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Active case finding in contacts of people with tuberculosis.
Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD008477.
DOI: 10.1002/14651858.CD008477.pub2.

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[Intervention Review]

Active case finding in contacts of people with tuberculosis

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: Unchanged, published in Issue 5, 2019.

Citation: Fox GJ, Dobler CC, Marks GB. Active case finding in contacts of people with tuberculosis. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD008477. DOI: 10.1002/14651858.CD008477.pub2.

ABSTRACT

Background

Tuberculosis is a major global health challenge that is caused by a bacteria which is spread by airborne droplets. Mostly patients are identified in high-burden countries when they visit health care facilities ('passive case finding'). Contacts of tuberculosis patients are a high-risk group for developing the disease. Actively screening contacts of people with confirmed tuberculosis may improve case detection rates and control of the disease.

Objectives

This study aims to compare whether active case finding among contacts of people with confirmed tuberculosis increases case detection compared to usual practice.

Search methods

In April 2011 we searched CENTRAL (*The Cochrane Library* 2011, Issue 2), MEDLINE, EMBASE, LILACS and mRCT. We also checked article reference lists, the *International Journal of Tuberculosis and Lung Disease* and contacted relevant researchers and organizations.

Selection criteria

Randomized and quasi-randomized trials of active case finding to detect tuberculosis disease among close and casual contacts of patients with microbiologically proven pulmonary tuberculosis (by sputum smear and/or culture).

Data collection and analysis

Two authors independently assessed eligibility and the methodological quality of the trials that were extracted using a search method that was outlined previously.

Main results

No trials met the inclusion criteria for this review. One RCT did test the effect of active case finding in contacts, but the intervention in that trial also included screening for, and treatment of, LTBI in contacts; and the separate effect of active case finding could not be estimated.

Authors' conclusions

There are currently insufficient data from randomized controlled trials or quasi-randomized controlled trials to evaluate the effect of active case finding for tuberculosis among contacts of patients with confirmed disease. While observational studies show that contacts have a higher risk of developing tuberculosis than the general population, further research is needed to determine whether active case finding among contacts significantly increases case detection rates.

17 April 2019

No update planned

Review superseded

This Cochrane Review has been superseded by Mhimbira 2017 https://doi.org/10.1002/14651858.CD011432.pub2

PLAIN LANGUAGE SUMMARY

Screening programmes for tuberculosis

Tuberculosis is a serious infectious disease that affects over nine million people each year. The disease is spread by airborne droplets, which arise in the infected lungs of tuberculosis patients. Despite widespread availability of treatment with effective antibiotic therapies, the disease remains common in many resource limited settings. This review aimed to determine whether systematic screening all the direct contacts with people with proven TB disease increases the early detection of tuberculosis. The review found that there are not currently any suitable randomized controlled trials to answer this question and there is insufficient evidence to show whether screening programmes for tuberculosis will improve the rate of diagnosis among contacts of tuberculosis patients or reduce the rate of tuberculosis in the community.Therefore there is a need for further research to determine the benefits of systematic screening of the contacts of tuberculosis patients.

BACKGROUND

Description of the condition

Tuberculosis is an infectious disease, caused by the *Mycobacterium tuberculosis bacterium,* that each year affects nine million people and kills almost two million people, primarily in resource limited settings (WHO 2010). The bacteria usually infects the lungs, but can involve any other organ. Disease (active tuberculosis) occurs in a minority of those who are infected. Usually the bacteria enters a dormant state (latent tuberculosis infection, LTBI), in which it remains for a period lasting from weeks to many years. (Barry 2009).

Tuberculosis control is a key priority within the sixth Millennium Development Goal (WHO 2006). However, despite concerted international efforts, disease control is hampered by complex challenges in tuberculosis diagnosis and management. Over recent decades, the rising prevalence of Human Immunodeficiency Virus (HIV) has also increased susceptibility to tuberculosis (Corbett 2003). In 2008, HIV co-infection was present in approximately 15% of all tuberculosis patients globally (WHO 2009).

Challenges of diagnosis

Diagnosing tuberculosis can often be challenging for a number of reasons, particularly in settings with limited resources.

- **The biology of the organism.** The slowly dividing nature of the organism means that the clinical disease is often subacute and remains undiagnosed for some weeks or even months. During this period the patient may be infectious to others.
- **Variability of clinical presentations.** Suspicion of tuberculosis is usually triggered by symptoms such as weight loss, cough, and sputum production. However, symptoms may be subtle or absent (Breen 2008), particularly early in the disease. This may delay self-referral to health services and allow further disease propagation.
- **Limitations of current diagnostic investigations.** Investigations for the diagnosis of active disease and for the diagnosis of LTBI are imperfect. In particular, only around 50% of cases of pulmonary tuberculosis are sputum smear positive and 70 to 80% are culture positive (Chan 1971; Levy 1989). Further, a positive mycobacterial culture is not specific for the diagnosis of tuberculosis. A specific mycobacteriological diagnosis requires confirmatory biochemical or molecular tests on the culture specimens. In addition, the collection of a good quality sputum specimen can be challenging, particularly in children (Reichler 2003).
- **Limited resources of health systems.** In countries with limited resources to spend on healthcare, the detection and effective treatment of symptomatic cases of tuberculosis generally takes priority over active case finding (WHO 2006).
- **Legal and ethical issues.** Screening programmes may inadvertently disclose the identities of patients with tuberculosis. This raises the difficult issue of maintaining privacy in settings where tuberculosis is often heavily stigmatised (Long 2001).

Testing for acid fast bacilli (AFB) in sputum is the standard initial investigation in most settings because it is inexpensive, quick, and identifies those who are most likely to transmit disease (WHO 2006). A positive result is usually presumed to indicate disease in settings with a high tuberculosis prevalence. Although the conventional sputum smear is specific, particularly in high-burden settings, its sensitivity is relatively low (Steingart 2006). Sputum culture is recommended where possible, to confirm the diagnosis by isolating *M. tuberculosis.* Culture and drug susceptibility testing are particularly important in the presence of suspected drug resistant disease. Liquid-based culture techniques are more sensitive than traditional solid culture methods, although careful quality control is essential (Anthony 2009). Chest radiography also has a key role in the diagnosis of intra-thoracic tuberculosis (WHO 2006). A range of specific tests, including smear, histological examination, and culture, are also used to confirm disease in the pleura, or extra-pulmonary disease. Nucleic acid amplification tests are useful in some diagnostic settings, with automated molecular-based methods showing considerable promise (Boehme 2010). However, these tests are currently expensive in comparison with smear and culture.

Comprehensive reviews and guidelines for tuberculosis diagnosis are available elsewhere (WHO 2006, Menzies 2007).

Approaches to tuberculosis case finding

There are several approaches to selecting individuals for tuberculosis testing (that is, identifying tuberculosis suspects). Health services may employ 'passive case finding' (where symptomatic patients self-present for assessment), 'active case finding' (where healthcare workers expectantly investigate populations by contact tracing, screening high-risk population sub-groups or surveys) (Ward 2004) or a combination of the two.More detailed definitions of these approaches are discussed below.

The World Health Organization (WHO) policy of Directly Observed Therapy Short-course (DOTS) does not recommend routine active case finding (WHO 2006), except in high-risk cases such as new childhood tuberculosis (WHO 2001) and people living with HIV (WHO 2008). The rationale for emphasising passive case finding is that resources should focus on effectively treating patients who are symptomatic and most likely to be infectious to others (WHO 2006). In contrast, many high-income countries have elaborate systems for performing 'contact tracing' for those who have been in contact with tuberculosis patients. The epidemiological argument is that in low-burden settings, contacts have high relative risk of developing disease compared to the low baseline risk in the general population (Marks 2000a).

Disease transmission

Tuberculosis is spread via airborne droplets, produced during coughing or breathing. A number of studies show that the risk of transmission is related to the infectivity of the source case, the duration and proximity of contact with the source case, and being in an enclosed space with the source case (Fok 2008, Greenaway 2003; Kenyon 1996). Consequently, those who spend the most time with the patient during their period of infectivity (usually weeks to months before diagnosis) are at the highest risk of infection. These contacts may either develop LTBI or have primary tuberculosis disease. In the case of LTBI the bacteria are dormant. The infected person is not infectious, but remains at risk of developing active tuberculosis. However, this risk can be significantly reduced by giving treatment for LTBI.

This systematic review will examine the evidence for screening contacts of patients with active tuberculosis for evidence of disease. It will also examine which subgroups of contacts (such

as people infected with HIV, diabetics or members of the same household) would benefit most from screening.

Description of the intervention

Active case finding among tuberculosis contacts

'Active case finding' refers to a strategy of actively searching for tuberculosis disease in a defined population. This population may be contacts of patients with tuberculosis, other specific high-risk groups or the general community. The aim of active case finding is to detect and treat tuberculosis cases earlier than they would otherwise be detected and treated and, therefore, to reduce further propagation of tuberculosis infection (Etkind 2000; Ward 2004). Currently there is no standard international approach to active case finding.

The term 'contact tracing' refers to a set of interventions that may include, but is not limited to, active case finding in contacts of patients with tuberculosis. It starts with the identification of people who have been in contact with patients with infectious forms of tuberculosis and then proceeds to the application of specific interventions in those identified contacts. These interventions may include: (1) active case finding in contacts of patients with tuberculosis and (2) testing for, and treatment of, latent tuberculosis infection in contacts of patients with tuberculosis. The former is a pre-requisite for the latter (since treatment of latent tuberculosis infection cannot proceed with out first excluding active disease). In low-burden countries, both interventions are usually implemented. However, at present there are no clear guidelines for contact tracing in high burden settings and capacity constraints as well as the high rate of ongoing transmission may mean that active case finding is a valid intervention but treatment of latent tuberculosis infection is not in these settings.

For this reason, the present review focuses on evaluating active case finding among tuberculosis contacts and excludes testing for, and treatment of, latent tuberculosis infection in contacts. It also excludes other active case finding strategies, such as community screening programmes, recently tested by Corbett (Corbett 2010) and Churchyard (Churchyard 2011).

Programmes involving active case finding among tuberculosis contacts

Active case finding among tuberculosis contacts may be limited to close contacts (such as family or household members) or extend to include casual contacts (individuals only briefly in contact with a patient). The choice of target group and investigations varies considerably depending upon the policies and health resources of each setting (BTS 2000; Marks 2000; Reichler 2003; Taylor 2005). Active case finding policies lie on a spectrum, ranging from limited to much more extensive forms.

- **Limited active case finding among contacts.** In countries with limited resources, the population chosen for screening may include only those at highest risk. This may include individuals known to have the greatest degree of exposure (such as household members) and those with the greatest susceptibility to infection (such as HIV positive contacts).
- **Extensive active case finding among contacts.** These programmes usually employ variations of the 'stone in the pond' principle (Veen 1992), where healthcare workers interview patients and their contacts in order to perform screening in concentric 'circles' around the source case. This usually begins with the most proximate contacts (such as household members) and progressively investigates contacts with more transient exposure to the index patient. In low-prevalence settings, active case finding among contacts is usually combined with screening and treatment for LTBI and the investigation may continue until the rate of LTBI approaches that in the background population. Extensive active case finding among contacts is favoured in low-prevalence settings, where the relative risk of infection in a contact is considerably higher than that of the general population. Detailed guidelines have been published to inform programmatic guidelines for active case finding and screening for LTBI (BTS 2000, Taylor 2005). The priority of investigation is typically based upon the immunocompetency of the contact, infectiousness of the patient (such as smear positive, cavitating pulmonary disease) and the proximity and duration of exposure.

The current WHO approach does not promote routine active case finding in resource limited settings (WHO 2006) except among HIV-infected individuals (WHO 2008). Instead, its DOTS approach includes five elements: political commitment, improved laboratory analysis, direct observation of patients while taking medications, a secure supply of free antituberculous drugs and an effective system of reporting diagnoses and treatment outcomes (WHO 2006). A separate Cochrane review evaluates the evidence for DOTS for treating tuberculosis (Volmink 2007).

Factors influencing the effectiveness of active case finding among contacts in reducing the incidence of TB disease

The effectiveness of active case finding among contacts is influenced by the risk of infection arising from exposure to infectious cases, the relative contribution of recent infection as opposed to reactivation of latent infection, and local prevalence of infection and disease. Although close or household contacts have a greater individual risk of infection than the general population, this is not necessarily due to household exposure alone (Aparicio 2000, Verver 2004). Other shared risk factors may also confer a higher risk of acquiring infection.

Long term studies in low-prevalence countries in Europe (Bauer 1998; Diel 2002; Gutierrez 1998, Van Soolingen 1999), the United States (Alland 1994; Small 1994) and Japan (Tsukishima 2007) have used molecular strain-typing to estimate recent transmission rates of between 34% and 60%. A meta-analysis of these and other studies included 33,473 patients from high- and low-prevalence countries (Fok 2008). The authors estimated that on average 44% of patients demonstrated recent transmission; however some technical aspects of this analysis have been challenged (Houben 2009). These studies were conducted in settings where the background intensity of transmission is lower, and it is likely that reactivation of LTBI causes a lower proportion of disease in high-burden settings.

The relative contribution of domestic exposure to an individual's overall risk of acquiring disease will also depend upon disease prevalence in the general population. Unsurprisingly, prevalence studies among contacts of tuberculosis patients in high-burden countries show that rates of latent and active disease are both higher (Reichler 2003).

Uncertainties in relation to active case finding among contacts

Policy decisions about whether to pursue active case finding must necessarily consider other competing priorities for the limited available health resources. This approach has resulted in markedly different approaches in low-prevalence and high-prevalence countries.

The cost-effectiveness of active case finding is heavily dependent upon inputs such as laboratory and labour costs, which vary between countries. Other factors that might influence the cost-effectiveness of active case finding, particularly in high-prevalence countries with well-established and effective DOTS programmes, have not been clearly established.

Finally, there is the question of which tests to perform to improve the yield, sensitivity and specificity of active case finding. The uncertainties relating to LTBI diagnostic testing further complicate the policy calculus.

How the intervention might work

Active case finding among contacts typically includes:

- interviewing index cases to determine 'high risk' contacts;
- interviewing identified contacts to screen for symptoms of disease and risk factors for developing the disease;
- case conferences to plan how case finding efforts should be concentrated;
- initial investigation of contacts for active disease including microbiological (sputum smear and/or culture), radiological (chest Xray)
- periodic follow-up of close contacts over time to identify evidence of active disease; and
- treatment of patients identified to have active disease during screening.

Why it is important to do this review

There has been a renewed interest in identifying cost-effective methods for active case finding (Becerra 2005; Diel 2006; Wrighton-Smith 2006).

Current practice varies considerably due to a number of factors, including differences in health care resources, the population prevalence of disease, the vulnerabilities of specific groups and other policy considerations. The prevalence of active tuberculosis among close contacts of TB patients in high-prevalence countries may be as much as five times higher than the general population (Claessens 2002, Morrison 2008). A clear articulation of the evidence for active case finding in this setting will potentially improve resource utilisation with a targeted approach and accelerate disease control in specific settings.

OBJECTIVES

To compare the diagnostic yield of tuberculosis disease achieved by active case finding in contacts of patients with proven pulmonary tuberculosis to that of passive case finding.

METHODS

Criteria for considering studies for this review

Types of studies

Studies to be included in this systematic review are randomized controlled clinical trials and quasi-randomized trials.

Types of participants

Close and casual contacts of patients with microbiologically proven pulmonary tuberculosis (by sputum smear and/or sputum culture).

Close contacts were defined as 'people from the same household sharing kitchen facilities, and very close associates such as boyfriend/girlfriend, or frequent visitors to the home of the index case' (BTS 2000). Contacts were also considered as 'close contacts' where there was evidence of prolonged frequent exposure (at least a total of 8 hours of direct exposure during the period of infectiousness preceding diagnosis of the index case) in other settings such as the workplace or prison.

Casual contacts were defined as people with brief exposure to the index case during their period of infectiousness, of an insufficient duration to be regarded as a close contact as defined by the study investigators.

Types of interventions

Intervention: Active case finding programmes where there is a systematic programme of investigation of contacts of patients with confirmed disease.

Control: Members of this group were contacts of known tuberculosis patients, but not subject to active case finding. Cases among contacts in the control group must have been diagnosed through the routine diagnostic pathways in both DOTS and non-DOTS programmes in public and private settings.

In this review, we exclude active case finding strategies that screen whole communities or whole populations at risk.

Types of outcome measures

Primary outcomes

- The rate of detection of microbiologically proven tuberculosis (by sputum smear and/or culture) among contacts of tuberculosis patients;

and

- The community-wide incidence rate of tuberculosis in the intervention population.

Secondary outcomes

Number of contacts tested per index case tested.

Search methods for identification of studies

We sought to include all relevant studies, regardless of publication status.

Electronic searches

In April 2011, we performed electronic searches using Medline, EMBASE, CENTRAL (*The Cochrane Library* 2011, Issue 2), Web of Science, Cochrane Infectious Diseases Group Specialized Register, LILACS and mRCT (meta Register of Controlled Trials) using the search terms outlined in Appendix 1.

Searching other resources

Grey literature

The grey literature such as conference proceedings and abstracts was searched for additional relevant studies.

Handsearching

The index for the *Journal of the International Union Against Tuberculosis and Lung Disease* was handsearched for relevant studies.

Reference lists

We also checked the reference lists of the studies identified in the above manner.

Correspondence

In order to identify studies which have not yet been published, or are currently awaiting publication, we contacted individuals from the following organizations: World Health Organization (WHO), Centres for Disease Control and Prevention (CDC USA), International Union Against Tuberculosis and Lung Disease (IUATLD).

Data collection and analysis

Selection of studies

Two reviewers (GJF and CCD) independently screened the selected citations by title and abstract review to identify relevant studies. Any discrepancies about study selection were resolved by consensus of the authors.

We applied the aforementioned inclusion criteria to all citations, using the title and abstract to exclude trials that obviously did not meet the criteria. If there was any uncertainty about the inclusion of a trial, the full text was obtained. Two reviewers independently assessed the eligibility for inclusion by completing a pre-formatted eligibility form. We attempted to contact the trial authors if the eligibility was unclear. We resolved any discrepancies in study selection by contacting an independent third person (GBM). Each of the trials' reports were be scrutinised to ensure that multiple publications from the same trial were included only once. We listed the excluded studies and the reasons for their exclusion.

Data extraction and management

Randomized controlled trials randomized by individual

We planned to include both randomized controlled trials that were randomized by individual and also those by cluster, since cluster randomization (such as randomization by research site) may be more practical in resource limited settings.

In order to find relevant randomized controlled trials, two reviewers independently extracted data from the studies and entered it in an electronic database with a pre-formatted template. Data to be extracted included the rates of active pulmonary tuberculosis, the nature of the relationship between the case and contact (household contact or other) and the country of origin of the study. We also extracted data on age, sex, socioeconomic status, smear status of the index case and comorbidity in the contacts. We collected information about the nature of the active case finding in the active intervention group, and the services available for case detection in the control group. We planned to report the percentages of subject follow-up in the table of study characteristics for all eligible studies.

We also planned to extract the numbers randomized and the numbers analysed in each treatment group, for each outcome.

For outcomes presented as dichotomous data in the report, we planned to extract the number of patients with the event and the total number of patients in the group for intervention and control arms. For outcomes presented as count data in the report, we planned to extract a rate ratio and a measure of variability comparing treatment to control, or the number of episodes and the total number of person years for intervention and control arms.

If there were any disagreements between reviewers arising from data extraction we initially resolved these by discussion. If disagreements persist, then the reviewers planned to contact the study authors. Any disagreements that could not be resolved by consensus would be reported in this review.

Randomized controlled trials randomized by cluster

In addition to the above search, for randomized controlled trials randomized by cluster we planned to extract the numbers randomized and the numbers analysed in each treatment group, for each outcome.

For cluster-randomized trials that adjusted for cluster sampling in the analysis, we planned to extract the measure of effect (such as risk ratio, odds ratio or mean difference) and a confidence interval or measure of variation, such as a standard error.

For cluster-randomized trials that did not adjust for clustering in the analysis, we would additionally extract the number of participants and number of clusters and the intra-cluster correlation coefficient. We would then determine the effective sample size, and adjust the standard error to account for clustering.

Missing data

We contacted study authors if we needed to obtain missing data or clarify information.

Assessment of risk of bias in included studies

Bias assessments for randomized controlled trials

Two authors (GJF and CCD) independently assessed each included study for methodological risk of bias using an assessment form. Any included randomized controlled trials were to be assessed for risk of bias by assessing the methods sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting bias and other biases, including comparability of study location. For randomized controlled trials randomized by cluster, we would also assess recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and compatibility with randomized controlled trials randomized by individual.

We planned to assign a judgement of high, low or unclear risk of bias for each trial and each primary outcome measure. We planned to group the secondary outcomes and assess them together for risk of bias.

We planned to assess each eligible study for the presence of blinding and comment upon studies where blinding was feasible.

We planned to attempt to contact the authors if any relevant information is not clear or not specified.

Measures of treatment effect

We planned to use the risk ratio to compare dichotomous data, and to use rate ratios to compare count data.

Unit of analysis issues

We planned that both index case clustering and community level clustering would be considered in the analysis using hierarchical methods. If cluster randomized trials have not adjusted for clustering in their analysis, we would adjust the results for clustering. If the intra-cluster coefficient (ICC) is not available, we would estimate this from external sources. If no similar trials exist, then we would conduct a sensitivity analysis using a range of estimates for the ICC to see if clustering could influence the individual trial's results.

Dealing with missing data

We planned to identify missing data by correspondence with study authors. If there was missing data we planned to perform a complete case analysis, otherwise we planned to perform an intention to treat analysis.

Assessment of heterogeneity

We planned to assess statistical heterogeneity by inspecting the forest plots to detect overlapping confidence intervals, applying the Chi^2 test with a P value of 0.10 used to indicate statistical significance, and also by using the I^2 statistic.

Assessment of reporting biases

We planned to assess included studies for reporting bias using funnel plots, and contact the authors for clarification where appropriate.

Data synthesis

The two authors planned to analyse relevant data using Review Manager 5. We planned to stratify the analyses according to the type of trial (randomized and quasi-randomized). Results from the randomized trials and quasi-randomized trials were to be reported in the meta-analysis, but the two types of trials would not be combined together.

Cluster-randomized trials that have adjusted for clustering in their analysis were to be analysed with randomized controlled trials randomized by individual, however cluster-randomized controlled trials that have not adjusted for clustering would not be combined with trials randomized by individual. Cluster-randomized controlled trials that have not been adjusted for clustering would be presented in a separate table.

We planned to stratify the analyses according to the following characteristics:

- Incidence of tuberculosis (<20, 20-100, and >100 incident cases per 100,000 population per year), defined by WHO estimates (WHO 2009).
- Nature of contacts: only close contacts versus close and casual contacts.
- Study design: randomized versus quasi-randomized.
- Study design: according to individual versus cluster level randomization.
- HIV incidence: <1% incidence versus 1% or greater among pregnant women in the general population (according to WHO / UNAIDS estimates) (WHO 2004).

We planned to use a fixed-effect model where there is no statistically significant heterogeneity, based upon the methods described in this review.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses according to the following factors where possible:

- Incidence of tuberculosis (<20, 20-100, and >100 incident cases per 100,000 population per year), defined by WHO estimates (WHO 2009).
- Nature of contacts: only close contacts versus close and casual contacts.
- HIV incidence: <1% incidence versus 1% or greater among pregnant women in the general population (according to WHO / UNAIDS estimates) (WHO 2004).

We planned to report when we use a fixed-effect model. We planned to use a random-effects model if there was heterogeneity but if there was substantial heterogeneity then we would not do a meta-analysis.

We planned to carry out subunit analysis for the unit of randomization.

Sensitivity analysis

If there were sufficient number of trials of varying risk of bias, we planned to conduct a sensitivity analysis to test the effect of methodological quality, including the adequacy of randomisation concealment, on the study outcomes.

RESULTS

Description of studies

We identified 31 studies using the pre-specified search strategy but none met the initial inclusion criteria for the review. One cluster randomised trial (Calvalcante 2010) did include an active case finding intervention in contacts. It compared neighbourhoods receiving routine DOTS to neighbourhoods receiving 'enhanced DOTS'. The 'enhanced DOTS' intervention incorporated screening household contacts for active tuberculosis and for LTBI using structured interview, clinical assessment, chest X-ray and tuberculin skin testing (TST). Calvalcante 2010 found that the annual tuberculosis incidence after 5 years decreased by 10% in 'enhanced DOTS' communities compared to a 5% increase in control communities. The authors calculated that this

reached statistical significance (with P value of 0.04). However, this study was excluded because the intervention included both active case finding and testing for, and treatment of, latent tuberculosis infection in contacts.Therefore, it was not possible to estimate the effect of active case finding alone on the study outcome.

Reasons for exclusion of other relevant studies are contained in table of Excluded studies. Three recent trials of active case detection were excluded, because they were community based trials. One used mobile vans in a community in Zimbabwe (Corbett 2010), one examined routine X-rays in miners in South Africa (Churchyard 2011) and the other conducted a house-to-house survey of the general community (Miller 2010).

Risk of bias in included studies

Not applicable.

Effects of interventions

This was not applicable.

DISCUSSION

Contacts of patients with infectious forms of tuberculosis are at high risk for the acquiring the disease. Active case finding in contacts of tuberculosis patients is a common practice in many low-prevalence countries (BTS 2000, Diel 2006).This strategy aims to detect early disease and, together with screening for and treatment of LTBI to prevent the onset of disease, thereby to control disease propagation within a population. Contact screening programmes are not well-established in low-income high burden countries because their limited resources are thought to be best spent on first improving the quality of treatment for patients identified by traditional conventional passive case finding. There is now growing interest in active case finding in resource-limited settings, particularly where DOTS therapy is well-established but tuberculosis incidence and prevalence rates remains high.

Although published cross-sectional and cohort studies show that contacts generally have a higher rate of disease than the general population (Morrison 2008), evidence for the impact of active case finding in this population is lacking. Recent evidence suggests that contacts of multi-drug resistant (MDR) patients (Becerra 2011), HIV positive contacts (Kranzer 2010) and children (Kruk 2008) are particularly important groups in which to consider screening due to their higher susceptibility or the more severe consequences of delayed diagnosis.

Of the small number of randomized-controlled trials addressing active case finding among contacts, none met our inclusion criteria. Some involved different interventions (such as education about sputum collection (Khan 2007), referrals to primary health facilities (Griffiths 2007) or screening of clinic patients (Fairall 2005)). Another excluded study used case notification rates, rather than microbiological testing, and also combined treatment for latent infection with the intervention of screening for active disease (Calvalcante 2010). Specific reasons for excluding studies are described below (Excluded studies).

Developing evidence for active case finding among tuberculosis contacts

In light of the limited high-quality evidence currently available, randomized controlled trials are now needed in order to assess the effectiveness of screening tuberculosis contacts for active disease. Wherever possible, the design of trials should include the random allocation of groups or individuals to screening or usual care, although blinding of participants is not feasible due to the nature of the intervention.

Such trials will require clearly defined end-points. In particular, studies screening for active disease will require a definite diagnosis of *M. tuberculosis* among contacts. Microbiological confirmation of tuberculosis, using sputum smear and/or culture, remains the most appropriate diagnostic tool for confirming pulmonary disease (WHO 2006b).

While sputum smear remains the usual standard for microbiological diagnosis in many resource-limited settings, this will miss a substantial proportion of disease. Sputum culture has a higher sensitivity and specificity than smear alone, particularly in patients living with HIV (Monkongdee 2009). Although typical chest X-ray findings and a clinical assessment are commonly used to reach a presumptive diagnosis of tuberculosis, these tools are subjective and therefore insufficiently specific. A composite end-point of 'case notification', such as that used in Calvalcante 2010, is therefore neither sufficiently specific or sensitive. For these reasons, we chose a microbiological diagnosis with sputum smear and/or culture as the primary end-point for studies selected for meta-analysis.

New highly sensitive and specific diagnostic tools for both active disease (Boehme 2010) and latent infection show promise (Wallis 2010), and may be incorporated into active case finding studies in the future. However these will require further validation in a range of settings.

Summary of main results

There are no randomised controlled trials to demonstrate or refute the effectiveness of active case finding among the contacts of tuberculosis patients in the case detection rate of disease.

One recent randomised controlled trial (Calvalcante 2010) found a significant difference between routine directly observed therapy and a screening intervention for both latent infection and tuberculosis disease. However, this study did not allow evaluation of the effectiveness of active case finding alone in contacts of patients with tuberculosis.

The present review only covers active case finding among contacts.

Potential biases in the review process

The review process may have missed some studies which have not been published. We attempted to minimise bias by following prescribed search criteria, and by having two authors review the abstract of each paper, and then compare their conclusions about their suitability for inclusion in the review.

Agreements and disagreements with other studies or reviews

Although we identified one paper which finds benefit from a composite intervention of active case finding and LTBI screening, we have not included that paper for the above reasons. We found no other high quality studies or meta-analyses which demonstrate a benefit for active case finding among contacts. A recent systematic review of the literature showed considerable heterogeneity among cross-sectional studies of active case finding (Morrison 2008), however available data are insufficient to inform a meta-analysis of the impact of screening programmes upon case detection rates among contacts of patients with active tuberculosis. A review of strategies using community screening is also required, in the light of recent published trials.

AUTHORS' CONCLUSIONS

Implications for practice

Current policies of active case finding among contacts seem to be based on research evidence demonstrating a high prevalence of active tuberculosis in household contacts with confirmed tuberculosis. A key assumption behind these policies is that active case finding among contacts will detect more cases, earlier in the course of disease, than waiting for this high-risk group to self-refer to health care facilities for treatment.

Current and planned policies, in the absence of trial evidence, need to take the high prevalence of active tuberculosis among contacts into account, along with the population prevalence of disease, available diagnostic tests, the degree of patient exposure, the availability of health system resources, factors influencing the susceptibility of contacts (including age and HIV status) and drug resistance of the organism. Improved case finding in high-burden countries is an important component of disease control programmes, and active case finding among contacts remains one option, even though we have no evidence from randomized controlled trials evidence providing an estimate of the effectiveness of this intervention.

Implications for research

This review identifies the need for further research of active case finding among contacts, evaluating the most effective strategies to carry out active case finding among contacts, and to compare it with other approaches to active case finding, such as interventions targeted at whole communities.

For ethical and practical reasons, it is important to ensure that active case finding programmes occur within the context of National Tuberculosis Programmes that have the capacity to deliver effective therapy once tuberculosis is diagnosed. In countries where the DOTS programme is not achieving good treatment success rates, the first priority for additional resources should be improving tuberculosis management.

Trials of active case finding among contacts should use verifiable end-points such as microbiologically confirmed disease. Operational research in high-burden settings should also employ interventions that are simple and affordable. Cluster randomization is likely to be more appropriate. An economic evaluation, including cost-effectiveness, will help decision making.

ACKNOWLEDGEMENTS

The authors are grateful to our affiliated Institutions and Organizations, and thank the referees and editors for their comments and encouragement. The editorial base for the Cochrane Infectious Disease Group is funded by the Department for International Development (DFID), UK, for the benefit of low- and middle-income countries.

REFERENCES

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Calvalcante 2010	The authors tested the effect of an 'enhanced DOTS' intervention, incorporating screening household contacts for active tuberculosis and for LTBI, compared to conventional DOTS using a matched pair cluster randomised trial. After 5 years the annual incidence of tuberculosis decreased by 10% in 'enhanced DOTS' communities compared to a 5% increase in control communities (P = 0.04). This study was excluded because the intervention included both active case finding and testing for, and treatment of, latent tuberculosis infection in contacts.Therefore, it was not possible to estimate the effect of active case finding alone on the study outcome.
Churchyard 2011	The study did not specifically examine contacts of known tuberculosis patients, and therefore does not meet our inclusion criteria. This study enrolled a population of gold miners, known to have a high prevalence of tuberculosis. The intervention was radiological screening, either three or five times over the two year follow-up period.
Corbett 2010	The study did not specifically examine contacts of known tuberculosis patients, and therefore does not meet our inclusion criteria. Instead, it was a randomised controlled trial of a community-based screening programme of symptomatic individuals. The participants were chosen based on their reported symptoms, not on their relationship to a known contact with tuberculosis.
Daitko 2009	A different intervention. This study involved health extension workers in tuberculosis case detection.
Fairall 2005	This study did not screen contacts of tuberculosis patients, but those attending primary care clinics.

Study	Reason for exclusion
Fairall 2010	This was not the primary study. See Fairall 2005.
Griffiths 2007	A different intervention, not involving tuberculosis contacts, but patients presenting to a primary care clinic.
Khan 2007	A different intervention, involving education about sputum collection and submission.
Lemos 2004	Cohort study.
Magkanas 2005	Cohort study examining prevalence of X-ray abnormalities in a defined population.
Miller 2010	This study compares two active case finding interventions in the general community. This does not address specifically not of contacts of known tuberculosis patients.
Noertjojo 2002	A retrospective cohort study of household contacts of tuberculosis patients.
Sekandi 2009	No control group.
Shargie 2006	This study does not target contacts of tuberculosis patients.
Styblo 1984	Non-randomized groups, and the study population is not contacts of tuberculosis patients.
Yimer 2009	A cross-sectional study with no control group.
Zachariah 2003	Cohort study with historical control group only.

APPENDICES

Appendix 1. Detailed search strategy

Search set	CENTRAL	MEDLINE	EMBASE	LILACS	Web of Science	mRCT
1	tuberculosis	tuberculosis [MeSH]	'tuberculosis':de	tuberculosis [descriptor]	ts=(tuberculosis)	tuberculosis
2	*Mycobacterium tuberculosis*	tuberculosis [m_titl]	'tuberculosis':ti	tuberculosis	ti=(tuberculosis)	*Mycobacterium tuberculosis*
3		*Mycobacterium tuberculosis* [MeSH]	'tuberculosis':ab		ts=(*Mycobacterium tuberculosis*)	
4	Contact tracing	Tuberculosis, Pulmonary [MeSH]	'Contact tracing':ti	contact	ts=(Contact tracing)	Contact tracing
5	contact$	contact$	'contact$':de	contact tracing [descriptor]	ts=(contact screen$)	contact$
6		tuberculosis contact$	'contact tracing':ab	surveillance	ti=(contact$)	

(Continued)

7		contact tracing [MeSH]	'transmission':ti	outbreak [title]	ti=(tuberculosis contact$)	
8		contact$ [m_titl]*	'screening':ti	household	ti=(outbreak$)	
9		disease outbreak$*	'case finding':ti	cluster analysis [descriptor]	ti=(household)	
10		spread$ [m_titl]	'household':ti			
11		contact screen$				
12		contact tracing [m_titl]*				
13		disease transmission, infectious [MeSH]				
14		case find$ [m_titl]				
15		cluster analys$				
16		household member$				
17		household contact$				
18		transmis$ [m_titl]				
19	1 or 2	1 or 2 or 3 or 4	1 or 2 or 3	1 or 2	1 or 2 or 3	1 or 2
20	4 or 5	6 or 7 or 8... or 18	4 or 5 or 6 or... or 10	4 or 5... or 9	4 or 5... or 9	4 or 5
21	19 and 20	19 and 20	19 and 20	19 and 20	19 and 20	19 and 20

CONTRIBUTIONS OF AUTHORS

Gregory J Fox and Claudia C Dobler extracted data according to the protocol and helped to write the review. Guy B Marks reviewed the inclusion of papers, and helped to write the review.

DECLARATIONS OF INTEREST

None identified.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Greg Fox is supported by a National Health and Medical Research Council (NH&MRC) Postgraduate Research Scholarship and an NH&MRC Project Grant, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None identified.

NOTES

The Contact Editor for this review was Dr Gerry Davies, with input from Professor Paul Garner and Dr David Sinclair.

INDEX TERMS

Medical Subject Headings (MeSH)

Contact Tracing [*methods]; Tuberculosis, Pulmonary [*diagnosis] [transmission]

MeSH check words

Humans