of training on tuberculosis, family health, HIV, first aid, and home-based care. **Control areas** • No intervention
Outcomes	**Outcomes included in the review** • Tuberculosis cases detected • Treatment completion • Tuberculosis cure • Tuberculosis mortality
Notes	Country: South Africa Setting: Rural Tuberculosis prevalence: Not stated HIV prevalence: Not stated Study dates: May 2000 to Sept 2000

	Study sponsors: Boland District Municipality, The Medical Research Council of South Africa, UK Department of International Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All the numbers were randomly drawn from containers and allocated sequentially to the intervention or control group"
Allocation concealment (selection bias)	Low risk	Comment: None described but cluster-randomized studies are generally at low risk of selection bias if the sequence generation is low risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: None described, however this is unlikely to bias the result
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: None described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No loss of clusters. A small number of people diagnosed with tuberculosis transferred out
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: No loss of cluster (low risk) Incorrect analysis: Primary outcome not adjusted for clustering (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Corbett 2010 ZWE

Methods	Trial design: Cluster-randomized trial Unit of randomization: Areas of residential suburbs - approximate size 2000 to 3000 adults Number of clusters per study arm: 23 Length of follow-up: 35 months Adjusted for cluster design: Yes
Participants	Target group: Adults aged 16 years or older Total population of intervention areas: Mobile van: 55,741 vs door-to-door: 54,691 Total number of people screened for tuberculosis: Mobile van: 5466 vs door-to-door: 4711 Exclusions: None Tuberculosis screening test: Symptom screen - cough > 2 weeks Tuberculosis diagnostic test: Sputum smear, mycobacteria culture, chest X-ray
Interventions	**Intervention area 1: Mobile van** • Did health workers look for tuberculosis cases outside of health facilities? Yes, a mobile van was located in each cluster for 5 days in each of 6 rounds. • Were there health promotion activities to encourage people to attend diagnostic services? Yes, a loudspeaker and leafleting encouraged people to attend. • Were health workers trained in tuberculosis diagnosis? Yes, the tuberculosis-HIV programme was strengthened at all clinics. **Intervention area 2: Door-to-door screening** • Did health workers look for tuberculosis cases outside of health facilities? Yes, all households were visited up to 3 times in each of 6 rounds by 2 teams of 3 lay field workers. • Were there health promotion activities to encourage people to attend diagnostic services? No. • Were health workers trained in tuberculosis diagnosis? Unclear, improvements in the skills of staff at the health clinics were not described.
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected • Prevalence of tuberculosis after the intervention
Notes	Country: Zimbabwe Setting: Residential suburbs in Harare Tuberculosis prevalence: Smear-positive 280 per 100,000 population HIV prevalence: 21% to 22% Study dates: January 2006 to November 2008 Study sponsor: Wellcome Trust

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done by selection of red and black coloured discs (23 of each colour), which were otherwise iden-

		tical, from an opaque bag held above eye-level."
Allocation concealment (selection bias)	Low risk	Quote: "Discs were withdrawn at a public meeting by community advisory board members representing each cluster. Before selection began, black was allocated to represent the door-to-door group, and red to represent the mobile van group"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Community health workers and cluster residents were not masked to the intervention" Comment: This is unlikely to bias the result separately from the effect of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Laboratory work and clinical management was done without reference to the intervention group, and interim data were not analysed by intervention group until the final analysis, allowing investigators and laboratory staff to be masked to intervention allocation"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Consent to participate in prevalence surveys was lower in men (57% to 65%) than in women (97% to 98%). The number of missing or contaminated sputum samples was not reported
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective outcomes reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: None (low risk) Incorrect analysis: Primary outcome adjusted for clustering (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Datiko 2009 ETH

Methods	Trial design: Community-randomized trial Unit of randomization: Kebele (lowest administrative unit) - approximate size 5000 people Number of clusters per study arm: 31 intervention versus 21 control Length of follow-up: 19 months Adjusted for cluster design: Yes
Participants	Target group: All ages Total population of intervention areas: 178,138 Total number of people screened for tuberculosis: Not stated Exclusions: None mentioned Tuberculosis screening test: Cough for more than 2 weeks Tuberculosis diagnostic test: Sputum smear microscopy +/- CXR
Interventions	**Intervention areas: Training of health extension workers to visit houses and screen for tuberculosis.** • Did health workers look for tuberculosis cases outside of health facilities? Yes, health extension workers visited all households in the kebeles. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, health extension workers conducted health education sessions at health posts. • Were health workers trained in tuberculosis diagnosis? Yes, health extension workers were trained to screen for chronic cough and collect, store, and transport sputum samples. **Control areas: No intervention** • Health extension workers did not receive training, but provided health services including health education about tuberculosis the people living in their kebeles.
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected • Tuberculosis cure • Treatment completion • Early default (prior to commencing treatment or during the intensive phase of treatment) • Tuberculosis mortality
Notes	Country: Ethiopia Setting: Rural districts of Sidama zone in Southern Ethiopia Tuberculosis prevalence: 122 per 100,000 population HIV prevalence: HIV test was not done and kits were not available during the study Study dates: September 2006 to April 2008 Study sponsor: The University of Bergen

Risk of bias

Bias	Authors' judgement	Support for judgement

Datiko 2009 ETH (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "We used the list of kebeles in the two districts and randomly allocated them to intervention and control groups using a table of random numbers."
Allocation concealment (selection bias)	Low risk	Comment: Allocation concealment was not described, however cluster-randomized studies are generally considered to be at low risk of bias for allocation concealment, as allocation takes place centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and personnel were not blinded. However, given the nature of the intervention, this was unlikely to introduce bias into the results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Although we did not blind the laboratory technicians, they were not informed whether the sputum specimens were from intervention or control kebels."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: There was no loss of clusters. 3/88 tuberculosis-positive patients were transferred out in the control group vs 0/230 in the intervention group. The number of sputum samples lost or contaminated was not reported
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: None (low risk) Incorrect analysis: Primary outcome adjusted for clustering (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Fairall 2005 ZAF

Methods	Trial design: Cluster-RCT Unit of randomization: Primary care clinics - approximately 200 consultations per day Number of clusters per study arm: 20 Length of follow-up: 3 months Adjusted for cluster design: Yes
Participants	Target group: Aged 15 years and older Total population of intervention areas: Not stated Total number of people screened for tuberculosis in intervention areas: 1006 Exclusions: People referred urgently elsewhere Tuberculosis screening test: Symptom screen: criteria not described Tuberculosis diagnostic test: Sputum microscopy and mycobacteria culture
Interventions	**Intervention clinics: Training nurse practitioners in tuberculosis diagnosis** • Did health workers look for tuberculosis cases outside of health facilities? No. • Were there health promotion activities to encourage people with symptoms to attend health services? No. • Were health workers trained in tuberculosis diagnosis? Yes, nurse practitioners received between 2 and 6 educational sessions. **Control clinics** • No intervention
Outcomes	**Outcomes included in the review** • Addional tuberculosis cases detected
Notes	Country: South Africa Setting: Urban and rural clinics at The Free State province Tuberculosis prevalence: 494 per 100,000 population HIV prevalence: 30.1% Study dates: May to November 2013 Study sponsor: International Development Research Centre, Canada, The South African Medical Council, the Free State Department of Health, and the University of Cape Town Lung Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Clinics were ranked by size and allocated to intervention or control arms using a random number table in blocks of four"
Allocation concealment (selection bias)	Low risk	Ouote: "Allocation was carried out by a trial statisticians before intervention or patient recruitment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients and field workers were blind to the intervention status of each clinic"

Fairall 2005 ZAF (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Field workers screened all eligible participants leaving the clinics (after they had seen the nurse). The field workers were blind to whether the nurse had received the training or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Loss to follow-up of 7%. The number of lost or missing sputum samples was not reported
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: Unclear risk Incorrect analysis: Outcomes adjusted for clustering. Comparability with RCTs randomizing individuals: Unclear risk

Jaramillo 2001 COL

Methods	Trial design: Controlled before-and-after study Intervention area: Cali, capital city of Valle del Cauca, Colombia Control area: Riseralda, an area bordering Valle del Cauca Length of follow-up: 2 years
Participants	Target group: All ages Total population of intervention area: 2 million Total number of people screened for tuberculosis: 67,168 had smear microscopy. Exclusions: None stated. Tuberculosis screening test: None stated. Tuberculosis diagnostic test: Sputum smear microscopy
Interventions	**Intervention clinics: Mass media tuberculosis health promotion** • Did health workers look for tuberculosis cases outside of health facilities? No. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, a mass media campaign using television and radio public service announcements and chat shows, and newspaper flyers and feature articles. • Were health workers trained in tuberculosis diagnosis? Yes, but no details given and no different from control areas. **Control group** • No intervention
Outcomes	**Outcomes included in the review** • Tuberculosis cases detected

Notes	Country: Colombia Setting: Urban Tuberculosis prevalence: 35 per 100,000 population HIV prevalence: Not stated Study dates: January 1993 to January 1995 Study sponsors: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Non-randomized
Allocation concealment (selection bias)	High risk	Comment: Non-randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Blinding was not done but this was unlikely to bias the result
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: None described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No losses described.
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective outcome reporting
Other bias	Low risk	**ROBINS-I bias domains** Confounding: No confounding expected (low risk). Selection of participants: All eligible participants were included (low risk) Classification of interventions: The assignment of the interventions was determined retrospectively (moderate risk) Deviations from intended interventions: "the sources used by the campaign made it likely that a substantial proportion of the population of the whole department of Valle had been was exposed to the media campaign" (moderate risk) Missing data: Data were reasonably complete (low risk). Measurement of outcomes: The outcome measure was unlikely to be influenced by

		the knowledge of the intervention (low risk) Selection of reported results: None (low risk)

Joshi 2015 NPL

Methods	Trial design: Non-RCT (retrospective review of records) Intervention area: 7 out of 10 districts where the intervention was implemented Control area: 7 districts chosen on the basis of size and population Length of follow-up: 1 year
Participants	Target group: Children aged 0 to 14 years Total population of intervention area: Approximately 1,489,785 children Total number of people screened for tuberculosis in intervention area: 16,740 Exclusions: None stated. Tuberculosis screening test: Symptom screening Tuberculosis diagnostic test: Sputum smear microscopy for AFB, chest radiography, and tuberculin skin test
Interventions	**Intervention areas** • Did health workers look for tuberculosis cases outside of health facilities? Yes, household contact tracing, mobile chest camps in hard-to-reach areas, home visits for children with HIV, and screening at schools and safe motherhood clinics • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, through safe motherhood services • Were health workers trained in tuberculosis diagnosis? Not described **Control areas** • No intervention
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases • Change in case registration rate per 100,000
Notes	Country: Nepal Setting: Not specified Tuberculosis prevalence: Not stated HIV prevalence: Not stated Study dates: March 2013 to March 2014 Study sponsor: The Union (Paris, France), MSF (Brussels Operational Centre, Luxembourg), the Department for International Development (UK), and the World Health Organization

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	High risk	Comment: Not randomized
Allocation concealment (selection bias)	High risk	Comment: Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: No blinding of participants and healthcare workers, however there is low risk of this causing any bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not described
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective outcome reporting
Other bias	High risk	**ROBINS-I bias domains** Confounding: Residual confounding of the population prognostic factors that determined the intervention (serious risk) Selection of participants: "the intervention districts were selected on the basis of poverty, higher population density and lower notification rates of childhood TB case finding" (serious risk) Classification of interventions: The assignment of the interventions was determined retrospectively for (moderate risk) Deviations from intended interventions: No deviations from the interventions (low risk) Missing data: Data were reasonably complete (low risk). Measurement of outcomes: The outcome measure was unlikely to be influenced by the knowledge of the intervention (low risk) Selection of reported results: None (low risk)

Khan 2012 PAK

Methods	Trial design: Non-RCT Intervention area: A section of Karachi, Pakistan (lower-income households) Control area: An adjacent section of Karachi Length of follow-up: 12 months
Participants	Target group: All ages Total population of intervention area: 915,767 Total number of people screened for tuberculosis in intervention area: 469,896 Exclusions: None Tuberculosis screening test: Cough for > 3 weeks or productive cough for > 2 weeks Tuberculosis diagnostic test: Sputum smear, GeneXpert, or chest X-ray
Interventions	**Intervention areas: Health promotion and screening at health centres** • Did health workers look for tuberculosis cases outside of health facilities? No, lay people were trained to screen patients at family clinics and outpatient departments. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, billboards, cable television advertisements, posters, flyers. • Were health workers trained in tuberculosis diagnosis? Yes, screeners were trained on tuberculosis awareness and screening. • Other activities? Screeners received financial incentives and were supervised by experienced community health workers. **Control areas** • No intervention
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases • Early default (prior to commencing treatment or during the intensive phase of treatment) • Tuberculosis cure • Treatment completion • Tuberculosis mortality
Notes	Country: Pakistan Setting: Primary healthcare clinics (family clinics) and outpatient departments in Karachi Tuberculosis prevalence: 364 per 100,000 population HIV prevalence: Not reported Study dates: 3 January 2010 to 31 December 2011 Study sponsor: TB REACH initiative of the Stop TB Partnership

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Not randomized, so susceptible to confounding by site
Allocation concealment (selection bias)	High risk	Comment: Not randomized, so susceptible to confounding by site

Khan 2012 PAK (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: No blinding of patients or health workers. However, this was unlikely to bias the result
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Similar assessment of the outcomes retrospectively by the tuberculosis programme investigators with no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No comment on missing outcome data
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	**ROBINS-I bias domains** Confounding: No confounding (low risk) Selection of participants: All eligible study participants were included in the study (low risk) Classification of interventions: Intervention status was well defined (low risk) Deviations from intended interventions: "Because several components were implemented simultaneously, we are unable to determine which one contributed most to the observed effect, and whether any one of the components in isolation would have had a substantial effect" (moderate risk) Missing data: None reported (low risk). Measurement of outcomes: Assessment of the outcome was comparable across the groups (low risk) Selection of reported results: No selective reporting (low risk)

Khan 2016 PAK

Methods	Trial design: Quasi-experimental exploratory study Intervention area: Punjab province in Pakistan Control area: 8 control districts Length of follow-up: 9 months
Participants	Target group: All ages Total population of intervention area: 662,249 Total number of people screened for tuberculosis in intervention area: 662,249 Exclusions: None Tuberculosis screening test: Tuberculosis symptom screening Tuberculosis diagnostic test: Sputum smear microscopy

Interventions	**Intervention areas: Health promotion and screening at health centres** • Where healthcare workers trained in tuberculosis management and diagnosis? Yes, 1) joint review of the participating facilities, reviewing the input availability, case management practices and indicator analysis of respective facilities, and 2) progress review and action plan of the diagnostic centre • Other activities? Developing the intervention monitoring guidelines and tools, which was done using a technical working group process that involved the national tuberculosis control programme **Control areas: No intervention**
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected (microbiologically confirmed) • Early default (prior to commencing treatment)
Notes	Country: Pakistan Setting: Outpatient departments in Punjab Tuberculosis prevalence: Not mentioned HIV prevalence: Not mentioned Study dates: April 2007 to January 2008 Study sponsor: UK aid

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Not randomized, so susceptible to confounding by site
Allocation concealment (selection bias)	High risk	Comment: Not randomized, so susceptible to confounding by site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Neither patients nor healthcare workers were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Outcomes were assessed retrospectively by the district tuberculosis co-ordinators with no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: No comment on missing data
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	**ROBINS-I bias domains** Confounding: No confounding expected (low risk)

		Selection of participants: Moderate bias as district health officers who did not agree to participate in the study were excluded (moderate risk) Classification of interventions: The interventions are well defined (low risk) Deviations from intended interventions: No deviations from the interventions (low risk) Missing data: Data were reasonably complete (low risk). Measurement of outcomes: The outcome measure could be influenced by knowledge of the intervention study participants received (moderate risk) Selection of reported results: None (low risk)

Miller 2010 BRA

Methods	Trial design: Cluster-RCT Unit of randomization: Neighbourhoods Number of clusters per study arm: 7 (total 15 clusters including 1 control) Length of follow-up: 283 days Adjusted for cluster design: Yes Study areas: A large favela in Rio de Janeiro, Brazil
Participants	Target group: Adults aged > 18 years Sample size: 58,587 Exclusions: None described. Tuberculosis screening test: Cough for > 3 weeks (as part of a 7-question tuberculosis symptom survey) Tuberculosis diagnostic test: Sputum sample x 2 for microscopy + abnormal CXR
Interventions	**Intervention 1: Door-to-door screening** • Did health workers look for tuberculosis cases outside of health facilities? Yes, community health agents visited all households to conduct a symptom screen and collect a sputum sample when indicated. • Were there health promotion activities to encourage people with symptoms to attend health services? A national television tuberculosis awareness campaign is described. • Were health workers trained in tuberculosis diagnosis? No specific training is described. • Other activities? No other activities **Intervention 2: Informational pamphlet** • Did health workers look for tuberculosis cases outside of health facilities? No. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, an informational pamphlet was delivered to each household

	describing the symptoms of tuberculosis and encouraging attendance at local health clinics for free care. • Were health workers trained in tuberculosis diagnosis? No specific training is described. • Other activities? None
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases • Time to diagnosis • Treatment completion
Notes	Country: Brazil Setting: Urban slums Tuberculosis incidence: 565 per 100,000 population HIV prevalence: not stated Study dates: 2005 to 2006 Study sponsor: United States Agency for International Development and National Institutes of Health grants

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: "14 neighbourhoods were matched into seven pairs with similar 2004 case notification rates using a constrained randomization scheme with a relative difference of 5% between marginal rates. One of these permutations was selected at random using MS Excel's RAND command (MicroSoft, Redmond, WA, USA)."
Allocation concealment (selection bias)	Unclear risk	Comment: None described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: None described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: None described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: None described.
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective outcome reporting

Miller 2010 BRA (*Continued*)

Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Matched study with similar characteristics (low risk) Loss of clusters: Low risk Incorrect analysis: Primary outcome not adjusted for clustering, Cochrane Review adjusts for this (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Morishita 2016 KHM

Methods	Trial design: Quasi-experimental cluster-randomized trial Unit of randomization: Operational district (OD) with estimated population of 100,000 to 200,000 Number of clusters per study arm: 15 ODs Length of follow-up: 1 year Study areas: Cambodia, selected 30 of the 71 ODs.
Participants	Target group: All ages Target population in the intervention: 2.9 million people Exclusions: None Tuberculosis screening test: Tuberculosis symptoms screening (cough, fever, weight loss, and/or night sweats of more than 2 weeks) Tuberculosis diagnostic test: CXR, clinical diagnosis, and Gene Xpert/MTB RIF
Interventions	**Intervention: House-to-house visits** • Did health workers look for tuberculosis cases outside of health facilities? Yes, trained healthcare workers and community volunteers conducted house-to-house visits. **Group 2: No intervention** • Tuberculosis was diagnosed as per national guidelines of self referral patients.
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases starting treatment • Additonal tuberculosis cases detected (microbiologically confirmed)
Notes	Country: Cambodia Setting: Urban/rural Tuberculosis incidence: 715 people with tuberculosis per 100,000 population HIV prevalence: Not mentioned Study dates: Year 1, February to December 2012; Year 2, May 2013 to March 2014 Study sponsor: Government of Japan through Ministry of Health, Labour and Welfare and Korean Centers for Disease Control and Prevention, Republic of Korea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Morishita 2016 KHM (*Continued*)

Random sequence generation (selection bias)	Low risk	Comment: "These 30 ODs were randomly allocated into intervention and control groups"
Allocation concealment (selection bias)	Low risk	Comment: Allocation concealment was not described, however cluster-randomized studies are generally considered to be at low risk of bias for allocation concealment as allocation takes place centrally
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and personnel were not blinded. However, given the nature of the intervention, this was unlikely to introduce bias into the results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: No blinding was done. However, the outcome measurement was unlikely to be biased due to the need for bacteriological confirmation. Also, diagnosis of bacteriologically negative tuberculosis and extra-pulmonary tuberculosis was made by clinicians based on all available evidence on the same day of the active case finding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not described
Selective reporting (reporting bias)	Unclear risk	Comment: Not described
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Not reported (unclear risk) Loss of clusters: None (low risk) Incorrect analysis: Primary outcome not adjusted for clustering, Cochrane Review adjusts for this (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Moyo 2012 ZAF

Methods	Trial design: Individually randomized controlled trial Study areas: Cape Winelands District of South Africa Length of follow-up: 2 years
Participants	Target group: BCG vaccinated infants Sample size: 4786 Exclusions: None described.

	Tuberculosis screening test: Tuberculosis contact or cough/fever/weight loss or loss of appetite for > 2 weeks tuberculosis diagnostic test: CXR, tuberculin test, early morning gastric washing, induced sputum, smear microscopy and culture
Interventions	**Intervention: Home visits and record surveillance** • Did health workers look for tuberculosis cases outside of health facilities? Yes, infants were visited at home every 3 months. • Were there health promotion activities to encourage people with symptoms to attend health services? No. • Were health workers trained in tuberculosis diagnosis? Unclear - not described • Other activities? Surveillance of tuberculosis records, hospital admission lists and records, surveillance of clinical and hospital X-rays **Group 2: Record surveillance only** • Surveillance of tuberculosis records, hospital admission lists and records, surveillance of clinical and hospital X-rays
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases • Mortality
Notes	Country: South Africa Setting: Rural Tuberculosis incidence: 1442 per 100,000 population HIV prevalence: Antenatal HIV prevalence of 12.8% in 2007 Study dates: 2005 to 2008 Study sponsor: Aeras Global TB Vaccine Foundation, Rockville, MD, USA

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Infants were randomised in a 1:1 ratio to Group 1 or Group 2 case finding using simple random allocation. These were assigned from a pre-generated randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "After obtaining consent from a parent or legal guardian, field workers telephoned the study administrator for the infant's randomisation group and study number"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and health workers were not blinded to study group. However, this was unlikely to have biased the outcomes

Moyo 2012 ZAF (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "CXRs were reviewed independently by a panel of three paediatric radiologists who were blinded to the clinical information"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: Moderate losses to follow-up but evenly spread across groups: 14.7% intervention versus 15.3% control group
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Comment: None noted.

Oshi 2016 NGA

Methods	Trial design: Prospective controlled before-and-after study Intervention area: 6 states of Southern Nigeria Control area: 6 states matched by "in most respects" Length of follow-up: 1 year
Participants	Target group: Children aged less than 15 years Total population of intervention area: 14,742,185 children Total number of people screened for tuberculosis in intervention area: 36,214 children Exclusions: None stated. Tuberculosis screening test: A symptom screen Tuberculosis diagnostic test: Sputum smear, Keith Edwards child tuberculosis score
Interventions	**Intervention areas** • Did health workers look for tuberculosis cases outside of health facilities? Yes, screening of home contacts • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, 6000 handbills were distributed in hospitals, schools, and homes; 1500 posters were distributed to communities, schools, and health facilities; and there were 20 visits to primary schools to provide education. • Were health workers trained in tuberculosis diagnosis? Yes, 120 medical officers and 150 nurses were trained in diagnosis and using job aids. • Other activities? 5000 units of PPD were distributed. Screening was also conducted at outpatient clinics and ART clinics. **Control areas** • No intervention
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases in the intervention areas. Data from the control areas were not presented.

Notes	Country: Nigeria Setting: Not specified Tuberculosis prevalence: Not stated HIV prevalence: Not stated Study dates: 1 July 2013 to 30 June 2014 Study sponsor: Canadian International Development Agency

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Comment: Not randomized
Allocation concealment (selection bias)	High risk	Comment: Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and personnel were not blinded, however there was a low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not described
Selective reporting (reporting bias)	Unclear risk	Comment: Tuberculosis cases detected in the control areas were not clearly reported
Other bias	Low risk	**ROBINS-I bias domains** Confounding: None expected (low risk). Selection of participants: All eligible participants were included (low risk) Classification of interventions: Facilities with highest number of children were purposefully selected (moderate risk) Deviations from intended interventions: Some of the interventions were not noted, though their impact is limited (moderate risk) Missing data: Expected to have similar missing data (low risk) Measurement of outcomes: The outcome measure could be minimally influenced by knowledge of the intervention (moderate risk) Selection of reported results: None (low risk)

Reddy 2015 IND

Methods	Trial design: Controlled before-and-after study Intervention area: 20 designated microscopy centres (which serve vulnerable populations) Control area: 11 designated microscopy centres (which serve less vulnerable populations) Length of follow-up: 6 months
Participants	Target group: Adults and children from vulnerable communities Total population of intervention area: Approximately 2 million Total number of people screened for tuberculosis in intervention area: 8468/115,119 households were visited Exclusions: None stated. Tuberculosis screening test: "presumptive" - probably clinical criteria Tuberculosis diagnostic test: Sputum smear
Interventions	**Intervention areas** • Did health workers look for tuberculosis cases outside of health facilities? Yes, trained community volunteers visited the homes of people in vulnerable communities. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, information, education, and communication materials were given to each visited house. • Were health workers trained in tuberculosis diagnosis? Yes, volunteers described as "trained". **Control areas** • Standard facility-based care
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected
Notes	Country: India Setting: 2 districts of Karnataka in Southern India Tuberculosis prevalence: Not stated HIV prevalence: Not stated Study dates: July to December 2013 compared to July to December 2012 Study sponsor: United States Agency for International Development (USAID)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Comment: Non-randomized trial
Allocation concealment (selection bias)	High risk	Comment: Non-randomized trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Participants and personnel were not blinded, however there was a low risk of bias

Reddy 2015 IND (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: Not described
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	**ROBINS-I bias domains** Confounding: Confounding expected (moderate risk). Selection of participants: Selected population that was vulnerable (moderate risk) Classification of interventions: The interventions were determined retrospectively (moderate risk) Deviations from intended interventions: None expected (low risk) Missing data: Not documented (low risk) Measurement of outcomes: Minimal errors related to outcome (moderate risk) Selection of reported results: None (low risk)

Shargie 2006 ETH

Methods	Trial design: Cluster-RCT Unit of randomization: Rural communities - approximate size 11,000 people Number of clusters per study group: 12 intervention versus 20 control Length of follow-up: 6 months Adjusted for cluster design: Yes
Participants	Target group: All ages Total population of intervention areas: 127,607 Total number of people screened for tuberculosis in intervention area: Not stated Exclusions: None stated. Tuberculosis screening test: Symptom screening; criteria not described Tuberculosis diagnostic test: Sputum smear microscopy
Interventions	**Intervention: Outreach clinics and health promotion** • Did health workers look for tuberculosis cases outside of health facilities? Yes, health workers conducted monthly outreach clinics in each kebele. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, health promoters visited houses, distributed leaflets and posters, and promoted messages at schools and public gatherings. • Were health workers trained in tuberculosis diagnosis? Yes, 4 days training on case

	finding, diagnostic procedures, handling of sputum. **Group 2** • No intervention
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases detected • Tuberculosis treatment completion • Default • Tuberculosis mortality
Notes	Country: Ethiopia Setting: Rural districts Tuberculosis prevalence: Not stated HIV prevalence: Not stated Study dates: 1 May 2003 to 30 April 2004 Study sponsor: The Centre for International Health, University of Bergen

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: Described as "randomised"; no further details given
Allocation concealment (selection bias)	Unclear risk	Comment: Not described, but usually low risk in cluster-randomized trials if the sequence generation is low risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: None described, but unlikely to bias the results of the trial
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: None described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No loss of clusters. No other losses described.
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: None (low risk) Incorrect analysis: Primary outcome adjusted for clustering. Comparability with RCTs randomizing in-

Shargie 2006 ETH (*Continued*)

		dividuals: Unclear risk

Talukder 2012 BGD

Methods	Trial design: Cluster-RCT Unit of randomization: Microscopy centres Number of clusters per study group: 18 Length of follow-up: 12 months Adjusted for cluster design: Not described
Participants	Target group: Children aged less than 14 years Total population of study areas: Not stated Total number of people screened for tuberculosis in intervention area: 1943 Exclusions: None stated. Tuberculosis screening test: None described. Tuberculosis diagnostic test: Keith Edwards tuberculosis score
Interventions	**Intervention: Training of health staff and health promotion** • Did health workers look for tuberculosis cases outside of health facilities? No. • Were there health promotion activities to encourage people with symptoms to attend health services? Yes, health education sessions using flip charts, posters and pamphlets at tuberculosis clubs, village doctor meetings, girl guide and boy scout meetings. • Were health workers trained in tuberculosis diagnosis? Yes, health workers were trained to weigh children, assess severe malnutrition, perform the Mantoux test, and use the Keith Edwards Child Tuberculosis score chart. **Control** • No intervention
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases
Notes	Country: Bangladesh Setting: Unclear Tuberculosis prevalence: 207 per 100,000 adults HIV prevalence: Not reported Study dates: 2007 to 2009 Study sponsor: Damien Foundation Bangladesh

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "One intervention centre was randomly selected from each district, and two from the larger districts containing more than the median number of centres. A similar number of control microscopy centres were selected in the same districts"

Talukder 2012 BGD (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment: Not described, but usually low risk for cluster-randomized trials if the random sequence is low risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: No blinding of participants or health workers described, but this is unlikely to bias the results separate from the effects of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: None described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: No loss of clusters occurred. No other losses reported
Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting.
Other bias	Low risk	Recruitment bias: Low risk Baseline imbalance: Similar characteristics (low risk) Loss of clusters: None (low risk) Incorrect analysis: Primary outcome not adjusted for clustering, Cochrane Review adjusts for this (low risk) Comparability with RCTs randomizing individuals: Unclear risk

Yassin 2013 ETH

Methods	Trial design: Non-RCT Intervention area: Sidima zone, Southern Ethiopia Control area: Hadiya zone, Southern Ethiopia Length of follow-up: 14 months
Participants	Target group: All ages Total population of intervention area: Over 3 million Total number of people screened for tuberculosis in intervention area: Not stated Exclusions: None stated. Tuberculosis screening test: Symptom screen: cough > 2 weeks Tuberculosis diagnostic test: Sputum smear microscopy
Interventions	**Intervention areas: Training of health extension workers to visit houses and screen for tuberculosis** • Did health workers look for tuberculosis cases outside of health facilities? Yes, health extension workers went house to house using a symptom screen. • Were there health promotion activities to encourage people with symptoms to

	attend health services? Yes, community meetings, campaigns, and local radio. • Were health workers trained in tuberculosis diagnosis? Yes, health extension workers were trained to screen for chronic cough and collect, store, and transport sputum samples. • Additional activities: Awareness creation workshops for political, community, and religious leaders, teachers and other stakeholders. Improvement in laboratory services, and supervision of health extension workers. **Control areas: No intervention** • Health extension workers did not receive training, but provided health services including health education about tuberculosis to people in their kebeles.
Outcomes	**Outcomes included in the review** • Additional tuberculosis cases • Tuberculosis cure • Treatment completion • Early default (prior to commencing treatment or during the intensive phase of treatment) • Tuberculosis mortality
Notes	Country: Ethiopia Setting: Community based Tuberculosis prevalence: 127 per 100,000 population HIV prevalence: Not stated Study dates: October 2010 to December 2011 Study sponsor: TB REACH Initiative of the Stop TB Partnership (through a grant from the Canadian International Development Agency)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: Not randomized
Allocation concealment (selection bias)	High risk	Comment: Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: Health workers and populations were not blind to the allocation, but this was unlikely to bias the effect of the intervention
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: The number of lost or invalid sputum smears was not reported

Yassin 2013 ETH (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: No evidence of selective reporting
Other bias	Low risk	**ROBINS-I bias domains** Confounding: Minimal confounding (moderate risk) Selection of participants: All study participants were included (low risk) Classification of interventions: Intervention status is well defined (low risk) Deviations from intended interventions: None expected (low risk) Missing data: None (low risk) Measurement of outcomes: Comparable between groups (low risk) Selection of reported results: None (low risk)

Abbreviations: AFB: acid-fast bacilli; ART: antiretroviral therapy; BCG: bacille Calmette-Guerin; CXR: chest X-ray; PPD: purified protein derivative; RCT: randomized controlled trial; TB: tuberculosis.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdurrahman 2017	No community-level interventions
Ade 2016	No community-level interventions
Adejumo 2016	No parallel control group
Anger 2012	No parallel control group
Arora 2004	No parallel control group reported. A control area is described, but TB outcomes are only reported for the area with the intervention
Atif 2013	No intervention to increase TB diagnosis
Bai 2008	No parallel control group
Balcha 2015	Intervention not at the primary care level. No parallel control group
Bassili 2011	No intervention to increase TB diagnosis

(*Continued*)

Bernard 2012	No parallel control group
Bothamley 2008	No intervention to increase TB diagnosis
Charles 2016	No parallel control group
Churchyard 2011	No community-level interventions. This study was conducted among gold mine workers, not the general population
Del Portillo-Mustieles 2013	No community-level intervention
Delva 2016	No parallel control group
den Boon 2008	No parallel control group
Dholakia 2016	No community-level interventions
Dobler 2016	No community-level interventions
Eang 2012	No parallel control group
Elden 2011	No parallel control group
Fatima 2016	No parallel control group
Fox 2012	No parallel control group
Furin 2007	No parallel control group
Gebi 2009	No parallel control group
Gilpin 1987	No parallel control group
Gonzalez-Ochoa 2009	No parallel control group
Gorbacheva 2010	No parallel control group
Gounder 2011	No parallel control group
Griffiths 2007	Done in low-burden settings
Hermans 2012	No community-level intervention
Hinderaker 2011a	No parallel control group. This paper describes 51 individual projects that aimed to detect TB cases. However, none of these projects had parallel control groups, and instead were compared with routinely collected data from the year before

(*Continued*)

Hossain 2010	No parallel control group
Kaboru 2013	No parallel control group
Kakinda 2016	No parallel control group
Khan 2007	No intervention to increase TB diagnosis
Kuznetsov 2014	No parallel control group
Lebina 2016	No parallel control group
Ntinginya 2012	No parallel control group
Oshi 2016	No parallel control group
Prasad 2016	No parallel control group
Pronyk 2001	Not a TB case-finding study
Ruutel 2011	Not a relevent comparison. This study screened intravenous drug users participating in a methadone substitution programme for TB. It then compares active referral with passive referral. Study does not compare a TB case-finding intervention with no intervention
Sanaie 2016	No parallel control group
Sekandi 2009	No parallel control group
Sekandi 2014	No parallel control group
Shapiro 2012	Not a relevent comparison. This study compares the prevalence of TB in houses with a TB contact and houses without a TB contact. It does not compare a TB case-finding intervention with no intervention
Shrivastava 2012	No parallel control group
Soares 2013	No parallel control group
Ssemmondo 2016	No parallel control group
Story 2012	No parallel control group
Szkwarko 2016	No parallel control group
Uwimana 2012	No outcomes relevent to this review
Wei 2015	No community-level intervention. This study was done in smokers

(*Continued*)

Yimer 2009a	No parallel control group
Yimer 2009b	No parallel control group
Zhang 2011	No parallel control group

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chen 1990

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Duanmu 2005

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Gadala 2015

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Grzybowski 1965

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Jensen 2015

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Nadu 2004

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Poliakova 2015

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

Ursov 1970

Methods	Not stated
Participants	Not stated
Interventions	Not stated
Outcomes	Not stated
Notes	Not stated

DATA AND ANALYSES

Comparison 1. Outreach tuberculosis screening versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	4	163043	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.86, 1.79]
2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence	4	163043	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.92, 1.46]
2.1 Prevalence < 5%	1	7125	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]
2.2 Prevalence 5%+	3	155918	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.10, 2.09]
3 Tuberculosis cases detected; subgrouped by intervention	4	163043	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.86, 1.79]
3.1 Outreach clinics plus health promotion	1	52405	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.76, 2.17]
3.2 House-to-house screening plus health promotion	3	110638	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.75, 2.08]
4 Tuberculosis cases detected (all forms)	1	28704	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.83, 1.98]
5 Tuberculosis treatment default	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.96]
6 Tuberculosis treatment success	3	849	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [1.00, 1.15]
7 Tuberculosis treatment failure	3	849	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.50, 4.92]
8 Tuberculosis mortality	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.43, 2.25]
9 Long-term tuberculosis prevalence	1		Risk Ratio (Fixed, 95% CI)	1.14 [0.65, 2.00]

Comparison 2. Health promotion activities compared to no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long-term tuberculosis prevalence	1		Risk Ratio (Fixed, 95% CI)	Totals not selected

Comparison 3. Training interventions compared to intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 4. Outreach tuberculosis services versus health promotion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	1		Risk Ratio (Fixed, 95% CI)	Totals not selected
1.1 Adjusted for cluster design	1		Risk Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 5. Outreach clinic versus house-to-house screening

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	1		Risk Ratio (Random, 95% CI)	Totals not selected
1.1 Adjusted for cluster design	1		Risk Ratio (Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 6. Active case-finding interventions versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence	5	164532	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.01, 1.53]
2.1 Prevalence < 5%	1	7125	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]
2.2 Prevalence 5%+	4	157407	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.20, 2.04]
3 Tuberculosis cases detected; subgrouped by intervention	7		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 House-to-house screening plus health promotion	3	305698	Risk Ratio (Random, 95% CI)	1.30 [0.84, 2.03]

3.2 Outreach tuberculosis diagnosis clinics plus health promotion	2	463323	Risk Ratio (Random, 95% CI)	1.43 [1.11, 1.84]
3.3 Health promotion activities alone	1	405788	Risk Ratio (Random, 95% CI)	1.31 [0.75, 2.29]
3.4 Health staff training in tuberculosis diagnosis	1	1999	Risk Ratio (Random, 95% CI)	1.68 [1.03, 2.73]
4 Long-term tuberculosis prevalence: subgrouped by intervention	1		Risk Ratio (Fixed, 95% CI)	1.22 [0.82, 1.82]
4.1 Contact tracing plus health promotion activities	1		Risk Ratio (Fixed, 95% CI)	1.14 [0.65, 2.00]
4.2 Health promotion activities alone	1		Risk Ratio (Fixed, 95% CI)	1.31 [0.75, 2.29]
5 Tuberculosis treatment success	3	862	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.00, 1.15]
6 Tuberculosis treatment default	4	3034	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.47, 0.83]
7 Tuberculosis treatment failure	3	862	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.50, 5.26]
8 Tuberculosis mortality	3	862	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.43, 2.31]
9 People with tuberculosis detected	3	134339	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.89, 1.44]
9.1 Prevalence < 5%	1	7125	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]
9.2 Prevalence 5%+	2	127214	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.07, 2.19]

Comparison 7. Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tuberculosis cases detected (microbiologically confirmed)	4	163043	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.86, 1.79]
2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence	4	163043	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.92, 1.46]
2.1 Prevalence < 5%	1	7125	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]
2.2 Prevalence 5%+	3	155918	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.10, 2.09]
3 Tuberculosis cases detected; subgrouped by intervention	4	163043	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.86, 1.79]
3.1 Outreach clinics plus health promotion	1	52405	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.76, 2.17]
3.2 House-to-house screening plus health promotion	3	110638	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.75, 2.08]
4 Tuberculosis cases detected (all forms)	1	28704	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.83, 1.98]
5 Tuberculosis treatment default	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Raw data	3	862	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.97]
5.2 Adjusted with ICC = 0.001	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.47, 0.96]
5.3 Adjusted ICC = 0.00052 (Datiko)	3	855	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.98]
6 Tuberculosis treatment success	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

6.1 Raw data	3	862	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [1.00, 1.15]
6.2 Cluster adjusted: ICC = 0.001	3	849	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [1.00, 1.15]
7 Tuberculosis treatment failure	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Raw data	3	862	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.50, 5.26]
7.2 Cluster adjusted: ICC = 0.001	3	849	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.50, 5.26]
8 Tuberculosis mortality	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Raw data	3	862	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.43, 2.25]
8.2 Cluster adjusted: ICC = 0.001	3	849	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.43, 2.25]
9 Long-term tuberculosis prevalence	1		Risk Ratio (Fixed, 95% CI)	1.14 [0.65, 2.00]

Analysis 1.1. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF (1)	60/3558	71/3567		33.4 %	0.85 [0.60, 1.19]
Datiko 2009 ETH (2)	58/44898	22/29911		25.5 %	1.76 [1.08, 2.87]
Morishita 2016 KHM (3)	19/14352	13/14352		17.2 %	1.46 [0.72, 2.96]
Shargie 2006 ETH (4)	24/18950	33/33455		23.9 %	1.28 [0.76, 2.17]
Total (95% CI)	**81758**	**81285**		**100.0 %**	**1.24 [0.86, 1.79]**

Total events: 161 (Intervention), 139 (Control)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.58$, df = 3 (P = 0.09); $I^2 = 54\%$

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

(1) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

(2) Adjusted for clustering with trial's ICC of 0.00052

(3) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

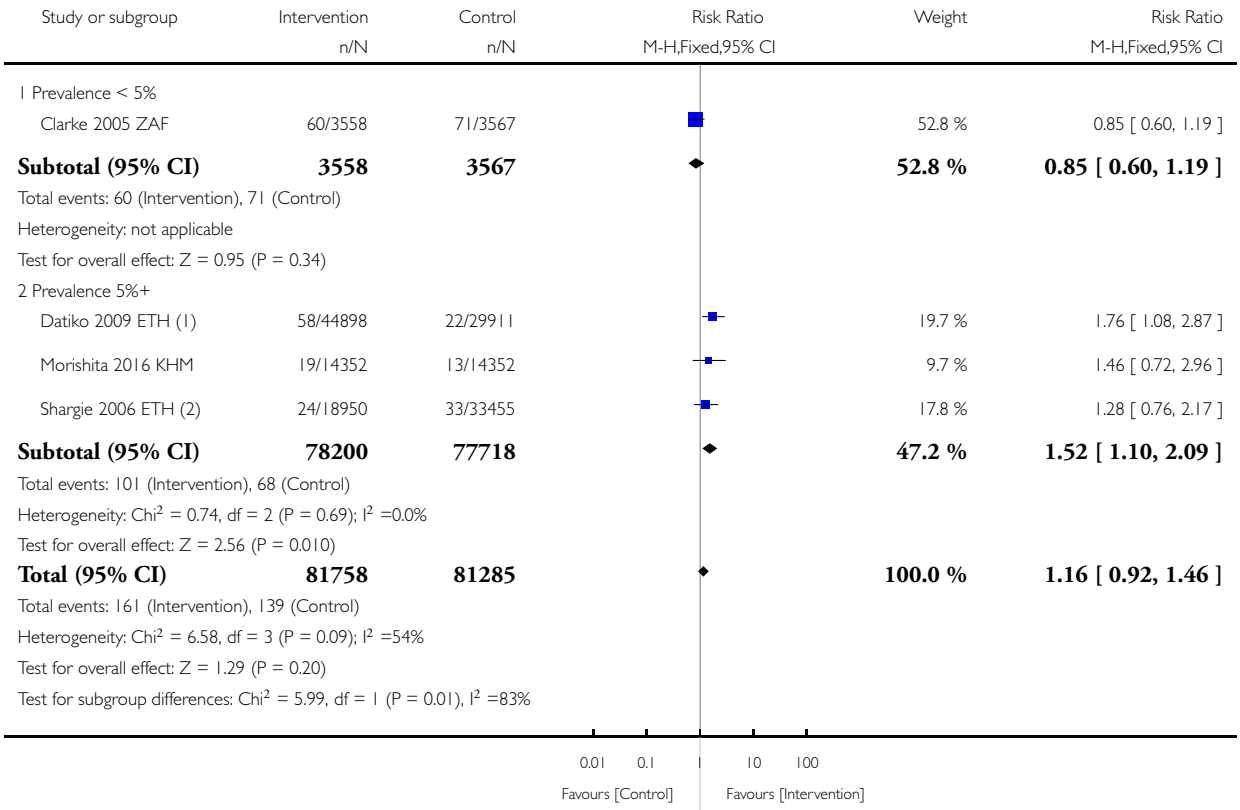
(4) Adjusted for clustering with trial's ICC of 0.00027

Analysis 1.2. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence



(1) Datiko 2009 ETH: This paper presented an ICC of 0.00052

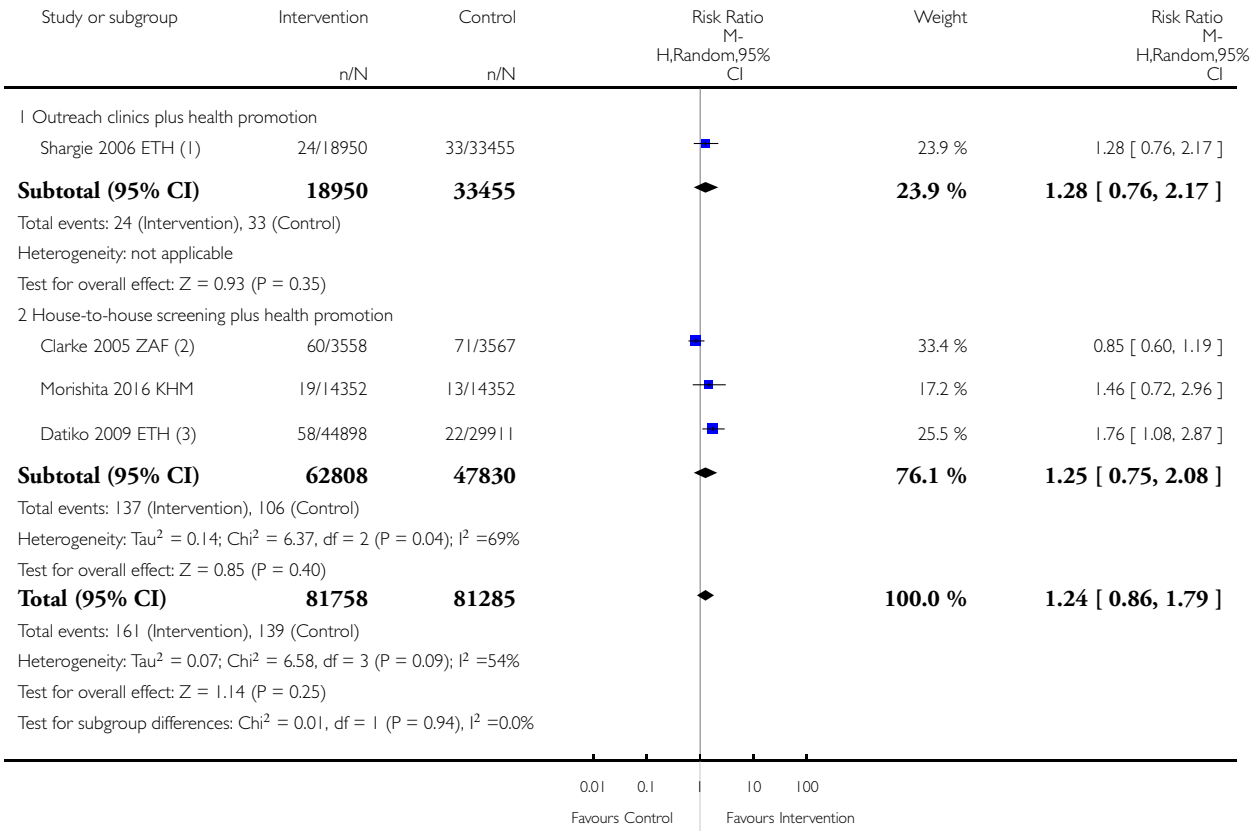
(2) Shargie 2006 ETH: This paper presented an ICC of 0.00027; when the raw data was approximately adjusted using this ICC the result was also not statistically significant.

Analysis 1.3. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 3 Tuberculosis cases detected; subgrouped by intervention.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 3 Tuberculosis cases detected; subgrouped by intervention



(1) Shargie 2006: Total diagnosed cases over 1 year follow-up

(2) Clarke 2005 ZAF:

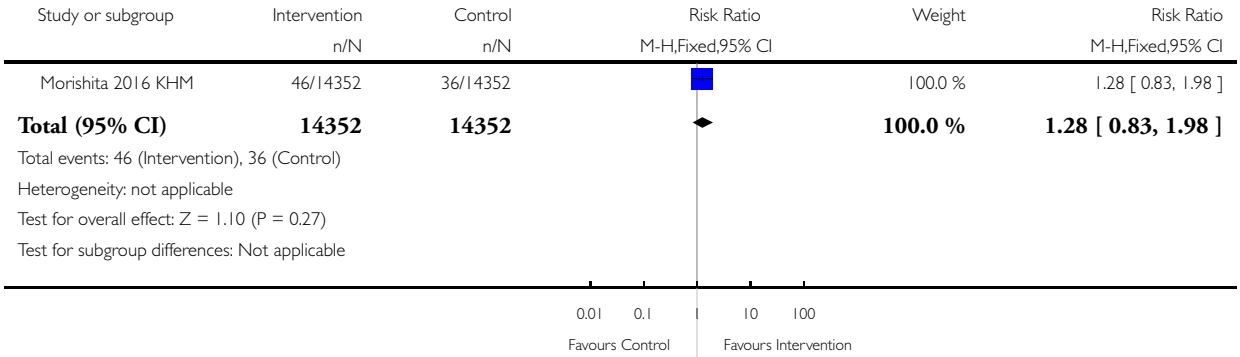
(3) Datiko 2009: Total diagnosed cases over 1 year follow-up

Analysis 1.4. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 4 Tuberculosis cases detected (all forms).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 4 Tuberculosis cases detected (all forms)

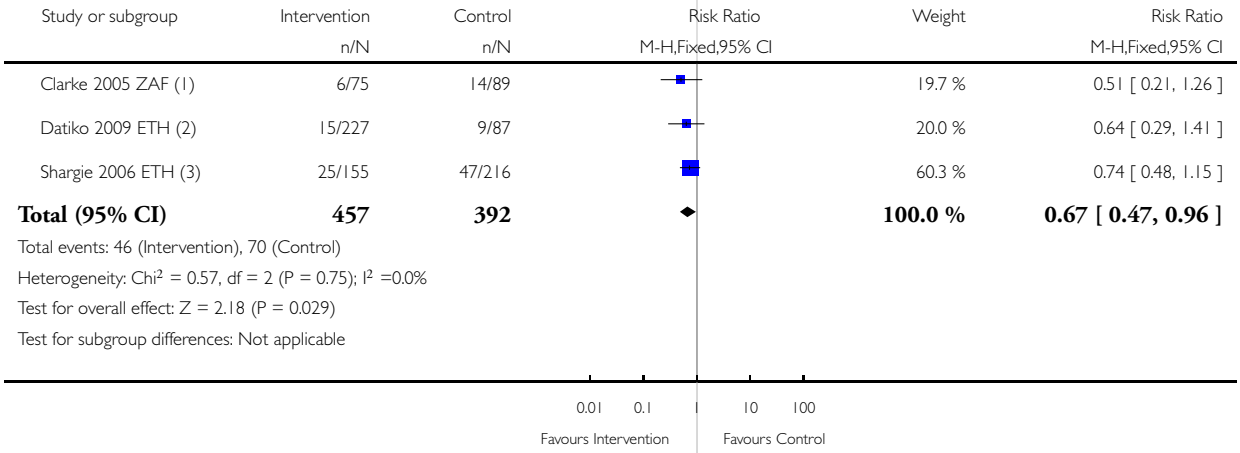


Analysis 1.5. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 5 Tuberculosis treatment default.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 5 Tuberculosis treatment default



(1) Adjusted for clustering with ICC of 0.001

(2) Adjusted for clustering with ICC of 0.001

(3) Adjusted for clustering with ICC of 0.001

Analysis 1.6. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 6 Tuberculosis treatment success.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 6 Tuberculosis treatment success

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clarke 2005 ZAF (1)	61/75	67/89		20.3 %	1.08 [0.92, 1.27]
Datiko 2009 ETH (2)	202/227	73/87		35.0 %	1.06 [0.96, 1.18]
Shargie 2006 ETH (3)	125/155	161/216		44.6 %	1.08 [0.97, 1.21]
Total (95% CI)	**457**	**392**		**100.0 %**	**1.07 [1.00, 1.15]**

Total events: 388 (Intervention), 301 (Control)

Heterogeneity: $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 2.03 (P = 0.042)

Test for subgroup differences: Not applicable

(1) Adjusted for clustering with ICC of 0.001

(2) Adjusted for clustering with ICC of 0.001

(3) Adjusted for clustering with ICC of 0.001

Analysis 1.7. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 7 Tuberculosis treatment failure.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 7 Tuberculosis treatment failure

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clarke 2005 ZAF (1)	5/75	3/89		58.1 %	1.98 [0.49, 8.00]
Datiko 2009 ETH (2)	2/227	0/87		15.3 %	1.93 [0.09, 39.80]
Shargie 2006 ETH (3)	0/155	1/216		26.6 %	0.46 [0.02, 11.31]
Total (95% CI)	**457**	**392**		**100.0 %**	**1.57 [0.50, 4.92]**

Total events: 7 (Intervention), 4 (Control)

Heterogeneity: $Chi^2 = 0.68$, df = 2 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 0.77 (P = 0.44)

Test for subgroup differences: Not applicable

(1) Adjusted for clustering with ICC of 0.001

(2) Adjusted for clustering with ICC of 0.001

(3) Adjusted for clustering with ICC of 0.001

Analysis 1.8. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 8 Tuberculosis mortality.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 8 Tuberculosis mortality

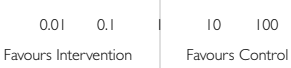
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Clarke 2005 ZAF (1)	1/75	3/89		23.9 %	0.40 [0.04, 3.72]
Datiko 2009 ETH (2)	8/227	2/87		25.2 %	1.53 [0.33, 7.08]
Shargie 2006 ETH (3)	5/155	7/216		50.9 %	1.00 [0.32, 3.08]
Total (95% CI)	**457**	**392**		**100.0 %**	**0.99 [0.43, 2.25]**

Total events: 14 (Intervention), 12 (Control)

Heterogeneity: $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.03 (P = 0.98)

Test for subgroup differences: Not applicable



(1) Adjusted for clustering with ICC of 0.001

(2) Adjusted for clustering with ICC of 0.001

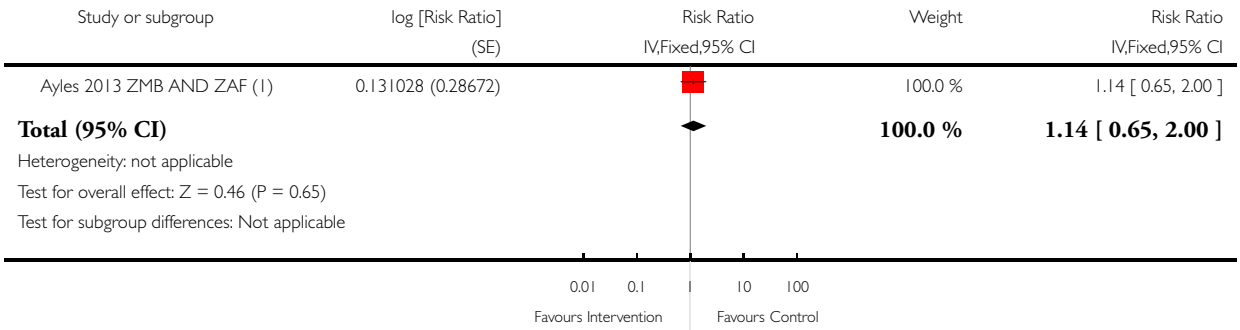
(3) Adjusted for clustering with ICC of 0.001

Analysis 1.9. Comparison 1 Outreach tuberculosis screening versus no intervention, Outcome 9 Long-term tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 1 Outreach tuberculosis screening versus no intervention

Outcome: 9 Long-term tuberculosis prevalence



(1) Ayles 2013: Adjusted for the cluster design.

Analysis 2.1. Comparison 2 Health promotion activities compared to no intervention, Outcome 1 Long-term tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 2 Health promotion activities compared to no intervention

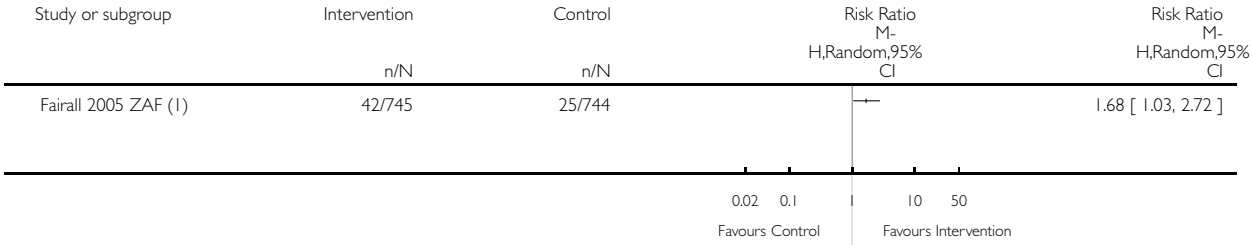
Outcome: 1 Long-term tuberculosis prevalence

Analysis 3.1. Comparison 3 Training interventions compared to intervention, Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 3 Training interventions compared to intervention

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)



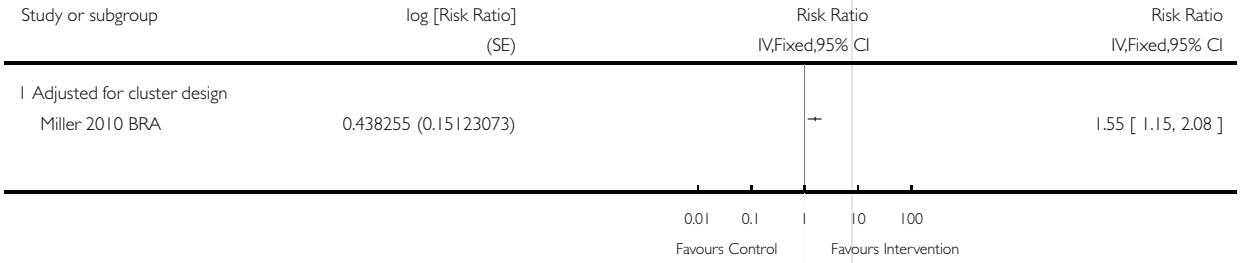
(1) Adjusted for clustering with ICC of 0.007

Analysis 4.1. Comparison 4 Outreach tuberculosis services versus health promotion, Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 4 Outreach tuberculosis services versus health promotion

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)

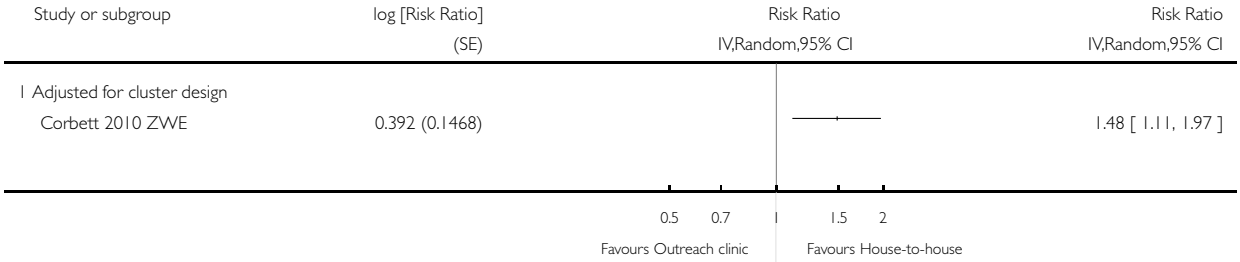


Analysis 5.1. Comparison 5 Outreach clinic versus house-to-house screening, Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 5 Outreach clinic versus house-to-house screening

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)

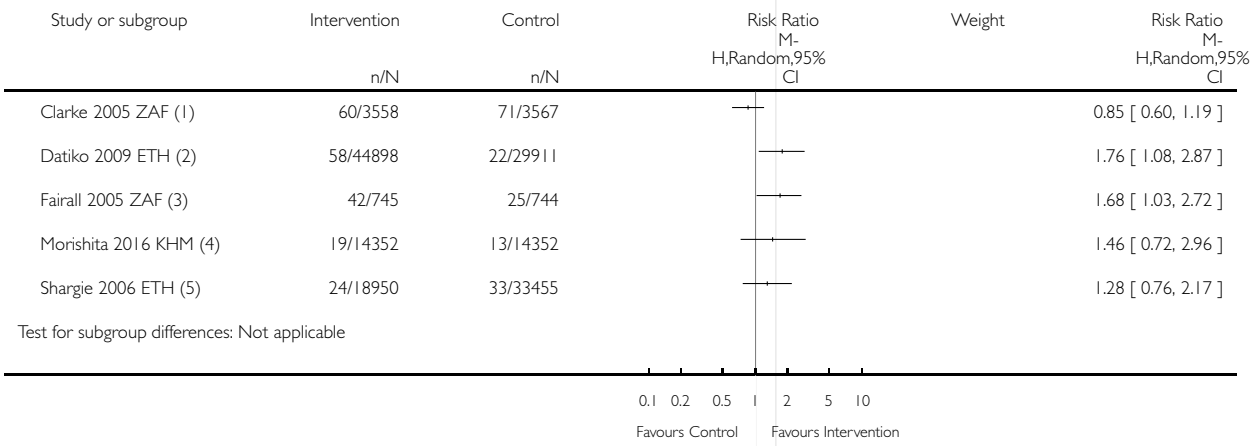


Analysis 6.1. Comparison 6 Active case-finding interventions versus no intervention, Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)



(1) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

(2) Datiko 2009 ETH: This paper presented an ICC of 0.00052

(3) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

(4) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

(5) Shargie 2006 ETH: This paper presented an ICC of 0.00027; when the raw data was approximately adjusted using this ICC the result was also not statistically significant.

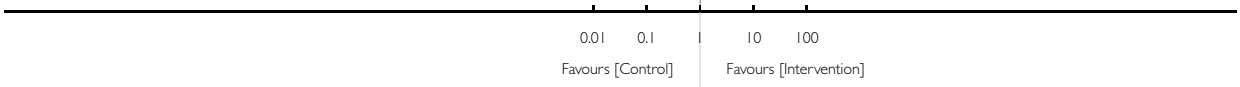
Analysis 6.2. Comparison 6 Active case-finding interventions versus no intervention, Outcome 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Prevalence < 5%					
Clarke 2005 ZAF	60/3558	71/3567		44.5 %	0.85 [0.60, 1.19]
Subtotal (95% CI)	**3558**	**3567**		**44.5 %**	**0.85 [0.60, 1.19]**
Total events: 60 (Intervention), 71 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
2 Prevalence 5%+					
Datiko 2009 ETH (1)	58/44898	22/29911		16.6 %	1.76 [1.08, 2.87]
Fairall 2005 ZAF	42/745	25/744		15.7 %	1.68 [1.03, 2.72]
Morishita 2016 KHM	19/14352	13/14352		8.2 %	1.46 [0.72, 2.96]
Shargie 2006 ETH (2)	24/18950	33/33455		15.0 %	1.28 [0.76, 2.17]
Subtotal (95% CI)	**78945**	**78462**		**55.5 %**	**1.56 [1.20, 2.04]**
Total events: 143 (Intervention), 93 (Control)					
Heterogeneity: Chi^2 = 0.87, df = 3 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 3.28 (P = 0.0010)					
Total (95% CI)	**82503**	**82029**		**100.0 %**	**1.24 [1.01, 1.53]**
Total events: 203 (Intervention), 164 (Control)					
Heterogeneity: Chi^2 = 8.47, df = 4 (P = 0.08); I^2 =53%					
Test for overall effect: Z = 2.06 (P = 0.039)					
Test for subgroup differences: Chi^2 = 7.70, df = 1 (P = 0.01), I^2 =87%					



(1) Datiko 2009 ETH: This paper presented an ICC of 0.00052

(2) Shargie 2006 ETH: This paper presented an ICC of 0.00027; when the raw data was approximately adjusted using this ICC the result was also not statistically significant.

Analysis 6.3. Comparison 6 Active case-finding interventions versus no intervention, Outcome 3 Tuberculosis cases detected; subgrouped by intervention.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 3 Tuberculosis cases detected; subgrouped by intervention

Study or subgroup	Experimental N	Control N	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 House-to-house screening plus health promotion						
Clarke 2005 ZAF (1)	4438	4449	-0.16252 (0.1746885)		34.7 %	0.85 [0.60, 1.20]
Datiko 2009 ETH (2)	178138	118673	0.565314 (0.24932423)		28.6 %	1.76 [1.08, 2.87]
Miller 2010 BRA (3)	0	0	0.438255 (0.15123073)		36.6 %	1.55 [1.15, 2.08]
Subtotal (95% CI)	**182576**	**123122**			**100.0 %**	**1.30 [0.84, 2.03]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.72$, df = 2 (P = 0.01); $I^2 = 77\%$						
Test for overall effect: Z = 1.17 (P = 0.24)						
2 Outreach tuberculosis diagnosis clinics plus health promotion						
Corbett 2010 ZWE (4)	55741	54691	0.392 (0.1468)		76.9 %	1.48 [1.11, 1.97]
Shargie 2006 ETH (5)	127607	225284	0.24686 (0.26764388)		23.1 %	1.28 [0.76, 2.16]
Subtotal (95% CI)	**183348**	**279975**			**100.0 %**	**1.43 [1.11, 1.84]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$						
Test for overall effect: Z = 2.78 (P = 0.0054)						
3 Health promotion activities alone						
Ayles 2013 ZMB AND ZAF	148090	257698	0.270027 (0.28587)		100.0 %	1.31 [0.75, 2.29]
Subtotal (95% CI)	**148090**	**257698**			**100.0 %**	**1.31 [0.75, 2.29]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.94 (P = 0.34)						
4 Health staff training in tuberculosis diagnosis						
Fairall 2005 ZAF (6)	1000	999	0.518794 (0.24772272)		100.0 %	1.68 [1.03, 2.73]
Subtotal (95% CI)	**1000**	**999**			**100.0 %**	**1.68 [1.03, 2.73]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.09 (P = 0.036)						
Test for subgroup differences: $Chi^2 = 0.68$, df = 3 (P = 0.88), $I^2 = 0.0\%$						

(1) Clarke 2005 ZAF:

(2) Datiko 2009 ETH: Compared house-to-house visits every 2-4 weeks plus health promotion activities versus standard care

(3) Miller 2010 BRA: Compared House-to-house visits versus health promotion activities: Therefore teh effects of house-house visits may be underestimated

(4) Corbett 2010 ZWE: Compared a 6 monthly mobile clinic versus 6 monthly house-to-house screening - Therefore the effect of outreach clinics may be underestimated

(5) Shargie 2006 ETH: Compared monthly TB diagnostic outreach clinics versus standard care

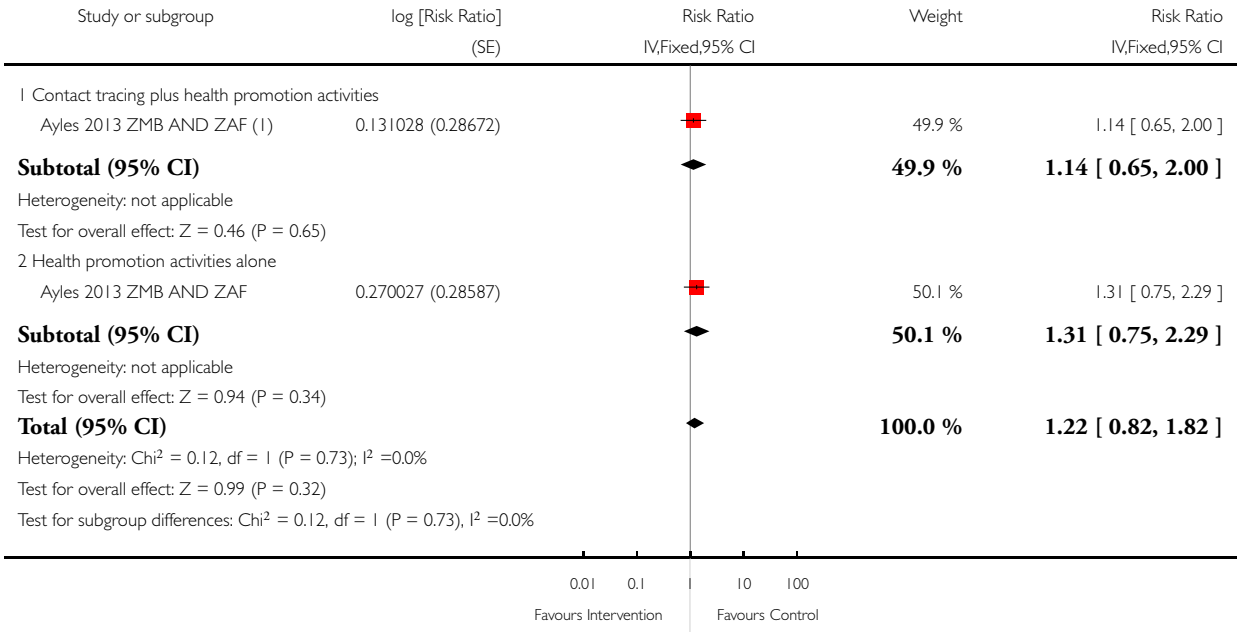
(6) Fairall 2005 ZAF: Compared 2-6 training session with nurses versus no intervention

Analysis 6.4. Comparison 6 Active case-finding interventions versus no intervention, Outcome 4 Long-term tuberculosis prevalence: subgrouped by intervention.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 4 Long-term tuberculosis prevalence: subgrouped by intervention



(1) Ayles 2013: Adjusted for the cluster design.

Analysis 6.5. Comparison 6 Active case-finding interventions versus no intervention, Outcome 5 Tuberculosis treatment success.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 5 Tuberculosis treatment success

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF (1)	61/75	67/89		17.5 %	1.08 [0.92, 1.27]
Datiko 2009 ETH (2)	205/230	74/88		44.0 %	1.06 [0.96, 1.17]
Shargie 2006 ETH (3)	128/159	165/221		38.5 %	1.08 [0.97, 1.20]
Total (95% CI)	**464**	**398**		**100.0 %**	**1.07 [1.00, 1.15]**

Total events: 394 (Intervention), 306 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.07$, df = 2 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 1.98 (P = 0.047)

Test for subgroup differences: Not applicable

(1) Clarke 2005 ZAF: 'Success' defined as the sum of those who were cured (had a negative smear during the last month of treatment) and those who completed treatment.

(2) Datiko 2009 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at 7 months) and those who completed treatment without confirmation by smear microscopy.

(3) Shargie 2006 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at the end of treatment) and those who completed treatment without confirmation by smear microscopy.

Analysis 6.6. Comparison 6 Active case-finding interventions versus no intervention, Outcome 6 Tuberculosis treatment default.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 6 Tuberculosis treatment default

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF (1)	6/75	14/89		9.9 %	0.51 [0.21, 1.26]
Datiko 2009 ETH (2)	15/230	9/88		13.0 %	0.64 [0.29, 1.40]
Morishita 2016 KHM	46/1725	23/447		33.7 %	0.52 [0.32, 0.85]
Shargie 2006 ETH (3)	26/159	48/221		43.4 %	0.75 [0.49, 1.16]
Total (95% CI)	**2189**	**845**		**100.0 %**	**0.62 [0.47, 0.83]**

Total events: 93 (Intervention), 94 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.48$, df = 3 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 3.24 (P = 0.0012)

Test for subgroup differences: Not applicable

(1) Datiko 2009 ETH: Default defined as: A patient who missed at least two months of treatment.

(2) Datiko 2009 ETH: Default defined as: A patient who missed eight consecutive weeks of treatment after receiving at leats 4 weeks of treatment.

(3) Shargie 2006 ETH: Default defined as: A patient who missed eight consecutive weeks of treatment after receiving at leats 4 weeks of treatment.

Analysis 6.7. Comparison 6 Active case-finding interventions versus no intervention, Outcome 7 Tuberculosis treatment failure.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 7 Tuberculosis treatment failure

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF (1)	5/75	3/89		71.2 %	1.98 [0.49, 8.00]
Datiko 2009 ETH (2)	2/230	0/88		15.2 %	1.93 [0.09, 39.73]
Shargie 2006 ETH (3)	0/159	1/221		13.6 %	0.46 [0.02, 11.28]
Total (95% CI)	**464**	**398**		**100.0 %**	**1.62 [0.50, 5.26]**

Total events: 7 (Intervention), 4 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.69$, df = 2 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 0.80 (P = 0.43)

Test for subgroup differences: Not applicable

(1) Clarke 2005 ZAF: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(2) Datiko 2009 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(3) Shargie 2006 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

Analysis 6.8. Comparison 6 Active case-finding interventions versus no intervention, Outcome 8 Tuberculosis mortality.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 8 Tuberculosis mortality

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF	1/75	3/89		14.1 %	0.40 [0.04, 3.72]
Datiko 2009 ETH	8/230	2/88		30.3 %	1.53 [0.33, 7.07]
Shargie 2006 ETH	5/159	7/221		55.6 %	0.99 [0.32, 3.07]
Total (95% CI)	**464**	**398**		**100.0 %**	**0.99 [0.43, 2.31]**

Total events: 14 (Intervention), 12 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.95$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.01 (P = 0.99)

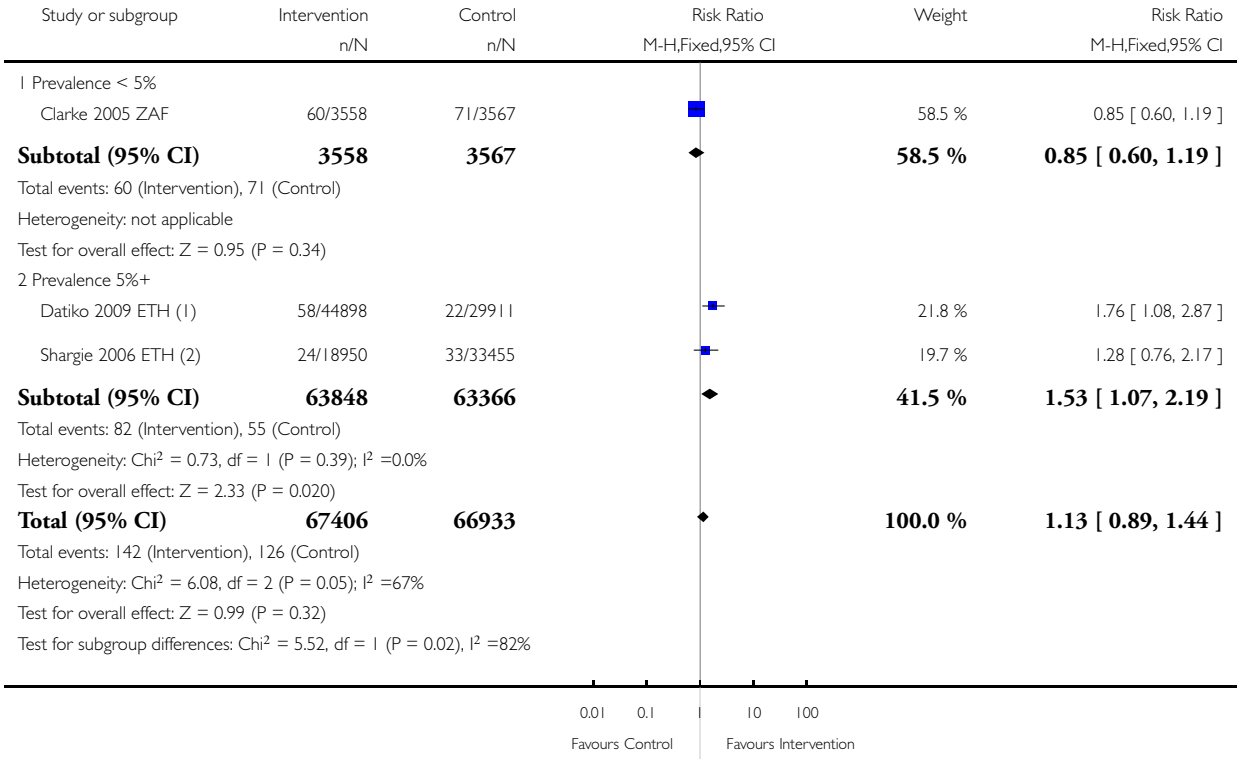
Test for subgroup differences: Not applicable

Analysis 6.9. Comparison 6 Active case-finding interventions versus no intervention, Outcome 9 People with tuberculosis detected.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 6 Active case-finding interventions versus no intervention

Outcome: 9 People with tuberculosis detected



(1) Datiko 2009 ETH: This paper presented an ICC of 0.00052

(2) Shargie 2006 ETH: This paper presented an ICC of 0.00027; when the raw data was approximately adjusted using this ICC the result was also not statistically significant.

Analysis 7.1. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 1 Tuberculosis cases detected (microbiologically confirmed).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 1 Tuberculosis cases detected (microbiologically confirmed)

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Clarke 2005 ZAF (1)	60/3558	71/3567		33.4 %	0.85 [0.60, 1.19]
Datiko 2009 ETH (2)	58/44898	22/29911		25.5 %	1.76 [1.08, 2.87]
Morishita 2016 KHM (3)	19/14352	13/14352		17.2 %	1.46 [0.72, 2.96]
Shargie 2006 ETH (4)	24/18950	33/33455		23.9 %	1.28 [0.76, 2.17]
Total (95% CI)	**81758**	**81285**		**100.0 %**	**1.24 [0.86, 1.79]**

Total events: 161 (Intervention), 139 (Control)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.58$, df = 3 (P = 0.09); $I^2 = 54\%$

Test for overall effect: Z = 1.14 (P = 0.25)

Test for subgroup differences: Not applicable

(1) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

(2) Adjusted for clustering with trial's ICC of 0.00052

(3) Adjusted for clustering with ICC of 0.00052 from Datiko 2009

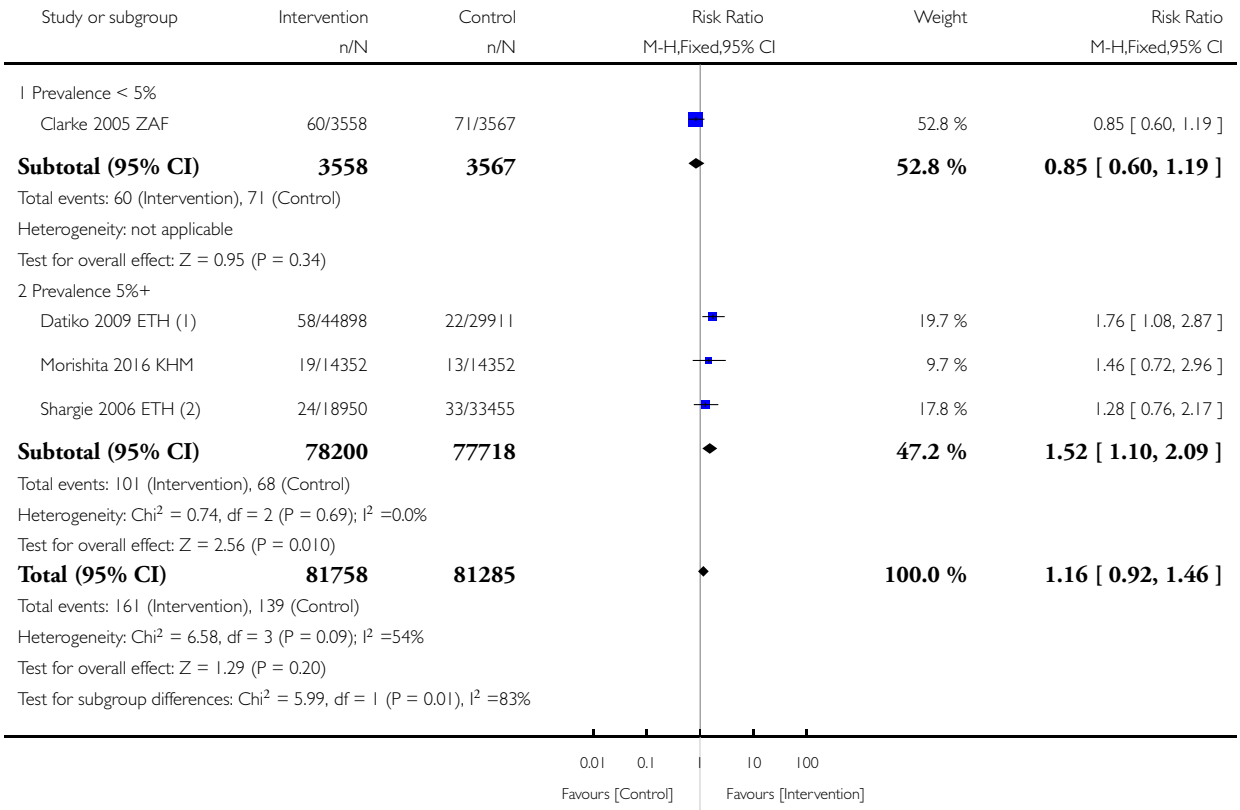
(4) Adjusted for clustering with trial's ICC of 0.00027

Analysis 7.2. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 2 Tuberculosis cases detected: subgrouped by tuberculosis prevalence



(1) Datiko 2009 ETH: This paper presented an ICC of 0.00052

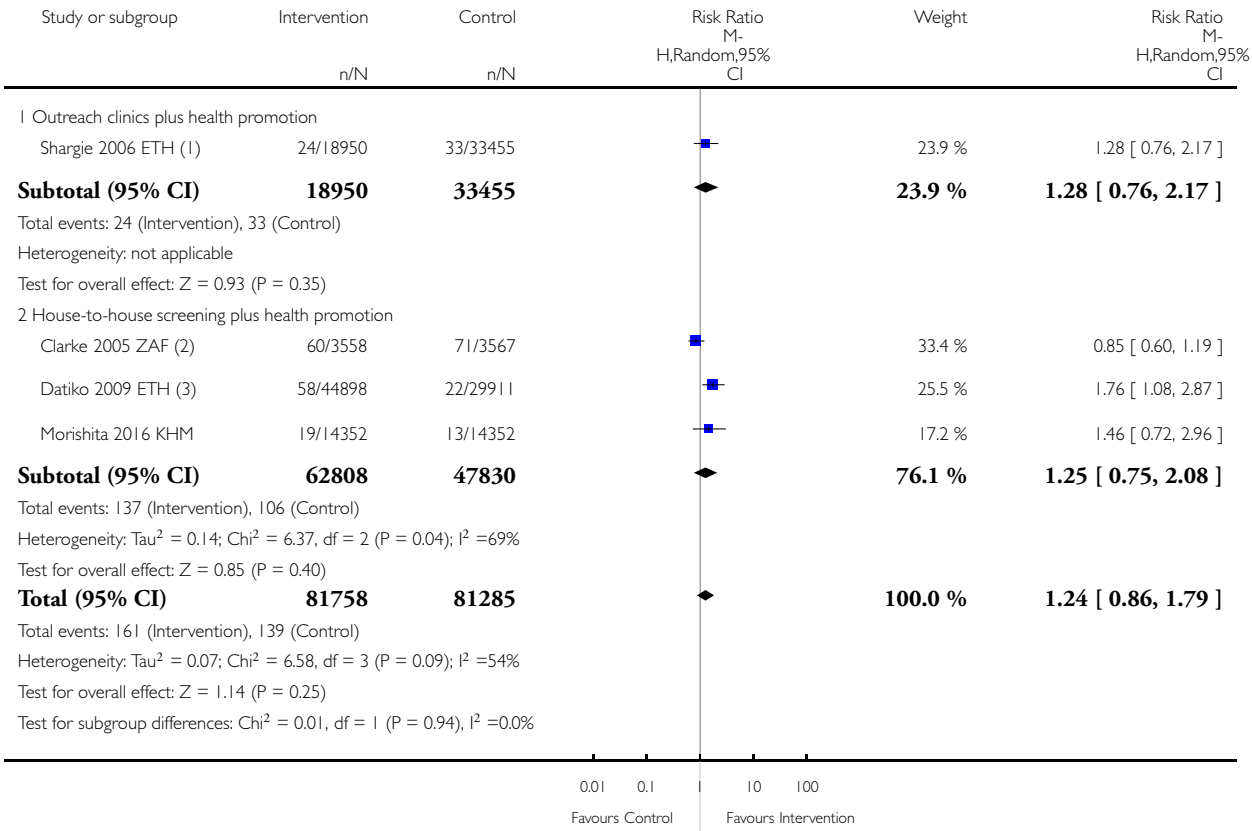
(2) Shargie 2006 ETH: This paper presented an ICC of 0.00027; when the raw data was approximately adjusted using this ICC the result was also not statistically significant.

Analysis 7.3. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 3 Tuberculosis cases detected; subgrouped by intervention.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 3 Tuberculosis cases detected; subgrouped by intervention



(1) Shargie 2006: Total diagnosed cases over 1 year follow-up

(2) Clarke 2005 ZAF:

(3) Datiko 2009: Total diagnosed cases over 1 year follow-up

Analysis 7.4. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 4 Tuberculosis cases detected (all forms).

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 4 Tuberculosis cases detected (all forms)

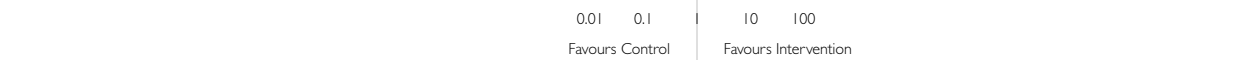
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Morishita 2016 KHM	46/14352	36/14352		100.0 %	1.28 [0.83, 1.98]
Total (95% CI)	**14352**	**14352**		**100.0 %**	**1.28 [0.83, 1.98]**

Total events: 46 (Intervention), 36 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

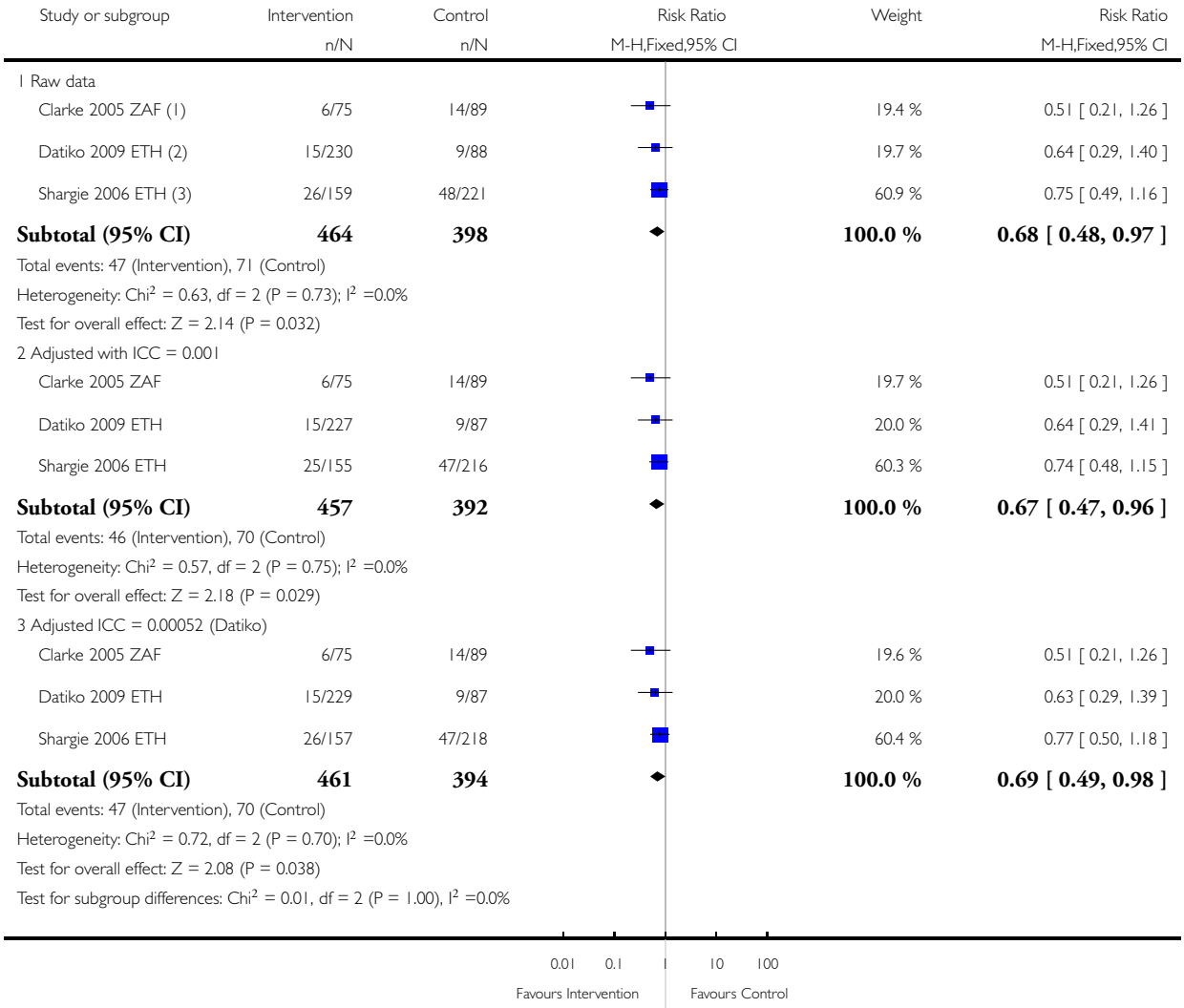


Analysis 7.5. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 5 Tuberculosis treatment default.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 5 Tuberculosis treatment default



(1) Datiko 2009 ETH: Default defined as: A patient who missed at least two months of treatment.

(2) Datiko 2009 ETH: Default defined as: A patient who missed eight consecutive weeks of treatment after receiving at leats 4 weeks of treatment.

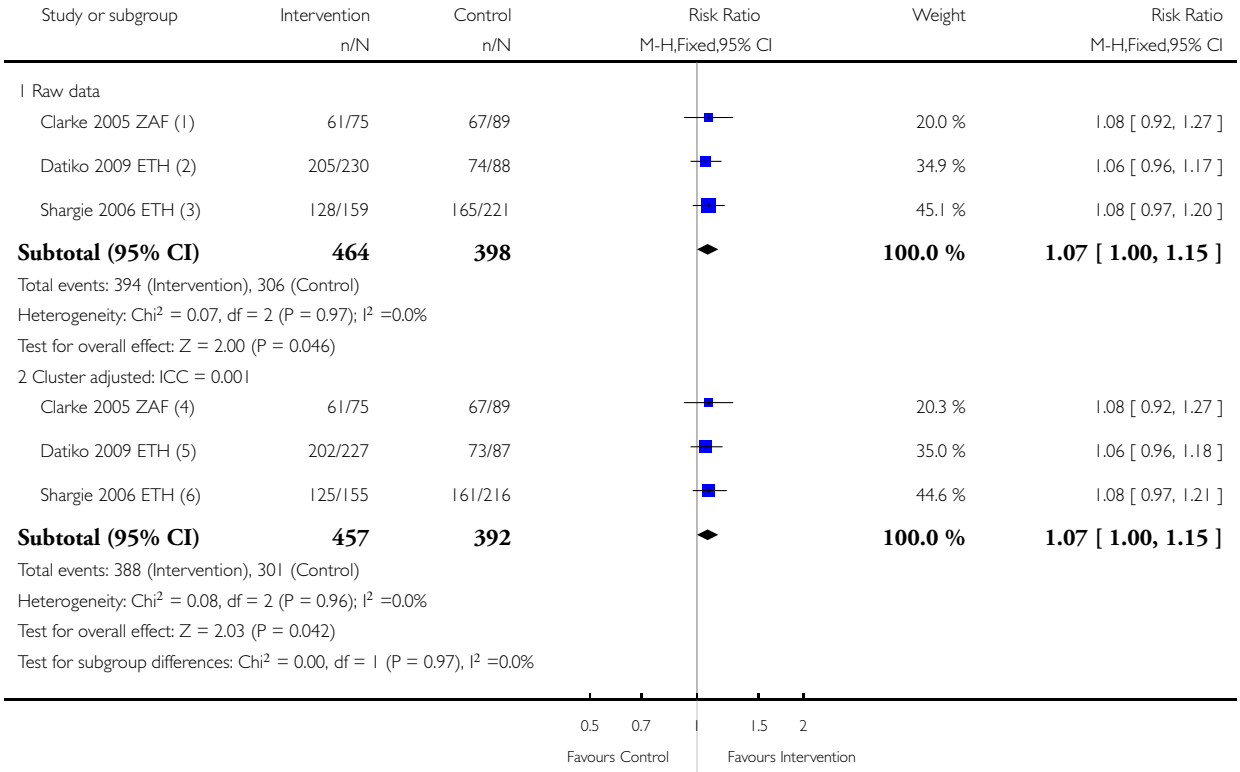
(3) Shargie 2006 ETH: Default defined as: A patient who missed eight consecutive weeks of treatment after receiving at leats 4 weeks of treatment.

Analysis 7.6. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 6 Tuberculosis treatment success.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 6 Tuberculosis treatment success



(1) Clarke 2005 ZAF: 'Success' defined as the sum of those who were cured (had a negative smear during the last month of treatment) and those who completed treatment.

(2) Datiko 2009 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at 7 months) and those who completed treatment without confirmation by smear microscopy.

(3) Shargie 2006 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at the end of treatment) and those who completed treatment without confirmation by smear microscopy.

(4) Clarke 2005 ZAF: 'Success' defined as the sum of those who were cured (had a negative smear during the last month of treatment) and those who completed treatment.

(5) Datiko 2009 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at 7 months) and those who completed treatment without confirmation by smear microscopy.

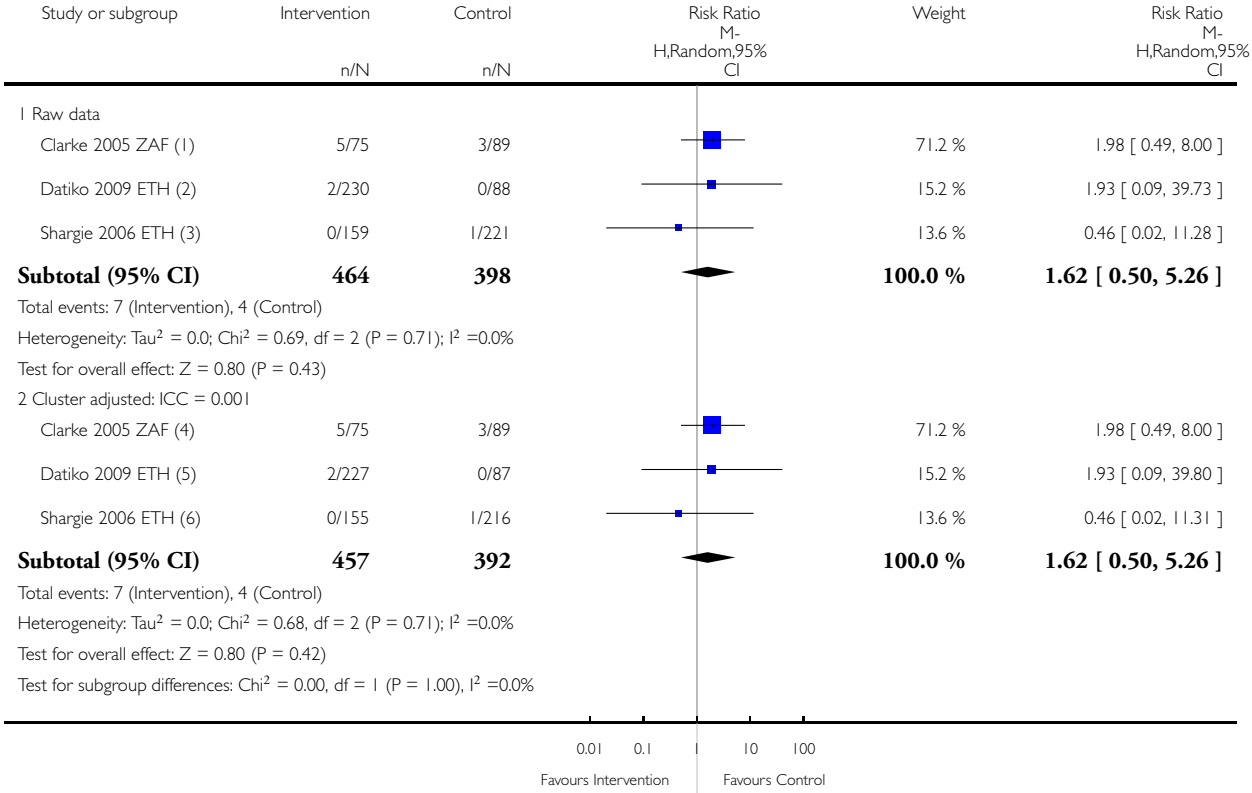
(6) Shargie 2006 ETH: 'Success' defined as the sum of those who were cured (at least two negative smears including one at the end of treatment) and those who completed treatment without confirmation by smear microscopy.

Analysis 7.7. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 7 Tuberculosis treatment failure.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 7 Tuberculosis treatment failure



(1) Clarke 2005 ZAF: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(2) Datiko 2009 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(3) Shargie 2006 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(4) Clarke 2005 ZAF: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

(5) Datiko 2009 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

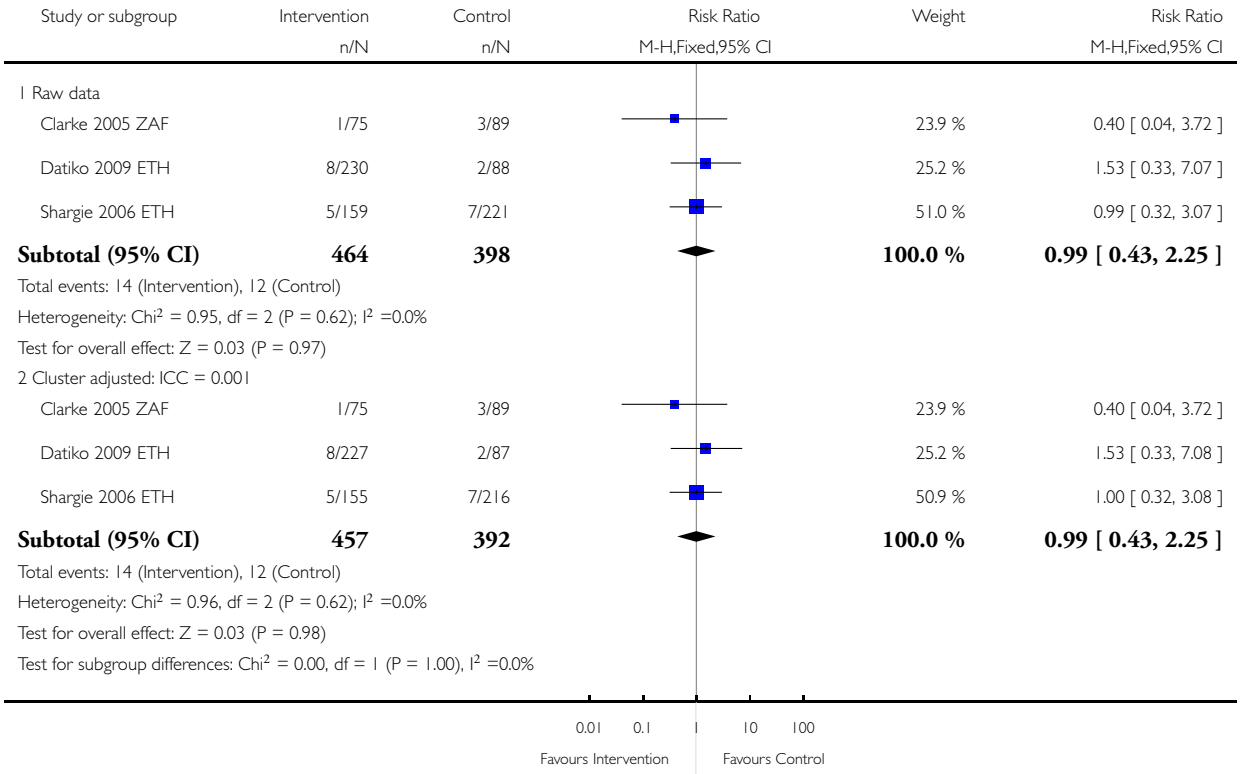
(6) Shargie 2006 ETH: Treatment failure defined as: Patients who remained or became smear positive at 5 months or later.

Analysis 7.8. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 8 Tuberculosis mortality.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 8 Tuberculosis mortality

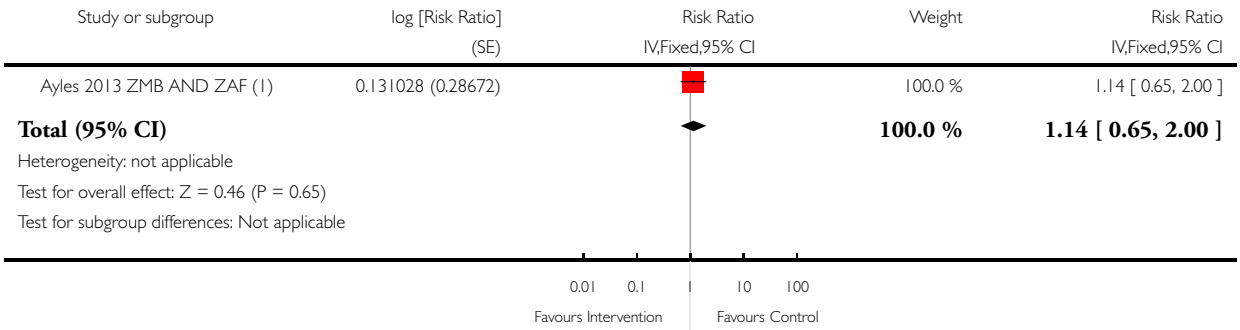


Analysis 7.9. Comparison 7 Outreach tuberculosis services versus no intervention (sensitivity analyses), Outcome 9 Long-term tuberculosis prevalence.

Review: Interventions to increase tuberculosis case detection at primary healthcare or community-level services

Comparison: 7 Outreach tuberculosis services versus no intervention (sensitivity analyses)

Outcome: 9 Long-term tuberculosis prevalence



(1) Ayles 2013: Adjusted for the cluster design.

ADDITIONAL TABLES

Table 1. Descriptions of study interventions: Interventions to increase tuberculosis case detection compared to no intervention

Study ID	Study design	1. Did health workers look for tuberculosis cases outside of health facilities?		2. Were there health promotion activities to encourage people with symptoms to attend health services?		3. Were health workers trained in tuberculosis diagnosis?		
		Yes/No	Where?	Yes/No	How were health promotion messages delivered?	Yes/No	Who was trained?	What training did they receive?
Ayles 2013 ZMB AND ZAF	Cluster-RCT	Yes	Households of people with new tuberculosis diagnosis	Yes	Community/school-based drama, meetings, leafleting, football matches, fashion shows	Unclear	-	-

Table 1. Descriptions of study interventions: Interventions to increase tuberculosis case detection compared to no intervention (*Continued*)

Shargie 2006 ETH	Cluster-RCT	Yes	Monthly community outreach clinics	Yes	Community promoters visited houses and distributed leaflets.	Yes	Nurses and health officers	4-day training on case identification, diagnostic process, and outreach coordination
Datiko 2009 ETH	Cluster-RCT	Yes	House-to-house visits every 2 to 4 weeks[1]	Yes	Health education sessions at health posts	Yes	Health extension workers	2-day training on symptoms, collection, storage, and transport of sputum samples
Clarke 2005 ZAF	Cluster-RCT	Yes	Monthly screening of all farm workers	No	-	Yes	Lay health workers	-
Yassin 2013 ETH	CBAS	Yes	House-to-house visits every 2 to 4 weeks	Yes	Community meetings, campaigns, and local radio Awareness workshops for religious leaders, teachers, and other stakeholders	Yes	Health extension workers and laboratory staff	Unclear how long the training was or what it covered
Joshi 2015 NPL	CBAS	Yes	Household contact tracing, mobile chest camps in hard-to-reach areas, home visits for children with HIV, and school-based screening	Yes	Through safe motherhood clinics	Unclear	-	-

Table 1. Descriptions of study interventions: Interventions to increase tuberculosis case detection compared to no intervention (*Continued*)

Oshi 2016 NGA	CBAS	Yes	Screening of home contacts, at outpatient clinics, and at ART clinics	Yes	Handbills and posters distributed in hospitals, schools, and homes, plus visits to primary schools	Yes	Medical officers and nurses	Tuberculosis diagnosis and using job aids
Reddy 2015 IND	CBAS	Yes	Community volunteers visited homes.	Yes	Information, education, and communication materials given to each visited house	Unclear	Volunteers described as "trained"	-
Morishita 2016 KHM	Cluster-RCT	Yes	Healthcare workers and community volunteers visited homes.	No	-	Yes	Healthcare workers and selected volunteers	How to screen target population
Ayles 2013 ZMB AND ZAF	Cluster-RCT	No	-	Yes	Community/school-based drama, meetings, leafleting, football matches, fashion shows	Unclear	-	-
Talukder 2012 BGD	Cluster-RCT	No	-	Yes	Health education sessions at health centres and community meetings	Yes	Tuberculosis control assistants and doctors	The 2-day training course included the use of the Keith Edwards Child Tuberculosis score chart, administration of the

Table 1. Descriptions of study interventions: Interventions to increase tuberculosis case detection compared to no intervention (*Continued*)

								Mantoux test, weighing children and interpreting level of malnutrition, referral of children to the doctor when needed and filling out a research questionnaire
Khan 2012 PAK	CBAS	No	-	Yes	Billboards, TV ads, posters, flyers	Yes	Lay people	Training session on NTP guidelines
Jaramillo 2001 COL	CBAS	No	-	Yes	Newspaper advertisements and inserts, television and radio announcements, and chat shows	No	-	-
Fairall 2005 ZAF	Cluster-RCT	No	-	No	-	Yes	Nurses	3 to 4 education sessions lasting 1 to 3 hours
Khan 2016 PAK	NRT	No	-	-	-	Yes	District tuberculosis co-ordinators and medical officers	Monitoring guidelines and tools

[1] Datiko 2009 ETH: the use of household visits is not explicitly described in the original paper. The frequency of visits was confirmed by personal communication with the author.

Abbreviations: ART: antiretroviral therapy; CBAS: controlled before-and-after study; NRT: non-randomized trial; NTP: national tuberculosis control programme; RCT: randomized controlled trial.

Table 2. Descriptions of study settings, tuberculosis screening protocols, and tuberculosis notification rates

Study ID	Study design	Country	Setting	Screening test	Confirmatory test	Tuberculosis CNR per 100,000 person years[1] (unadjusted for cluster design)		Baseline tuberculosis CNR comparable between study arms?
						Intervention	Control	
Ayles 2013 ZMB AND ZAF	Cluster-RCT	Zambia and South Africa	Urban and rural	Symptomatic and non-symptomatic individuals	Sputum smear microscopy and culture	-	-	Not reported
Shargie 2006 ETH	Cluster-RCT	Ethiopia	Rural	Symptom screen: criteria not defined	Sputum smear microscopy	125	98	Not reported
Datiko 2009 ETH	Cluster-RCT	Ethiopia	Rural	Symptom screen: cough for > 2 weeks	Sputum smear microscopy	129	74	Not reported
Clarke 2005 ZAF	Cluster-RCT	South Africa	Rural	Symptom screen: criteria not defined	Sputum smear microscopy and culture	1487	1843	Yes
Yassin 2013 ETH	Non-randomized	Ethiopia	Urban and rural	Symptom screen: cough > 2 weeks	Sputum smear microscopy	127	-	Not reported
Joshi 2015 NPL	Non-randomized	Nepal	Urban and rural	Symptom screen	Sputum smear microscopy or CXR, tuberculin test, and physician assessment	24.2	15.6	No
Oshi 2016 NGA	Non-randomized	Nigeria	Urban and rural	Symptom screen	Sputum smear microscopy or Keith Edwards Tu-	-	-	Not reported

Table 2. Descriptions of study settings, tuberculosis screening protocols, and tuberculosis notification rates (*Continued*)

					berculosis score chart			
Reddy 2015 IND	Non-randomized	India	Urban and rural	Unclear	Sputum smear microscopy	-	-	Not reported
Talukder 2012 BGD	Cluster-RCT	Bangladesh	Urban and rural	None described.	Keith Edwards Child Tuberculosis Score Chart	-	-	Not reported
Khan 2012 PAK	Non-randomized	Pakistan	Urban	Symptom screen: cough > 3 weeks or productive cough > 2 weeks	Sputum smear microscopy, GeneXpert, or CXR	343	41	No
Jaramillo 2001 COL	Non-randomized	Colombia	Urban	None described.	Sputum smear microscopy	-	-	Not reported
Fairall 2005 ZAF	Cluster-RCT	South Africa	Urban and rural	Symptom screen: criteria not defined	Sputum smear microscopy and culture/ CXR, clinical diagnosis (evidence-treatment card)	-	-	Not reported
Corbett 2010 ZWE	Cluster-RCT	Zimbabwe	Urban	Symptom screen: cough for > 2 weeks	Sputum smear microscopy and culture	427	380	Yes
Miller 2010 BRA	Cluster-RCT	Brazil	Urban	Symptom screen: cough for > 3 weeks	Sputum smear x 2 plus CXR	934	604	Yes
Morishita 2016 KHM	Cluster-RCT	Cambodia	Urban and rural	Symptoms screening: cough, fever, weight loss, and/or	Gene Xpert MTB/RIF	323	254	Yes

Table 2. Descriptions of study settings, tuberculosis screening protocols, and tuberculosis notification rates (*Continued*)

				night sweats of more than 2 weeks and household contacts without symptoms				
Moyo 2012 ZAF	Individual-RCT	South Africa	Urban	Tuberculosis symptom screening and tuberculosis contact	Sputum smear microscopy and culture	-	-	-

[1]The tuberculosis case notification rate (CNR) was calculated by dividing the total number of tuberculosis cases by the duration of the trial (in years), then dividing by the population of the intervention area and multiplying by 100,000.

Abbreviations: CNR: case notification rate; CXR: chest X-ray.

Table 3. Primary tuberculosis case-finding outcome for studies of tuberculosis outreach diagnostic services

Study ID	Study design	Outcome measure	Intervention	Control	Effect estimate (95% CI)	Adjusted for cluster design	Comment
Ayles 2013 ZMB AND ZAF	Cluster-RCT	-	-	-	-	NA	Tuberculosis case detection is not reported. The primary outcome is long-term tuberculosis prevalence
Shargie 2006 ETH	Cluster-RCT	Tuberculosis case notification rate per 100,000 person years during the intervention	125	98	**Difference 27** (-19 to 72)	Yes	P = 0.12 ICC = 0.00027
Datiko 2009 ETH	Cluster-RCT	Tuberculosis case detection rate as a percentage of the average annual case detection rate	122.2%	69.4%	**Difference 52.4%** (39.8 to 65.4)	Yes	P < 0.001 ICC = 0.00052

Table 3. Primary tuberculosis case-finding outcome for studies of tuberculosis outreach diagnostic services (*Continued*)

Clarke 2005 ZAF	Cluster-RCT	The number of clusters with higher case finding during the intervention period	26/106	18/105	**Difference 8.9%** (-0.7 to 24.9)	NA	P = 0.29
Yassin 2013 ETH	Non-randomized	Tuberculosis case notification rate per 100,000 person years	127	-	-	NA	Only the intervention area data are presented as a before-and-after analysis. No statistical significance testing was done
Joshi 2015 NPL	Non-randomized	Change in childhood tuberculosis case notification per 100,000 compared to previous year	+6%	+2.2%	**Difference 3.8%** (2.7 to 5.2)	NA	P < 0.001
Oshi 2016 NGA	Non-randomized	Change in tuberculosis cases identified	+31%	Not stated	Not stated	NA	Only data from the intervention areas are presented.
Reddy 2015 IND	Non-randomized	Change in number of smear-positive tuberculosis cases compared to previous year	+8.8%	-8.6%	-	NA	Only the number of cases detected is presented, without denominators

Abbreviations: CI: confidence interval; ICC: intraclass correlation coefficient; NA: not applicable; RCT: randomized controlled trial.

Table 4. Primary tuberculosis case-finding outcome for studies of health promotion

Study ID	Study design	Outcome measure	Intervention	Control	Effect estimate (95% CI)	Adjusted for cluster design	Comment
Ayles 2013 ZMB AND ZAF	Cluster-RCT	-	-	-	-	NA	Tuberculosis case detection was not reported. The primary outcome was long-term tuberculosis prevalence
Talukder 2012 BGD	Cluster-RCT	Number of tuberculosis cases diagnosed	175	130	No significance testing was done between intervention and control areas	NA	The number of tuberculosis cases diagnosed in the intervention area was higher during the intervention compared to pre-intervention (P = 0.001)
Khan 2012 PAK	Non-randomized	Tuberculosis case detection per 100,000	343	41	No significance testing was done between intervention and control areas	NA	The tuberculosis case notification in the intervention area increased 2-fold during the intervention (P = 0.000)
Jaramillo 2001 COL	Non-randomized	Number of tuberculosis cases/number of people tested	-	-	No significance testing was done between intervention and control areas	NA	A temporal association is noted between the number of people being tested and the intervention. There is not a convincing corresponding increase in the number of new tuberculosis diagnoses

Abbreviations: CI: confidence interval; NA: not applicable; RCT: randomized controlled trial

Table 5. Tuberculosis case-finding outcome for studies of health staff training in tuberculosis diagnosis

Study ID	Study design	Outcome measure	Intervention	Control	Effect estimate (95% CI)	Adjusted for cluster design	Comment
Fairall 2005 ZAF	Cluster-RCT	New tuberculosis cases detected per 1000 patients	57	34	**Odds ratio 1.72** (1.04 to 2.85)	Yes	P = 0.04 ICC = 0.007
Khan 2016 PAK	Non-randomized	The proportion of new tuberculosis cases that were diagnosed in primary care	20/7670	6/7536	**Odds ratio 3.28** (1.26 to 9.97)	Yes	P = 0.007 ICC = 0.00052

Abbreviations: CI: confidence interval; RCT: randomized controlled trial.

Table 6. Descriptions of study interventions: Direct comparisons of different interventions to increase tuberculosis case detection

Study ID	Study design	Study arm	1. Did health workers look for tuberculosis cases outside of health facilities?		2. Were there health promotion activities to encourage people with symptoms to attend health services?		3. Were health workers trained in tuberculosis diagnosis?		
			Yes/No	Where?	Yes/No	How were health promotion messages delivered?	Yes/No	Who was trained?	What training did they receive?
Ayles 2013 ZMB AND ZAF	Cluster-RCT	1	Yes	Households of people with new tuberculosis diagnosis	Yes	Community/ school-based drama, meetings, leafleting, football matches, fashion shows	Unclear	-	-

Table 6. Descriptions of study interventions: Direct comparisons of different interventions to increase tuberculosis case detection (*Continued*)

		2	No	-	Yes	Community/ school-based drama, meetings, leafleting, football matches, fashion shows	Unclear	-	-
		3	Yes	Households of people with new tuberculosis diagnosis	No	-	Unclear	-	-
Miller 2010 BRA	Cluster-RCT	1	Yes	All households visited.	No	-	Not described	-	-
		2	No	-	Yes	All households received an informational pamphlet linked with a national TV campaign encouraging those with symptoms to seek free care	Not described	-	-
Corbett 2010 ZWE	Cluster-RCT	1	Yes	Mobile van situated in each cluster for 5 days every 6 months	Yes	A loud speaker and leafleting encouraging people to attend	Not described	-	-

Table 6. Descriptions of study interventions: Direct comparisons of different interventions to increase tuberculosis case detection (*Continued*)

		2	Yes	House-to-house visits every 6 months, with up to 3 visits each round (including 1 weekend day) to ensure coverage	Yes	Leaflets explained the rationale and benefits.	Not described	-	-

Abbreviations: RCT: randomized controlled trial.

Table 7. Primary tuberculosis case-finding outcome for studies comparing different interventions

Study ID	Study design	Outcome measure	Intervention	Control	Effect estimate (95% CI)	Adjusted for cluster design	Comment
Outreach tuberculosis services versus health promotion							
Ayles 2013 ZMB AND ZAF	Cluster-RCT	-	-	-	-	NA	Tuberculosis case detection was not reported. The primary outcome was long-term tuberculosis prevalence
Miller 2010 BRA	Cluster-RCT	Tuberculosis case notification rate per 1000 person years during the intervention period	9.34	6.04	**Rate ratio 1.55** (1.10 to 1.99)	Yes	The authors report a second analysis including cases detected during the first 60 days postintervention. The result was no longer statistically significant
Outreach tuberculosis clinic versus household screening							

Table 7. Primary tuberculosis case-finding outcome for studies comparing different interventions (*Continued*)

Corbett 2010 ZWE	Cluster-RCT	Mean cumulative yield of tuberculosis smear-positive cases per 1000 adults per cluster over 3 years' follow-up	4.22	2.46	**Risk ratio 1.71** (1.27 to 2.31)	Yes	A second analysis also adjusted for cluster-level variation in household crowding, age, sex, HIV infection, and pre-study tuberculosis notification rates was also statistically significant

Abbreviations: CI: confidence interval; NA: not applicable; RCT: randomized controlled trial.

APPENDICES

Appendix 1. Search strategy

Search set	Embase
1	Tuberculosis [Emtree]
2	Tuberculosis [ti, ab]
3	Mycobacterium tuberculosis [Emtree]
4	Case* detection ti, ab
5	Case* finding ti, ab
6	Systematic screening* ti, ab
7	Case finding [Emtree]
8	1 or 2 or 3
9	4 or 5 or 6 or 7

(*Continued*)

10	Diagnos* OR detect* OR screen* OR assess* ti, ab
11	8 and 9 and 10

Search set	MEDLINE
1	tuberculosis [MeSH]
2	tuberculosis [ti, ab]
3	Mycobacterium tuberculosis [MeSH]
4	Case* detection ti, ab
5	Case* finding ti, ab
6	Systematic screening* ti, ab
7	1 or 2 or 3
8	4 or 5 or 6
9	Diagnos* OR detect* OR screen* OR assess* ti, ab
10	7 and 8 and 9
11	-

The Cochrane Library

#1 tuberculosis
#2 MeSH descriptor: [Tuberculosis] explode all trees
#3 MeSH descriptor: [Mycobacterium tuberculosis] explode all trees
#4 #1 or #2 or #3
#5 “case detection” or “case finding” or “systematic screening”
#6 #4 and #5

Web of Science Core Collection

You searched for: TOPIC: (tuberculosis) *AND* TOPIC: ((case finding) OR (case detection) OR (systematic screening)) *AND* TOPIC: (diagnos* OR detect* OR screen* OR assess) *AND* TOPIC: (intervention* OR program* OR community OR random* OR trial* OR before) ...MoreTOPIC: (tuberculosis) *AND* TOPIC: ((case finding) OR (case detection) OR (systematic screening)) *AND* TOPIC: (diagnos* OR detect* OR screen* OR assess) *AND* TOPIC: (intervention* OR program* OR community OR random* OR trial* OR before)
Indexes: SCI-EXPANDED, SSCI,

BIOSIS Previews

You searched for: TOPIC: (tuberculosis OR TB) *AND* TOPIC: ((case finding) OR (case detection) OR (systematic screening)) *AND* TOPIC: ((intervention* OR program* OR community OR random* OR trial* OR before)) ...More TOPIC:(tuberculosis OR TB) *AND* TOPIC:((case finding) OR (case detection) OR (systematic screening)) *AND* TOPIC: ((intervention* OR program* OR community OR random* OR trial* OR before))
Indexes: BIOSIS Previews.

Scopus

(TITLE-ABS-KEY (tuberculosis) AND TITLE-ABS-KEY ((case detection) OR (case finding) OR (systematic screening)) AND TITLE-ABS-KEY (intervent* OR program* OR initiative OR trial* OR random* OR before)) AND SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal OR mult OR arts OR busi OR deci OR econ OR psyc OR soci) AND (LIMIT-TO (SUBJAREA , "MEDI"))

CONTRIBUTIONS OF AUTHORS

All review authors jointly developed the protocol and provided comments and feedback. FM, AM, and DS performed data extraction and analysis, and all authors wrote the manuscript. All authors agreed on the content of the final review and its submission for publication.

DECLARATIONS OF INTEREST

Francis A Mhimbira has no conflicts of interest to declare.

Professor Luis Cuevas has received seven awards from the TB REACH programme of the Stop TB Partnership. This programme aims to increase tuberculosis case detection in low-income countries, which often includes community-based interventions, which is the focus of the current review.

Russell Dacombe was part-funded by a European & Developing Countries Clinical Trials Partnership grant (TB-NEAT, IP.2009.32040.009) which included support to the preparation of this review.

Abdallah Mkopi has no conflicts of interest to declare

David Sinclair: was supported as an author and editor with the Cochrane Infectious Diseases Group by the Effective Health Care Research Consortium.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- Cochrane South Africa, South Africa.
- South African Medical Research Council, South Africa.
- European & Developing Countries Clinical Trials Partnership, Netherlands.

Grant (TB-NEAT, IP.2009.32040.009)

External sources

- Department for International Development (DFID), UK.

Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following are the changes between the protocol and the review.

- We changed “additional tuberculosis cases starting treatment” to “tuberculosis cases detected (all forms)”.
- We changed “additional tuberculosis cases detected (microbiologically confirmed)” to “tuberculosis cases detected”.
- Primary outcome: We used “tuberculosis cases detected (microbiologically confirmed)” instead of “tuberculosis cases detected (all forms)” .