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Contact tracing strategies in household and congregate environments to identify cases of tuberculosis in low- and moderate-incidence populations (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Contact tracing strategies in household and congregate environments to identify cases of tuberculosis in low- and moderate-incidence populations

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness of novel methods of contact tracing versus current standard of care to identify latent and active cases in low- to moderate-incidence settings.

BACKGROUND

Description of the condition

Mycobacterium tuberculosis is an infectious disease that causes tuberculosis infection in susceptible individuals. These bacteria are spread through the expectoration of respiratory droplets, and the disease can be transmitted to other individuals (contacts) by infected people (index cases) prior to treatment interventions. Exposure to tuberculosis can result in active disease or latent tuberculosis infection (LTBI); the latter demonstrates no clinical symptoms or radiological (X-ray) evidence of disease (Young 2016). In this way, the endemic nature of tuberculosis is propagated and tuberculosis infection is currently thought to affect 10 million people annually with severe disease, resulting in approximately 1.4 million deaths a year (WHO 2016).

In order to reduce the incidence of tuberculosis, relevant services engage in contact tracing; this is the evaluation of contacts of infected people for tuberculosis disease. While there are a number of defined screening methods to identify latent and active disease, methodologies used to identify those individuals deemed to be contacts are less obvious. The aim of effective contact tracing is to identify those exposed individuals with infection (either latent or active disease) as quickly and efficiently as possible.
Identifying the contacts of people with tuberculosis usually occurs once an index case has been identified. This screening process can identify a substantial group of contacts depending on the index case's home, work, and travel arrangements.

Description of the intervention

Contact tracing in low- (fewer than 30 per 100,000) and moderate-incidence (30 to 100 per 100,000) countries aims to identify individuals with latent or active tuberculosis infection, or both (WHO 2016). This approach often differs from areas of high incidence (greater than 100 per 100,000) where the emphasis remains on identifying and treating active cases as a priority. Given the large number of cases in high-incidence settings and limited resources, this is the most cost-effective approach.

The currently adopted approach utilises a 'stone-in-pond' model (Veen 1992), with each 'ripple' representing a social circle with varying degrees of physical proximity to the index case, thus suggesting a way to limit screening sizes in contact tracing scenarios. This involves screening individuals deemed to fall within different risk strata to the patient; thus family is the most proximal relationship, is therefore seen to have the highest risk, and family members are screened as a priority, followed by close friends deemed to have the next highest exposure risk, casual contacts, and so on. Screening contacts thus proceeds from the innermost (most proximal/perceived highest risk) social circle to the least-related (Veen 1992).

The stone-in-pond model relies on assumed, consistent social relationships for all infected people, as a negative screen in a closer contact group results in the cessation of further contact tracing (for example, if household contacts were negative, no further groups would be screened). This consistency in social relationships and presumed proximity for all individuals may not be universally applicable. The utility of this approach compared to alternate approaches has not been evaluated.

Traditional contact tracing methods may not take into account areas of congregation (that is, areas of common social aggregation; for example, occupational, educational, recreational, and transport environments), which have been shown to be potential sources of transmission for tuberculosis, especially for at-risk population groups (Barnes 1996). In addition, people with tuberculosis may have varying degrees of contact with alternate groups that do not fit with perceived proximity circles (for example, college students spending more time with close friends than family).

Apart from the above stone-in-pond model, we are not aware of any named, contact tracing methodologies in clinical use. Recent research papers have examined alternate approaches using methods to draw on non-linear social interactions in congregate settings, an approach known as social network analysis. Patients are questioned as to possible contacts but, importantly, also social activities, hobbies, alcohol and drug use, work and recreational activities. This geotemporal data collection provides clinicians with possible locations of interaction where transmission of disease may have occurred thus expanding the pool of potential contacts. When combined with whole genome sequencing, a novel genomic approach to diagnosis and typing of tuberculosis strains, outbreaks can be mapped to a higher resolution and clearer links between contacts made. This method is not in general clinical use.

How the intervention might work

The effectiveness of the current contact tracing methodology (stone-in-pond approach) is called into question by whole-genome sequencing, where genetic links are found between otherwise unscreened/epidemiologically unrelated contacts, demonstrating deficiencies in current methods. Some research groups have demonstrated the utility of alternative contact tracing approaches, including social network analysis. These methodologies could provide a higher yield of case detection whilst not allowing tuberculosis incidents to propagate and provide epidemiological links that more closely model genetic links (Gardy 2011). Assessing for alternative contact tracing methodologies could provide a much-needed evidence base to current clinical practice or if lacking, demonstrate the need for more evidence.

Why it is important to do this review

We are not aware of any published reviews that have examined alternative contact tracing approaches for a higher rate of latent and active case detection. In addition, there is a paucity of evidence of the appropriate contact tracing approach in public settings versus household settings. Our Cochrane Review may better inform resource allocation.

This review will add to the evidence base for meaningful strategies in the early detection and prevention of tuberculosis targeting low- and moderate-incidence settings and will assist in achieving the World Health Organization (WHO) tuberculosis elimination goal (Young 2016).

New developments in genomic diagnostics, such as whole-genome sequencing, and studies that suggest the benefit of social network analysis raise the prospect of alternative approaches that should be evaluated. It is likely that there will not be many randomized controlled trials (RCTs) that compare contact tracing methodologies. However, by highlighting the lack of comparative evidence and raising the prospect of alternatives, this Cochrane Review could form the basis for future research comparing contact tracing strategies.

OBJECTIVES

To assess the effectiveness of novel methods of contact tracing versus current standard of care to identify latent and active cases in low- to moderate-incidence settings.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and cluster-RCTs.

Types of participants

People of any age, gender and ethnicity living in low (< 30 per 100,000) and moderate (30 to 100 per 100,000 population) tuberculosis incidence settings.

Types of interventions

Intervention

Any contact tracing strategy to identify tuberculosis infection cases other than a stone-in-pond screening approach (standard care).

Controls

Stone-in-pond contact screening approach (standard care).
The stone-in-pond method describes the contact tracing approach of prioritising contacts by risk-stratifying cases based on assumed proximity. Household contacts therefore have the highest presumed risk and are the closest circle to be screened followed by the next 'ripple' which may be close friends then casual friends, and so on. This set of outwardly expanding concentric circles is similar to the appearance of a stone being dropped in a pond with the ripples generated representing concentric circles of risk proximity.

Types of outcome measures

Primary outcomes

- Number of people with tuberculosis infection identified through screening strategies.

Secondary outcomes

- The number of contacts with disease (latent and active tuberculosis versus non-infected contacts) identified between the two screening approaches.

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); LILACS (BIREME); CINAHL (EBSCOHost); Science Citation Index-Expanded and Social Sciences Citation Index (Web of Science). We will search the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/), ClinicalTrials.gov (clinicaltrials.gov/ct2/home), and the Clinical Trials Unit of the International Union against Tuberculosis and Lung Disease (IUATLD; www.theunion.org), for trials in progress, using 'tuberculosis", 'contact tracing' and 'contact screening' as search terms.

Searching other resources

We will search the following conference proceedings for abstracts of relevant studies: World Congress on TB, World Lung Conferences of the International Union Against Tuberculosis Lung Disease (IUATLD), American Thoracic Society Meetings Proceedings, and the British Society for Antimicrobial Therapy. We will contact researchers and experts in the field to identify any additional eligible studies. We will also check the references of all included studies to identify additional studies (Lefebvre 2011).

Data collection and analysis

In the event that we identify studies, we will contact study authors to identify any additional, relevant unpublished data or results where applicable.

Selection of studies

Two review authors (DBM, BM) will independently screen all study abstracts and citations identified by the above search criteria using a study selection form. We will obtain full texts of studies that potentially meet the eligibility criteria. Two review authors will independently assess the full texts and will record exclusions and reasons for exclusions in a 'Characteristics of excluded studies' table. We will resolve any discrepancies that arise between review authors through discussion until we reach a consensus. Where there is ongoing disagreement, we will consult a third review author (MD). Where clarification on study methodology is required, we will contact the study authors. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors will independently extract data using a data extraction form. Where disagreements arise, we will resolve these

through discussion or by consulting the third review author (MD). We will extract information on the following.

- Study details: start and end dates, study location, study design, funding, tuberculosis prevalence (as stated by the study authors), conflict of interests.
- Participant details: demographic details (age and sex), geographic location, index case description. Description of contact relationship.
- Details of the intervention: how were these individuals identified as contacts, and the methodology used. Outcome as active or latent.
- Details of any co-interventions: did the methodology differ depending on the setting (congregate versus household). Where household setting would be the shared living accommodation and congregate setting describes a non-household, area of common social aggregation, for example, occupational, educational, recreational, and transport environment.
- Details of the control: standard of care employing stone-in-pond model of contact tracing. We will identify the number of contacts identified from each described outbreak or incident event. The number of contacts identified and screened with tuberculosis infection (active or latent disease - numerator) over the total number of contacts identified and screened (denominator). An outbreak/incident event is declared where multiple contacts are identified in relation to a new index case. The number of contacts varies, and usually a congregate setting is involved for an outbreak/incident event to be identified. Where the unit of analysis in studies is the same, we will group studies.
- Cluster-RCTs: we will record the number, size and method used for clustering. In addition, we will note the clustered measure of effect and variance if this was adjusted for by study authors. If the study authors did not make any adjustment for clustering, we will extract the number of participants experiencing the event and the number randomized to each group (for dichotomous outcomes). For continuous outcomes, we will extract the summary effect (mean or median) and the measure of variance (standard deviation or range).

After data extraction, two review authors (DBM and BM) will enter data into Review Manager 5 (RevMan 5) (RevMan 2014). We will contact study authors to clarify any unclear data or in the event of missing or incomplete data. For continuous outcomes, we will record the measure of effect (mean or median) and variance (SD or range). For dichotomous outcomes, we will note the number of participants with the outcome event and the total number of participants in each intervention group.

Assessment of risk of bias in included studies

Two review authors (DBM and BM) will independently assess the risk of bias of each included study using the Cochrane 'Risk of bias' tool (Higgins 2017). We will resolve any differences of opinion through discussion and, if necessary, a third review author (MD) will arbitrate. Where there is missing, unclear, or incomplete data, we will contact study authors for further information.

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 will record the methods used by the study authors to reduce the risk of bias and assign a judgment of 'low risk of bias', 'high risk of bias', or 'unclear'.

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

We will summarize 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

In order to assess the treatment effect, we will examine continuous and dichotomous data separately. For continuous data, we will assess effect by mean differences and for dichotomous data, we will use risk ratios. We will present 95% confidence intervals (CIs) and ranges.

Unit of analysis issues

Where study authors have not adjusted the results of cluster-RCTs for the effect of the cluster design, we will adjust the sample sizes using the methods described in Section 16.3.4 or 16.3.6 (Higgins 2011), using an estimate of the intra-cluster correlation coefficient (ICC). Where possible, we will derive the ICC from the trial itself, or from a similar trial. If an appropriate ICC value is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of ICC values.

Dealing with missing data

Where there is missing or incomplete data, we will try to contact trial authors for further information. Further than this, there will be no imputation measures for missing data.

Assessment of heterogeneity

We will assess statistical heterogeneity between trials by visual inspection of the forest plots to detect overlapping CIs, and applying the Chi^2 test and I^2 statistic (Higgins 2003). We will consider a Chi^2 P value less than 0.05 as statistically significant, and an I^2 statistic value greater than 75% as representing considerable heterogeneity (Deeks 2017).

Assessment of reporting biases

We will examine the likelihood of reporting bias using funnel plots, provided that there are at least 10 included trials (Sterne 2017).

Data synthesis

We will analyse data using RevMan 5 (RevMan 2014). The primary analysis will be stratified by study design (cluster-RCTs and individual RCTs) and we will not perform meta-analysis across different trial designs.

We will stratify outcomes according to number of cases detected at a particular time point per contact tracing strategy. Where appropriate, we will group time points and will perform a meta-analysis (for example, changing number of contacts over time in a single contact tracing episode).

We will tabulate results from cluster-RCTs that cannot be adjusted for clustering. We will use a random-effects model in the presence of significant statistical heterogeneity and a fixed-effect model in the absence of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We will investigate potential causes of heterogeneity by performing subgroup analyses by study setting (congregate versus home), screening test used, risk factors in demography (drug and alcohol use, immunosuppressive states), occupation, age of participants, and tuberculosis prevalence in study area.

Sensitivity analysis

We will perform sensitivity analyses if a minimum of 10 trials meet the inclusion criteria. We will conduct sensitivity analyses on the robustness of the results to the 'Risk of bias' components.

Certainty of the evidence

We will use the GRADE approach to assess the certainty of the evidence and we will create 'Summary of findings' tables and Evidence Profiles (GRADEpro 2015).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

#1	tuberculosis [MesH]
#2	tuberculosis or TB Title/Abstract
#3	Mycobacterium tuberculosis [MesH]
#4	#1 or #2 or #3
#5	“Contact Tracing”[Mesh]
#6	“contact tracing” Title/Abstract
#7	“contact screening” or “contact management” Title/Abstract
#8	“contact investigation*” Title/Abstract
#9	“transmission dynamics” Title/Abstract
#10	Referral Title/Abstract
#11	“stone in pond” Title/Abstract
#12	“household screening” Title/Abstract
#13	“social network*” Title/Abstract
#14	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

(*Continued*)

#15	#4 and #14[a]

[a]We will use search terms in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011). This is the preliminary search strategy for MEDLINE (PubMed). It will be adapted for other electronic databases. We will report all search strategies in full in the final review version.

CONTRIBUTIONS OF AUTHORS

All review authors jointly contributed to the development of the protocol.

DECLARATIONS OF INTEREST

DBM has no known conflicts of interest.

BM has no known conflicts of interest.

MD has no known conflicts of interest.

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