RECOMMENDATIONS FOR INVESTIGATING CONTACTS OF PERSONS WITH INFECTIOUS TUBERCULOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

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RECOMMENDATIONS FOR INVESTIGATING CONTACTS OF PERSONS WITH INFECTIOUS TUBERCULOSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

CONTENTS

ACRONYMS AND ABBREVIATIONS

DOTS	brand name of the internationally recommended strategy for tuberculosis control until 2005 and the basis of the Stop TB Strategy initiated in 2006
HIV	human immunodeficiency virus
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
PLHIV	person living with HIV infection
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

ACKNOWLEDGEMENTS

These guidelines for investigating contacts of tuberculosis (TB) patients were prompted by requests from the managers of many national TB programmes. The document was prepared by Philip Hopewell, Elizabeth Fair and Cecil Miller at the University of California at San Francisco, USA, and the American Thoracic Society.

A steering committee was established by the World Health Organization (WHO) to identify the elements that should be included in the document, the questions to be addressed and the systematic reviews to be conducted. The steering committee comprised: Leopold Blanc, Angelito Bravo, Daniel Chemtob, Dennis Falzon, Malgosia Grzemska, Ernesto Jaramillo, Knut Lonnroth, Paul Nunn, Salah Ottmani, Delphine Sculier, and Mukund Uplekar from the WHO Stop TB Department, Geneva, Switzerland, Jacob Creswell and Sahu Suvanand from the Stop TB Partnership, Geneva, Switzerland, and Elizabeth Fair and Philip Hopewell from the American Thoracic Society.

An expert panel reviewed the responses to the questions and drafted recommendations. The members of the expert panel were:

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The expert panel was chaired by Holger Schünemann (McMaster University, Canada), an expert in the methodology of summarizing evidence and formulating guidelines. Greg Fox (Australia and Viet Nam), Fran DuMelle (American Thoracic Society), Cecily Miller and Margareth Harris (WHO) were observers at the expert panel meeting.

Greg Fox and Guy Marks (University of Sydney, Australia) conducted the systematic review that provided much of the evidence for the recommendations.

Elizabeth Fair, Adithya Cattamanchi (USA), Cecily Miller and Philip Hopewell updated the review conducted by Morrison et al. published in 2008.

The near-final draft was reviewed and input provided by Draurio Barreira (Brazil), Rosella Centis (Italy), Mark Cotton (South Africa), Liat D'Ambrosio (Italy), Masoud Dara (WHO regional office for Europe, Denmark), Anne Detjen (Germany), Penny Enarson (International Union Against Tuberculosis and Lung Disease, France), Steve Graham (Australia), Anneke Hesseling (South Africa), Cleotilde Hidalgo How (Philippines), Anna Mandalakas (USA), Ben Marais (South Africa), Giovanni Battista Migliori (Italy), Fatima Razia (Pakistan), Andreas Reis (WHO), Simon Schaaf (South Africa), Michael Selgelid (Australia), Maryse Wanlin (Belgium) and Jean-Pierre Zellweger (Switzerland).

Preparation of the document was coordinated by Salah Ottmani (WHO) and Fran DuMelle (American Thoracic Society)

All GDG members and the external reviewers, who provided comments on the document, completed and signed the WHO form on conflict of interest. No conflicts of interest were identified. There was no disclosure of any intellectual conflict of interest of the GDG members and reviewers.

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FOREWORD

Tuberculosis (TB) contacts are people who have close contact with patients with infectious TB. As they are at high risk for infection (and in line with the Stop TB strategy), TB contacts should be investigated systematically and actively for TB infection and disease. Such interventions are called 'tuberculosis contact investigations'. They contribute to early identification of active TB, thus decreasing its severity and reducing transmission of *Mycobacterium tuberculosis* to others, and identification of latent TB infection (LTBI), to allow preventive measures.

Contacts are commonly investigated in high-income countries with low TB burdens and in settings in which a TB elimination policy is implemented, in order to identify persons with early active TB or who have recently been infected. People identified as infected are then treated for LTBI with isoniazid for at least 6 months (usually 9 months) or with shorter combination regimens including isoniazid and rifampicin.

TB contact investigations are rarely and inconsistently carried out in resource-limited settings. In most low- and middle-income countries, it is included in the national policy to control and prevent TB; however, in the vast majority of countries, it is either not undertaken or is implemented on the basis of no or poor standards, because of the absence of clear definitions of index cases, contacts and procedures. Furthermore, the health personnel who should be involved are usually not clearly identified. Information on the contribution of routine contact investigations to early TB case detection is scarce in these countries or is non-standardized, thus precluding an assessment of its impact on reducing transmission.

Many studies in countries with a high TB incidence have shown that the prevalence may reach 5% or more among contacts, particularly among household members. Other data suggest that contact investigations could be particularly useful for identifying childhood TB. Furthermore, contact investigation can help identify people who require careful follow-up, such as those who were exposed to an index case of multi-drug-resistant or extensively drug-resistant TB or people infected with HIV, whose risk for rapid progression to active TB is very high.

Effective investigation of TB contacts within national TB programmes and other services can result in the detection of a significant number of cases. WHO estimates show that, worldwide, highly infectious, smear-positive pulmonary TB develops in over 4 million people annually. If we assume that each of these patients has at least three close contacts, such as in their household, and that the prevalence of active TB among the close contacts is 2.5%, the number of early TB cases that could be identified among close contacts is at least 300 000 per year. Early identification means a better chance of cure and, especially, a reduction in further transmission. Furthermore, contact investigation allows identification of people who are latently infected and at high risk for active TB, who can be treated preventively.

This WHO policy document was prepared to guide national TB programme staff and all agencies and organizations involved in TB prevention, care and control to establish strategies for sound TB contact investigation practices. The document was elaborated after an extensive literature review and with contributions from experts around the world. It states the fundamental principles and procedures for an appropriate approach to TB contact investigation, and annexes 1 and 2 provide further details to understand these principles. The hope is that these evidence-based guidelines will be translated into country policy and practice, so that an additional neglected intervention can be put in place and, ultimately, contribute to elimination of TB.

Dr Mario Raviglione
Director, Stop TB Department, World Health Organization

EXECUTIVE SUMMARY

The main purpose of these recommendations is to assist national and local public health tuberculosis (TB) control programmes in low- and middle-income countries to develop and implement case finding among people exposed to infectious cases of TB.

Systematic evaluation of people who have been exposed to potentially infectious cases of tuberculosis (TB) can be an efficient, targeted approach to intensified TB case finding that is within the purview of TB control programmes. There are, however, no comprehensive global recommendations for programmes. WHO, the International Union against Tuberculosis and Lung Disease and the *International Standards for Tuberculosis Care* all recommend that children < 5 years of age and persons living with HIV (PLHIV) who are exposed to infectious cases of TB be evaluated for active TB and considered for treatment of latent tuberculosis infection (LTBI) if active TB is excluded. With these exceptions, there are no recommendations at global level to:

- define the epidemiological and programme conditions under which contact investigation is indicated;
- describe TB index patients on whom contact investigation should be focused;
- identify TB contacts who should be investigated (other than children < 5 years of age and PLHIV); and recommend the procedures to be used for identifying, screening and tracking TB contacts.

The following recommendations are based on recent systematic reviews of the literature on contact investigation in low- and middle-income countries. The reviews are summarized in annexes 1 and 2.

Note: The definitions in Section 4 should be read to fully understand the recommendations.

These recommendations were prepared following the WHO procedures for guideline development. A steering committee consisting of Stop TB Department staff met twice to determine the scope of the document, to identify relevant questions and to review the plan. A guideline development group (GDG) consisting of experts in relevant areas was selected. Additional input was provided by an external stakeholders group. All GDG members and the external reviewers, who provided comments on the document, completed and signed the WHO form on conflict of interest. No conflicts were identified.

Recommendation 1 It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- has sputum smear-positive pulmonary TB,
- has multi-drug-resistant TB (MDR-TB or extremely-resistant TB (XDR-TB) (proven or suspected),
- is a PLHIV or
- is a child < 5 years of age.

Strong recommendation, very low-quality evidence

Recommendation 2 It is suggested that contact investigation be conducted for household and close contacts of all other index cases with pulmonary tuberculosis, in addition to the index cases covered in Recommendation 1.

Conditional recommendation, very low-quality evidence

Recommendation 3 Clinical evaluation of household and close contacts for active TB is recommended as a priority on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to:

- people of all ages with symptoms suggestive of TB,
- children < 5 years of age,
- people with known or suspected immunocompromising conditions (especially PLHIV) and contacts of index cases with MDR-TB or XDR-TB (proven or suspected).

Strong recommendation, very low-quality evidence

Recommendation 4 In settings of high HIV prevalence it is recommended that all household and close contacts be counselled and tested for HIV.

Strong recommendation, very low-quality evidence

Recommendation 5 It is recommended that all household contacts of an index case who is a PLHIV should be counselled and tested for HIV.

Strong recommendation, very low-quality evidence

Recommendation 6 It is recommended that all household and close contacts of people with TB who have symptoms compatible with active TB should receive counselling and testing for HIV as part of their clinical evaluation.

Conditional recommendation, very low-quality evidence

Recommendation 7 PLHIV who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed LTBI as per WHO guidelines.

Strong recommendation, high-quality evidence

Recommendation 8 Children < 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed LTBI as per WHO guidelines.

Strong recommendation, high-quality evidence

1.
INTRODUCTION

1.1 CHAPTER OBJECTIVES

This chapter presents the purpose, target audience, scope and rationale for the recommendations for contact investigations.

1.2 PURPOSE AND TARGET AUDIENCE

The main purpose of these recommendations is to assist national and local public health tuberculosis (TB) control programmes in low- and middle-income countries to develop and implement case finding among people exposed to infectious cases of TB. Specific approaches to implementing the recommendations will require local adaptation based on the epidemiological circumstances and the capacity of TB control programmes.

These recommendations are relevant not only to TB control programmes but also to all providers who evaluate and treat patients with TB in the public and private sectors, especially in institutional settings, and high-risk populations. Providers outside TB programmes may find it feasible and effective to collaborate with local public health authorities in conducting contact investigations, rather than undertaking such investigations themselves. These recommendations should be consistent with and complement overall case finding strategies and programme policies.

1.3 OBJECTIVES

The overall objectives of these recommendations are to enable TB programmes to:

- identify and prioritize TB index cases around whom contact investigation should be focused,
- identify and prioritize TB contacts who require clinical evaluation and
- to provide guidance on procedures to be used in clinical evaluation of TB contacts.

1.4 RATIONALE

Systematic evaluation of people who have been exposed to potentially infectious cases of TB can be an efficient, targeted approach to intensified case finding that is within the purview of TB control programmes; however, there are no comprehensive, global recommendations to guide programmes in this activity. WHO, the International Union against Tuberculosis and Lung Disease and the *International Standards for Tuberculosis Care* all recommend that children < 5 years of age and people living with HIV (PLHIV) who are exposed to infectious cases of TB be evaluated for active tuberculosis and considered for treatment of latent TB infection (LTBI) if active TB is excluded (1–4). Guidelines exist for Europe (5) and the United States (6), but there are no recommendations at global level for low- and middle-income countries to:

- define the epidemiological and programme conditions under which contact investigation is indicated,
- describe TB index patients on whom contact investigation should be focused,
- identify TB contacts who should be investigated (other than children < 5 years of age and PLHIV) and
- recommend the procedures to be used in identifying, screening and tracking TB contacts.

As described below, systematic reviews of published studies show that a pooled average of 3.5–5.5% (the equivalent of a prevalence of 3500–5500 per 100 000 population) of household members or other close contact with a person who has infectious TB are themselves found to have previously undiagnosed, active TB, although there is considerable heterogeneity in these results (7,8). These findings suggest that contact investigation may result in earlier identification of cases, possibly decreasing disease severity and reducing transmission of *Mycobacterium tuberculosis*. Despite this potential benefit, routine contact investigation is performed in only a few countries with high to medium incidences of TB.

At least six current concerns suggest that the evidence for broadened contact investigation guidelines and recommendations should be reviewed:

- Diagnostic delay is increasingly recognized as an impediment to effective TB control (9,10).
- Some countries are seeking to improve suboptimal programme performance.
- Some countries that are performing well are ready to enter a new phase of TB control: to identify all TB cases. Contact investigation would be an appropriate next step.
- Intensified case finding has been shown to minimize the impact of TB in PLHIV, and contact investigation is a targeted approach to intensified case finding (4).
- Because of the high risk of children < 5 years of age for TB, contact investigation may result in early detection of disease and identify candidates for treatment of LTBI per WHO recommendations (1).
- Systematic investigation of contacts of known or suspected cases of multi-drug-resistant TB (MDR-TB) may be effective for reducing the ongoing transmission of drug-resistant strains of *M. tuberculosis* in a community, although this as yet unproven.

1.5 METHODS

These recommendations were prepared following the WHO procedures for guideline development (11). A steering committee consisting of Stop TB Department staff met twice to determine the scope of the document, to identify relevant questions and to review the plan. A panel of experts in relevant areas was selected as the Guideline Development Group (GDG)The near-final draft was submitted to 45 reviewers in late November 2011.These reviewers were selected based on their partner affiliation, expertise, perspectives and geographic regions. They were solicited to review and submit comments. Nineteen of them did so. Their comments were taken into account in finalizing the document

All GDG members and the external reviewers, who provided comments on the document, completed and signed the WHO form on conflict of interest. No conflicts were identified. Input from the expert group was obtained by a face-to-face meeting in September 2011, conference calls and e-mail. A draft for comments was presented to a meeting of stakeholders at the World Conference of the International Union Against Tuberculosis and Lung Disease in Lille, France, in October 2011.

1.6 STRENGTH OF RECOMMENDATIONS

A judgement about the strength of the recommendations was based on the quality of the evidence, values, costs and opinions about trade-offs between benefit and harm. The group graded the strength of each recommendation to reflect the degree of confidence that the desirable effects of adherence to the recommendation would outweigh the undesirable effects. Although degree of confidence is necessarily a continuum, we used two categories: strong and conditional. The quality of the evidence was assessed according to the GRADE method (12).

'Moderate' quality of evidence indicates that the estimate of an effect of the intervention might be uncertain, and further research may affect confidence in the estimate while 'low' quality of evidence suggests that the estimate of the effect is highly uncertain, and further research is likely to affect confidence in the estimate. In contrast, for high-quality evidence, further research is unlikely to change confidence in the estimated effect.

A strong recommendation indicates that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects. The words 'should' or 'should not' are used in strong recommendations. No alternatives are listed. A conditional recommendation indicates that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects, but the trade-offs are uncertain. Reasons for lack of certainty include:

- lack of high-quality evidence to support the recommendation,
- few benefits of implementing the recommendation,
- the benefits may not justify the costs or
- it was not possible to arrive at precise estimates of benefit.

Conditional recommendations contain the word 'may'. Alternatives may be listed.

Table 1 shows the differences between strong and conditional recommendations in terms of both wording and the factors used to judge their strength. Strong and conditional recommendations have different implications for policy-makers, patients and health care providers; these are also summarized in Table 1.

In this document recommendations 1, 3, 4, and 5 are categorized as "strong" even though the evidence is graded as "very low". These recommendations are so categorized because the systematic reviews indicated benefits with little potential harms, but there were no data on alternative approaches, cost, or overall programmatic impact. Recommendation 2 was categorized as "conditional" based "very low" quality evidence because the studies cited in the systematic reviews, by-and-large, included only household contacts of sputum smear positive patients so the data do not directly relate to the contacts covered by the recommendation. Recommendation 6 is categorized as "conditional" with "very low" quality evidence because the existing data are very limited, but HIV testing of symptomatic persons is standard clinical practice, at least in high HIV prevalence areas.

Table 1. Characteristics of 'strong' and 'conditional' recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries

	'Strong' recommendation	'Conditional' recommendation
PHRASING OF RECOMMENDATION	'Should' or 'should not'; no alternatives are proposed.	'Optimal', 'may' or 'it is not recommended'; alternatives are often proposed.
FACTORS USED TO JUDGE STRENGTH		
Quality of evidence	High	Low
Balance between desirable and undesirable effects on patients and public health	Large, certain net benefit or difference between benefits and harms or burden	Small or uncertain gradient
Resources required	Low cost or little uncertainty about whether the intervention represents a wise use of resources	High cost or much uncertainty about whether the intervention represents a wise use of resources
Uncertainty about values and preferences; variation by patient	Small	Large
IMPLICATIONS		
For policy-makers, including national tuberculosis programme managers	The recommendations should be used unequivocally for setting policy.	Use of the recommendations for setting policy will require extensive debate.
For patients	Most would want the recommended course of action.	The recommended course of action can be adjusted on the basis of feasibility and acceptability.
For health care providers	Most patients should be treated according to the recommended course of action. Adherence to this recommendation is a reasonable measure of good-quality care.	

1.7 PUBLICATION, IMPLEMENTATION, EVALUATION AND EXPIRY DATE

This document will be published in English in hard copies and will also be available on the WHO web site. The Stop TB department will work closely with the WHO regional and country offices, the Stop TB Partnership and partners involved in tuberculosis control services to ensure its wide dissemination. It will be translated into French, Spanish and Russian and distributed through the appropriate networks. It will be presented and promoted at global meetings and conferences as well as at meetings of national TB programme managers in the WHO regions. Regional workshops will be organized on investigation of TB contacts in order to promote use of these guidelines. The document will be promoted in countries through Global Fund proposals, the TBREACH mechanism and other relevant initiatives.

Implementation of the guidelines and use of the recommendations will be evaluated in collaboration with WHO regional and country offices and with partners to identify potential barriers to implementation and to assess the outcomes of implementation.

The WHO Stop TB Department will review and update these guidelines 3–5 years after their publication or as needed when new evidence becomes available.

2.
QUESTIONS AND REVIEW FINDINGS

2.1 CHAPTER OBJECTIVES

This chapter presents the five questions identified by the steering group as essential for formulating recommendations. The summary results of the systematic reviews are also presented.

2.2 MAIN QUESTIONS ADDRESSED

The steering committee agreed on five main questions:

1. In what proportion of contacts of new or recurrent cases (index cases) of TB does contact investigation lead to identification of previously undiagnosed TB?

   Outcome: Percentage of contacts evaluated who are found to have TB

2. Who should be considered an index case for the purposes of initiating contact investigation?

   Outcome: Characteristics of patients who are most likely to transmit the infection

3. How can the contacts at greatest risk for TB be identified?

   Outcome: Characteristics of contacts who have the highest likelihood of having TB

4. In what proportion of contacts of an index case with HIV infection does contact investigation lead to identification of previously undiagnosed TB?

   Outcome: Percentage of contacts evaluated who are found to have TB

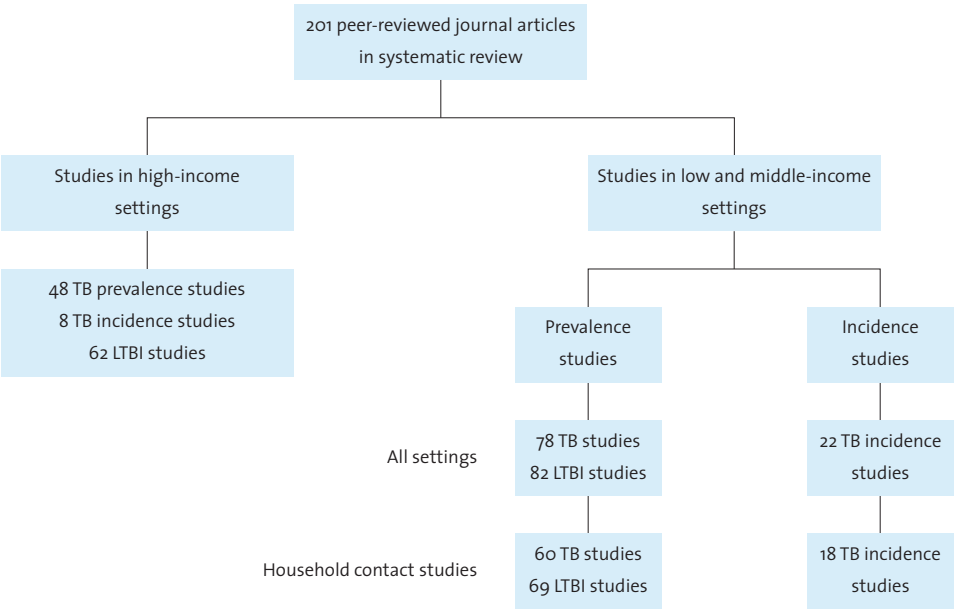
5. In what proportion of contacts of an index case with MDR-TB or XDR-TB does contact investigation lead to identification of previously undiagnosed TB?

   Outcome: Percentage of contacts evaluated who are found to have TB

2.3 SYSTEMATIC REVIEWS

The five questions specified above were addressed in two systematic reviews. These reviews undertaken by Fox G et al. (8) and by Fair E et al. (summary available at online Annex 4: http://www.who.int/tb/Systematicreviewcontact_investigation.pdf), updating the review by Morrison et al. (7), are summarized in annexes 1 and 2. The two reviews had similar findings. Inclusion of studies in the systematic review by Fox et al. is illustrated in Figure 1. For the purposes of the recommendations, only studies conducted in low- and middle-income countries were included in the review.

Figure 1. Numbers of studies included in the systematic review by Fox G et al. (Annex 1)



TB, tuberculosis; LTBI, latent tuberculosis infection

Interpretation of the literature presented significant challenges, as there were substantial variations in the populations studied, the definition of index cases, the contacts (household, close, other), the methods used for screening and clinical evaluation, the diagnostic criteria for TB (microbiological confirmation with either microscopy or culture or clinical or radiographic diagnoses), the age stratification of children and inclusion only of 'co-prevalent cases' found at initial evaluation or 'incident cases' detected during various periods of follow-up. For these reasons, the evidence base for most of the recommendations was judged to be very weak.

In addition to the variations among the studies, there are significant gaps in the literature. No studies were found that addressed the following questions:

- Does contact investigation lead to a reduction in the incidence of TB in a population?
- Is contact investigation cost–effective in terms of the cost per new case identified?
- How does contact investigation fit into the context of other active case-finding strategies?
- What are the optimal approaches to screening and clinical evaluation of contacts?

As a consequence of these major gaps in the literature, programme decisions about whether to undertake contact investigation can be based only on published estimates of the prevalence or yield of active TB among contacts (the number of new cases found, as reported in tables 2–5) rather than on evidence about the effectiveness of the intervention.

Table 2. Overall yield (prevalence) of active tuberculosis among contacts in studies included in the systematic review by Fox G et al. (8)

Contacts	No. of studies included	No. of contacts investigated	No. of cases found	Prevalence (%) (95% CI)
All	77	883 213	22 803	3.1 (2.3–4.2)
Close	62	847 646	22 032	3.6 (2.6–5.1)
Household	60	843 606	21 930	3.6 (2.5–5.1)

CI, confidence interval

Table 3. Overall yield (prevalence) of bacteriologically confirmed tuberculosis among contacts in studies included in the systematic review by Fox G et al. (8)

Contacts	No. of studies included	No. of contacts investigated	No. of cases found	Prevalence (%) (95% CI)
All	30	818 171	1083	0.9 (0.6–1.3)
Close	26	805 462	1068	1.0 (0.6–1.6)
Household	25	805 110	1022	0.9 (0.6–1.4)

CI, confidence interval

Table 4. Yield (prevalence) of active tuberculosis by characteristics of index cases in studies included in the systematic review by Fox G et al. (8)

Index patients	No. of studies included	No. of contacts investigated	No. of cases found	Prevalence (%) (95% CI)
All	78	898 619	38 209	3.5 (2.3–5.4)
+ AFB	43	36 533	1 861	4.5 (3.0–6.7)
+ MDR-TB	6	5 584	176	5.5 (2.5–11.7)
+ HIV	6	1 526	90	5.4 (2.2–12.4)

CI, confidence interval; AFB, acid-fast bacilli; MDR-TB, multi-drug-resistant tuberculosis; HIV, human immunodeficiency virus

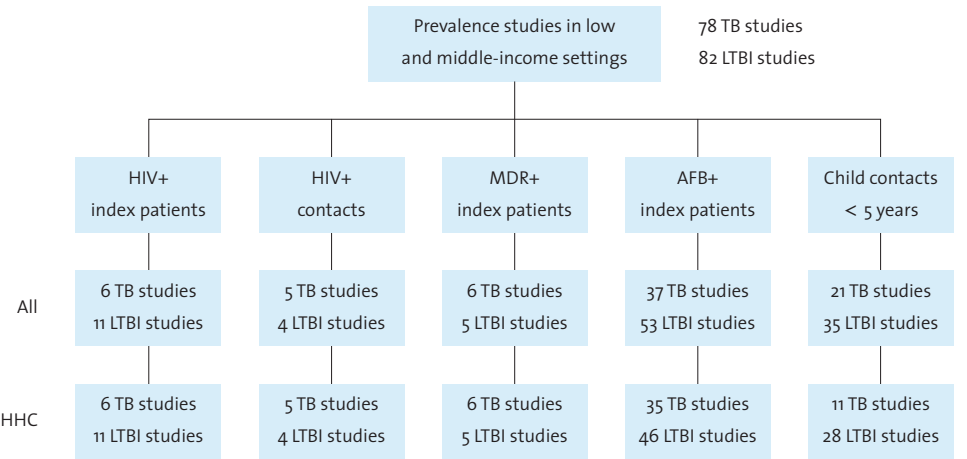
Table 5. Yield (prevalence) of active tuberculosis by characteristics of contacts among children and people living with human immunodeficiency virus (HIV) in studies included in the systematic review by Fox G et al. (8)

Contacts	No. of studies included	No. of contacts investigated	No. of cases found	Prevalence (%) (95% CI)
All	78	898 619	38 209	3.5 (2.3–5.4)
Children < 5 years	21	6 617	856	9.6 (5.5–16.0)
Children 5–14 years	11	5 366	300	4.5 (1.6–12.3)
HIV-infected	5	282	79	28.4 (9.8–59.2)

CI, confidence interval; HIV, human immunodeficiency virus

To provide answers to the questions and thus support the evidence base for the recommendations on contact investigation, the panel focused on prevalence studies from low- and middle-income countries. The studies were examined as shown in Figure 2 to obtain detailed information for answering the questions.

Figure 2. Studies used to analyse specific subgroups in the systematic review by Fox G et al. (Annex 1)



TB, tuberculosis; LTBI, latent tuberculosis infection; HIV, human immunodeficiency virus; MDR-TB, multi-drug-resistant TB; AFB, acid-fast bacillus; HHC, household contacts

The objectives of the reviews were:

Determine the overall yield of contact investigation for active TB (question 1).

- Stratify by:
  - index cases with known HIV status (question 4)
  - contacts with known HIV status (question 3)
  - index cases with known MDR-TB (question 5)
  - age of contacts (0–4, 5–14, > 14 years) (question 3)
  - contacts with other identified risks (co-morbid conditions, especially diabetes) (question 3). *Note: There were insufficient data to answer this question.*

Determine the features of index cases that are associated with active TB in contacts (question 2).

- Stratify by:
  - sputum status (smear-positive, smear-negative culture-positive, smear-negative–culture-negative–X-ray-positive)
  - HIV status
  - MDR-TB (from above).

3.

MOLECULAR EPIDEMIOLOGICAL STUDIES

3.1 CHAPTER OBJECTIVES

This chapter presents a brief overview of the findings from studies of the molecular epidemiology of TB as it relates to contact investigation.

3.2 BACKGROUND

Genotyping of *M. tuberculosis* has been used to study the transmission dynamics of the organism since the early 1990s, and a number of lessons have been learnt from this approach (13). For certain reasons, however, including variations in the typing methods used, the populations examined, the definitions used and study designs, the molecular epidemiology of tuberculosis is difficult to review systematically. This should not diminish the importance of the lessons learnt from use of such methods. Although a number of publications give the results of genotyping of *M. tuberculosis* in low- and middle-income settings, only a few were designed to identify the features of transmission and are thus relevant to contact investigations.

Some of the applications of molecular epidemiology that, coupled with conventional epidemiological methods, have led to a better understanding of the distribution and dynamics of TB are:

- identification or confirmation of outbreaks,
- identification of sites at which transmission occurs,
- identification of characteristics of TB disseminators,
- characteristics of people at increased risk for acquiring TB infection and for rapid progression to TB,
- detection of unsuspected transmission,
- determination of the potential for reinfection,
- detection of laboratory cross-contamination and
- evaluation of TB control activities designed to prevent transmission.

3.3 SUMMARY OF FINDINGS

Perhaps the most relevant lesson from molecular epidemiology for contact investigation is that substantial transmission of *M. tuberculosis* may occur outside households, such as in social settings like bars and in multi-resident housing such as hotels and shelters for the homeless (14–16). Thus, contact investigations should not focus exclusively on the household, depending on the circumstances. Molecular epidemiology has also been used to identify groups at increased risk for acquiring infection and rapid progression to active TB. PLHIV obviously fall into this category, but homelessness and substance abuse are also risk factors. In addition, in population-based molecular epidemiological studies in British Columbia, Canada, The Netherlands and San Francisco, USA, 12–17% of new cases were the result of transmission from smear-negative, culture-positive cases (17–19). Thus, although a large majority of cases result from contact with a smear-positive case, smear-negative cases can also transmit the disease.

Of particular relevance is the finding that in PLHIV infection with *M. tuberculosis* may progress quite rapidly to active TB with little, if any, latency (20). Consequently, it is important to identify quickly any PLHIV who are likely to have been infected with *M. tuberculosis* as a result of recent exposure, to evaluate them promptly for both active TB and LTBI and to treat them appropriately.

Several molecular epidemiological studies have demonstrated reinfection with a new strain of *M. tuberculosis*, although the frequency with which this occurs varies (21–23). Thus, even contacts who have had TB should be evaluated again if they are exposed to an infectious case.

In three recent systematic reviews (24–26), the impact of the commonly investigated risk factors for clustering of TB cases was estimated, with stratification by TB incidence (with 25 per 100 000 cases per year as the cut-off between low and high or intermediate incidence settings). A meta-analysis showed significant estimated odds ratios for several risk factors at both levels of TB incidence. Alcohol abuse, injection drug use and homelessness were consistently, significantly associated with TB in settings with a low incidence.The authors concluded that more research is needed to better understand TB transmission in high-burden settings.

Molecular epidemiology, if used in a population-based manner over several years, can be highly sensitive for measuring the effectiveness of control programmes in general and for evaluating the effectiveness of contact investigation in reducing the incidence of TB in particular (27,28). Any case in a cluster (with an identical genotype) that is likely to be secondary to an identified index case represents a failure of the programme. The questions that should be asked are "Why was this person not identified as a contact at the time of contact investigation?" and, if identified, "Why was the case not prevented by treatment for LTBI?" Molecular epidemiology has not been used in this manner in high-incidence settings. Perhaps, as mycobacterial culture and less expensive, faster methods for genotyping come to be used more widely, molecular epidemiology will become a practical tool in high-incidence settings.

4.
DEFINITIONS

4.1 CHAPTER OBJECTIVES

This chapter defines the terms used in the recommendations.

4.2 DEFINITIONS

Index case (index patient)

The initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed

Remark

An index case is the case around which a contact investigation is centered. Because the investigation generally focuses on a defined group of potentially exposed people in which other (secondary) cases may be found, the index case is generally the case identified initially, although she or he may not be the source case. Contact investigation may center on secondary cases if the exposed group differs from that exposed to the original index case.

Contact

Any person who has been exposed to an index case (as defined above)

Remark

Exposure may be intense or casual, easily identified or obscure. Close exposure, such as sharing a living or working space, is generally easily identified and quantified, whereas casual exposure, such as on public transport or in social situations, may be unidentifiable.

Household contact

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode

Remark

Definitions of 'household' vary considerably and must be adapted to the local context. Within households, there is a gradation of exposure, ranging from sharing the same bed as the index case to living in the same compound but not in the same enclosed space. Quantification of the amount of exposure, estimated as the time spent with the index case, is likely to be highly subjective. For this reason, the infectious period for the index case is set somewhat arbitrarily at 3 months before initiation of treatment rather than relying on recall by the index case of the time symptoms began. The 3-month period is a general guideline; the actual period of infectiousness may be longer or shorter. For example, prolonged infectiousness may be associated with nonadherence (if directly observed treatment is not being used) or with unrecognized or untreated MDR-TB or XDR-TB.

Close contact

A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

Remark

Out-of-household exposure is as likely to result in transmission as household exposure in many situations. Molecular epidemiological studies showed that transmission was likely to occur in social settings such as informal bars in Mexico and South Africa and in facilities such as correctional institutions and hospitals (14,15). Such sites (particularly social settings) are difficult to identify and require knowledge of the culture and of behavioral patterns in order to focus contact investigations.

Contact investigation

A systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for LTBI to identify possible candidates for preventive treatment. Contact investigation consists of two components: identification and prioritization, and clinical evaluation.

Remark

The rationale for contact investigation is that people who were recently infected with M. tuberculosis are at increased risk for the development of active TB within 1–2 years after acquisition of the infection. It is assumed that people exposed to a person with infectious TB might recently have been infected and are thus at increased risk for currently having TB or for development of the disease in the near future.

Contact identification and prioritization

A systematic process to identify contacts with or at increased risk for development of TB. For the purposes of these recommendations, the definition of contact identification and prioritization includes an interview with the index case to obtain the names and ages of contacts and an assessment of contacts' risk for having (generally based on the presence of symptoms compatible with TB) or developing TB, to determine those for whom clinical evaluation (defined below) is indicated.

Remark

At a minimum, all index cases should be assessed with the above criteria to determine whether contact investigation should be undertaken. For example, contact investigation would not usually be conducted for an index case with only extrapulmonary TB, except children < 5 years of age, in whom investigations would be undertaken in an attempt to identify the source case.

Contact clinical evaluation

A systematic process for the diagnosis or exclusion of active TB among contacts. Clinical evaluation is undertaken if the results of contact identification and prioritization indicate a risk for having or developing TB. For the purposes of these recommendations, the definition of contact clinical evaluation includes, at a minimum, a more extensive assessment of symptoms compatible with TB. Additional components may include:

- a more detailed medical history,
- a physical examination,
- microbiological assessment of specimens from sites of suspected involvement,
- radiographic examinations and
- invasive diagnostic tests.

Implementation of these components will depend on the clinical circumstances and the available resources. In addition, depending on the epidemiological circumstances and resources, a tuberculin skin test or an interferon gamma release assay for LTBI may be part of the clinical evaluation.

Remark

The goal of contact investigation is to find previously undiagnosed cases of active TB. The goal of clinical evaluation is to diagnose or exclude TB and, in some situations, to identify and possibly treat LTBI. The approaches used depend on resources and circumstances; however, in all situations, contacts should be interviewed to determine whether they have symptoms consistent with TB, and they should be further evaluated if symptoms are present (29–31).

5.
RECOMMENDATIONS FOR CONTACT INVESTIGATIONS

5.1 CHAPTER OBJECTIVES

This chapter presents the expert panel's recommendations for conducting contact investigations, with the strength of the recommendation and the quality of the evidence supporting the recommendation.

5.2 RECOMMENDATIONS

The reviews of the literature showed limited information on the approaches to and benefits of contact investigation in high-burden, low-resource settings. Thus, most of the recommendations are based on very low-quality evidence.

Recommendation 1 It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- sputum smear-positive pulmonary tuberculosis,
- MDR-TB or XDR-TB (proven or suspected),
- is a PLHIV or
- is a child < 5 years of age.

Strong recommendation, very low-quality evidence

Remark 1

Designation as an index case does not necessarily imply that contact investigation must be undertaken. In high-burden settings, because of competing demands on time and resources, a decision must be taken on whether to undertake contact investigation and, if so, how to prioritize index cases. Detailed clinical information on the index case is the foundation of contact investigation. Sputum smear microscopy and radiographic features establish the degree of infectiousness and correlate independently with the likelihood of infection among contacts (32,33). Contacts of known or suspected cases of MDR-TB and XDR-TB should be evaluated as described for contacts of drug-sensitive cases but with greater urgency because of the potential consequences of drug-resistant TB should it develop in the contact. Additional information to be obtained from index patients should include a description of their residence and, when relevant, of other sites in which transmission might have occurred. Information that is essential for determining the potential risk posed by the index case includes:

- the results of sputum smears or other microbiological evaluations;
- radiographic features of the disease (if available);
- the severity, type and duration of symptoms (especially cough);
- the presence of risk factors for drug resistance;
- known or presumed HIV infection; and
- the setting in which exposure occurred.

Remark 2

Accurate identification of an index patient with MDR-TB or XDR-TB requires that drug susceptibility testing be available and used. Even when such testing is available, several weeks are required to determine susceptibility or resistance. Thus, for the purpose of contact investigation, suspected cases of MDR-TB or XDR-TB should be considered in the same way as those with proven MDR-TB or XDR-TB. Identification of the index case suspected of having MDR-TB and XDR-TB will depend on the individual circumstances and factors related to the region and health service in which the individual lives or was treated. An index patient is more likely to have MDR-TB or XDR-TB in a region that it is known to have a high background rate from representative drug susceptibility testing. The likelihood that a patient has MDR-TB or XDR-TB after failing an initial standardized treatment regimen has been shown to be highly variable but definitely increased. The proportion of cases with MDR-TB or XDR-TB among patients who fail standardized re-treatment regimens is also variable but generally higher (65–89%) than the proportion of those failing initial regimens (34). Index patients who are chronically smear positive nearly always have MDR-TB or XDR-TB.

Remark 3

Different rationales apply to each of the four priorities:

- As, with few exceptions, only patients with pulmonary TB can transmit *M. tuberculosis* and because people with a positive sputum smear by microscopy are more infectious than people with negative smears, contact investigation should generally be limited to new or recurrent cases with positive sputum smears (32,33).
- It is not known whether MDR-TB and XDR-TB organisms are more infectious or pathogenic; however, commonly, index cases who were initially treated with ineffective therapy are infectious for a longer time and thus their contacts will be more likely to have been infected with these organisms. Contact investigation can potentially result in earlier diagnosis, and appropriate treatment can be started sooner, thus possibly minimizing the severity and decreasing transmission (35).
- When an index case is a PLHIV, there is a greater likelihood that people living in the same household also have HIV infection and are at great risk for the development of active TB if infected.
- Generally, children do not have highly infectious forms of TB; however, when a child < 5 years of age develops TB, it is likely that the infection was acquired from a person in the household. The rationale for assigning high priority to contacts of index cases < 5 years of age is to find the source of the infection, not to find secondary cases from the child.

Recommendation 2 It is suggested that contact investigation be conducted for household and close contacts of all other index cases with pulmonary tuberculosis, in addition to the index cases covered in Recommendation 1.

Conditional recommendation, very low-quality evidence

Remark

Although priority should be given to index cases, as described in Recommendation 1, if the resources are available, programmes and clinicians may wish to conduct contact investigation for index cases of lower priority. Such investigations should not detract from high-priority situations. Transmission can occur from smear-negative cases. Molecular epidemiological studies in San Francisco showed that approximately 17% of new cases resulted from transmission from smear-negative, culture-positive cases (17). In British Colombia (18) and The Netherlands (19), transmission from smear-negative cases accounted for 16% and 12%, respectively, of new cases.

Recommendation 3 Clinical evaluation of household and close contacts for active TB is recommended as a priority on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to:

- people of all ages with symptoms suggestive of TB,
- children < 5 years of age,
- people with known or suspected immunocompromising conditions (especially PLHIV) and
- contacts of index cases with MDR-TB or XDR-TB (proven or suspected).

Strong recommendation, very low-quality evidence

Remark 1

This recommendation complements and to some extent overlaps with Recommendation 1 but focuses on the contact rather than the index case. Prioritization of contacts for clinical evaluation is based on an assessment of the risks posed by the index case, the circumstances of the exposure and features of the contact. Given that overall about 3.5–5.5% of all household contacts (9.6% in young children) are found to have TB at the time of initial evaluation, identification of contacts with symptoms is a critical step in contact investigation. All prioritized contacts identified should be evaluated for symptoms of TB, including cough, fever, night sweats, weight loss and haemoptysis. Symptomatic contacts should be evaluated as for any person suspected of having TB. Contacts with cough should submit sputum specimens for microscopy, as recommended for suspected cases of TB. Contacts with negative sputum smears should be evaluated according to the guidelines for smear-negative TB (3). Contacts of PLHIV and children may be less likely

to have cough as the predominant symptom and should be fully evaluated if they have systemic symptoms such as fever, night sweats and weight loss as well as local symptoms such as lymph node swelling suggestive of extrapulmonary sites of involvement (29). Table 6 shows the relative risks for TB associated with various contact-related conditions.

Table 6. Incidence of active tuberculosis in people with a positive tuberculin test, by selected risk factors

Risk factor	No. of cases of tuberculosis/ 1000 person-years
Recent tuberculosis infection	
Infection within < 1 year	12.9
Infection within 1–7 years	1.6
HIV infection	35.0–162
• HIV seropositive	76.0
• HIV seronegative or unknown	10.0
Silicosis	68
Radiographic findings consistent with previous tuberculosis	2.0–13.6
Weight deviation from standard	
• Underweight by ≥ 15%	2.6
• Underweight by 10–14%	2.0
• Underweight by 5–9%	2.2
• Weight within 5% of standard	1.1
• Overweight by ≥ 5%	0.7

From reference 36

Remark 2

Because children < 5 years of age are highly vulnerable to TB and may have more severe forms of the disease, they should be evaluated promptly. Children aged 5–15 years do not have the same risk as younger children and should be managed in the same way as adult contacts.

Remark 3

HIV infection results in the progression from infection with *M. tuberculosis* to active TB more rapidly than any other known factor, with disease rates estimated at 35–162 per 1000 person-years of observation and an increased likelihood of disseminated and extrapulmonary disease (36). Thus, contacts with known or suspected HIV infection should be evaluated promptly, keeping in mind an increased likelihood for extrapulmonary TB, manifested by local and systemic, rather than pulmonary, symptoms. As contacts with HIV infection are a priority for

evaluation and for receiving isoniazid preventive treatment, knowledge of the HIV status of contacts is important. If HIV testing cannot be done, epidemiological risk factors and clinical features suggesting HIV infection should be sought in the evaluation.

People with other immunocompromising conditions, such as leukaemia or lymphoma, or who are receiving immunosuppressive therapy such as high-dose corticosteroids or TNFα inhibitors, are also a high priority for evaluation and appropriate treatment (37).

Remark 4

Because of the potential severity of MDR-TB and XDR-TB, contacts of all cases of proven or suspected pulmonary MDR-TB or XDR-TB should be given high priority for investigation, regardless of the index patient's sputum smear result. Contacts of known or suspected MDR-TB and XDR-TB cases should be evaluated as described for contacts of drug-sensitive cases but with greater urgency because of the potential consequences of TB should it develop. One of the factors thought to contribute to the emergence of MDR-TB and XDR-TB is transmission of the responsible organisms in communities. Studies indicate that close contacts of MDR-TB patients who develop active TB usually have drug-resistant disease (38,39). Systematic investigation of contacts of known or suspected cases of MDR-TB and XDR-TB may be an effective means of halting the transmission of drug-resistant strains of TB in a community, although this is not yet proven. In addition, when treatment is available, early diagnosis may reduce the severity of illness and the likelihood of dying.

Remark 5

The aim of the initial contact evaluation is to identify active TB (also called co-prevalent cases) and also contacts who were recently infected, Because the risk for developing TB is increased for 1–2 years after infection, all contacts should be informed about the increased risk and about the symptoms that could indicate TB. The index case, particularly if he or she is a family member, should also be instructed about possible indicators of TB in contacts and about the need for prompt evaluation if any of these indicators develops. TB control programmes may consider follow-up screening, particularly in the first year after exposure (such as after 6 or 12 months), to identify incident cases.

Recommendation 4 In settings of high HIV prevalence it is recommended that all household and close contacts be counselled and tested for HIV.

Strong recommendation, very low-quality evidence

Remark

Because PLHIV who are exposed to a person with infectious TB are at high risk for developing active TB, they should be managed differently from contacts who do not have HIV infection, with regard to evaluation

for both current TB and LTBI (including treatment). Thus, it is imperative that HIV counselling, testing and, when appropriate, referral for specialized care be offered to contacts, especially (but not exclusively) in areas of high HIV prevalence.

Recommendation 5 It is recommended that all household contacts of an index case who is a PLHIV should be counselled and tested for HIV.

Strong recommendation, very low-quality evidence

Remark

Because household contacts of a PLHIV index case are more likely also to be HIV positive and because PLHIV who are contacts should be managed differently from contacts who do not have HIV infection, household contacts should have counselling and testing for HIV infection.

Recommendation 6 It is recommended that all household and close contacts of people with TB who have symptoms compatible with active TB should receive counselling and testing for HIV as part of their clinical evaluation.

Conditional recommendation, very low-quality evidence

Remark

This recommendation is consistent with existing recommendations that people suspected of having TB should have counselling and testing for HIV infection (39).

Recommendation 7 PLHIV who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed LTBI as per WHO guidelines.

Strong recommendation, high-quality evidence

Remark 1

HIV-positive household or close contacts who are adults or adolescents and whose clinical evaluation suggests that they are unlikely to have active TB should receive preventive treatment with isoniazid at 300 mg/day for at least 6 months (4). It is conditionally recommended that the duration of isoniazid preventive treatment of PLHIV with no active TB be prolonged to 36 months (4).

Remark 2

HIV-positive household or close contacts who are children with no active TB should receive preventive treatment with isoniazid at a dose of 10 mg/kg body weight for 6 months (4).

Recommendation 8 Children < 5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be treated for presumed LTBI as per WHO guidelines.

Strong recommendation, high-quality evidence

Remark

Household or close contacts aged < 5 years who do not have active tuberculosis should, irrespective of their HIV status, receive preventive treatment with isoniazid at a dose of 10 mg/kg body weight for 6 months. This remark is consistent with existing guidelines (1).

6.
GENERAL OPERATIONAL CONSIDERATIONS

6.1 CHAPTER OBJECTIVES

This chapter presents operational considerations that should be taken into account in conducting contact investigations.

6.2 OPERATIONAL CONSIDERATIONS

6.2.1 Written guidelines

All TB control programmes should have written guidelines for the use of and approaches to contact investigation. Contact investigation is an acknowledged standard component of TB control programmes and should therefore be included in programme manuals. At a minimum, the guidelines should include the emphasis to be placed on contact investigation, priorities for evaluation and the roles and responsibilities of programme personnel in investigations and in collecting and recording relevant data. If contact investigation is to be undertaken, written, standardized protocols and procedures should be prepared and followed. Such standardized protocols improve the efficiency and uniformity of an investigation and allow evaluation.

6.2.2 Determining the level of emphasis for contact investigation

National and local TB control programmes should determine how much emphasis to place on contact investigation on the basis of the local epidemiology of TB, operational capacity and resources. In general, contact investigation should be assigned a lower priority in countries or areas in which treatment success is < 85%. Where there is a high prevalence of HIV or MDR-TB or XDR-TB, all of which reduce treatment success rates, contact investigation may be valuable. Moreover, there may be cities or regions within countries where the local programme is performing adequately even though the national rates for treatment success are below the goal. Such localized areas may consider adopting additional case detection strategies, such as contact investigation.

Case study: routine contact investigation in Morocco

Morocco is a low–middle-income country where DOTS has been implemented successfully since 1991. TB contact investigations are a routine activity of the national TB programme. The results of contact investigations undertaken between 1993 and 2004 were recently reviewed (40). The proportion of contacts identified among those screened, the prevalence of active TB cases among those screened and the proportion of cases identified in contacts among all new cases registered were calculated for each year and for each diagnostic category. More than 1 million household contacts were identified in about 200 000 investigations. On average, 77% of identified contacts were evaluated for TB each year. The overall prevalence of any type of TB among screened household contacts was 2.5%, and the proportion of all new TB cases identified during contact investigation was 5.6%; the proportion of all cases in children < 10 years of age was significantly higher (19.5%). The authors concluded that performing contact investigation as a routine activity of the national TB programme was feasible and useful in low–middle-income countries.

6.2.3 Adaptation of recommendations

These recommendations must be adapted to the local epidemiological context and programme. National and local programmes should determine the potential value and feasibility of contact investigation in their setting, the extent to which it should be undertaken and its scope. The approaches will depend on programme factors such as the availability of staff and resources, and the definitions depend on the diagnostic methods used and the customs and living conditions of the population. Pilot studies should be conducted before implementation to guide the design of local guidelines, determine the diagnostic yield in the setting and determine the factors that influence the feasibility of full implementation.

6.2.4 Timing of interviews and identification of contacts

If contact investigation is to be initiated, the index case should be interviewed as soon as possible after diagnosis (generally within 1 week) to elicit the names of household and close contacts. The focus should be on household members, but people in the workplace and other settings in which there is exposure should not be ignored. Moreover, contacts in residential care facilities, long-term care facilities, gaols and prisons and acute medical care facilities, especially when exposure is by coughing, should be evaluated. Ideally, the interview should be conducted by a person who speaks the same language as the index patient and is familiar with his or her social and cultural context. Investigations should be conducted for patients who have died, if information can be gathered from family members.

A sense of urgency should be conveyed in contact investigations, including prompt interviewing of the index case. Occasionally, a second interview is useful to elicit additional contacts. Information from the interview should be recorded on standardized forms (see Annex 3).

6.2.5 Conducting the investigation

If the human resources are available, the person conducting the contact investigation should visit the home of the index patient to conduct interviews and ensure referral of all household contacts for evaluation. A home visit will underscore the importance of identifying and evaluating contacts and can ensure a more accurate view of the circumstances of exposure. The home visitor can make an environmental assessment of the residence and provide family counselling and education on the symptoms that should prompt contacts to seek medical attention. This is especially true for children and people with HIV infection, in whom TB can progress rapidly. Home visits may also provide an opportunity for identifying a need for social support and for education on TB and infection control measures.

6.2.6 Monitoring and evaluation

Data from the contact investigation should be collected in a standardized format; examples of forms that may be used are given in Annex 3. TB control programmes should routinely evaluate the effectiveness of contact investigations and design interventions to improve performance. The yield of contact investigations and the incidence of active TB and LTBI should be evaluated to determine whether the intervention is giving the desired results. At a minimum, the following information should be collected: number of contact investigations carried out; number, age (especially children < 5 years of age), sex and HIV status of the contacts identified; the number who completed medical evaluation and relevant investigations; the number with active TB; and the numbers of children < 5 years of age and PLHIV given isoniazid preventive treatment. Data collection during contact investigations has multiple purposes.

First, good information is important for the management and follow-up of index cases and their contacts. Secondly, systematic collection of data will permit analyses of the yield of contact investigations overall and for specific groups and epidemiological settings. Thirdly, data on indicators of care are useful for evaluating programme performance objectives. Data collection and storage require significant work; an investment must be made in designing data collection tools and setting up protocols for the collection, entry and analysis of data. If data are collected but not analysed and used to guide the programme, the effort is wasted.

6.2.7 Confidentiality and consent

Maintaining confidentiality during contact investigation is a challenge because of the social connections between and among index cases and their contacts. All persons should be treated with respect, and confidentiality should be maintained. Programme guidelines on confidentiality and consent should be adhered to.

6.2.8 Staffing and training

Contact investigations should be a routine activity of TB control programmes. Where contact investigation has not previously been done, having dedicated staff, if possible, will greatly facilitate the process. Depending on resources, the people who conduct contact investigations, if trained properly, may be community volunteers, former TB patients or health care providers. Regardless of their background, the health care workers who screen index patients and conduct the contact investigation should speak the language of the patients and contacts and be familiar with the social and cultural milieu of the communities in which they work. They should be trained in the importance of contact investigation in TB control and in interviewing, data collection, follow-up and reporting.

6.2.9 Use of treatment for LTBI among contacts as an individual health intervention

Tests for LTBI, including the tuberculin skin test and interferon-gamma release assays, can be used to identify people at increased risk for developing active TB and who are therefore candidates for treatment of LTBI (other than children < 5 years of age and PLHIV, for whom isoniazid preventive treatment is recommended without testing for LTBI (1,4)), once active TB is excluded. As the value of providing treatment for LTBI in low- and middle-income countries is not proven, it is not recommended as a broad programme approach. In caring for patients exposed to an infectious index case who are at increased risk for developing TB if infected, clinicians may, however, test them for LTBI with a tuberculin skin test or interferon-gamma release assay and treat them with isoniazid preventive treatment if LTBI is present. As the risks and benefits of treating LTBI, documented by a recent tuberculin conversion (1) or associated with other diseases (such as diabetes mellitus) and conditions, are quantified, the indications for treatment may be broadened. Unless a plan includes policies and procedures for treating LTBI, testing for LTBI should not be undertaken.

7.
IDENTIFICATION OF INFORMATION GAPS AND RESEARCH NEEDS

7.1 CHAPTER OBJECTIVES

This chapter describes the areas in which information is lacking, as identified by the expert panel.

7.2 INFORMATION GAPS AND RESEARCH NEEDS

The panel identified major gaps in the evidence for use of contact investigation as a routine intervention in TB control. There is no evidence that identification and evaluation of contacts reduces TB incidence or mortality. Although studies of the impact of the intervention would be difficult, a cluster randomized or step-wedge design would be a reasonable approach. In addition, mathematical modelling, including cost–effectiveness estimates, would provide useful information. A comparison of contact investigation with other forms of active case finding could provide information to guide the choice of interventions, although contact investigation is best implemented by TB control programmes.

A major weakness in the literature is the lack of standardized protocols for studies. Such standardization would allow comparisons of use of the same approach under different conditions and enable identification of country-specific barriers to implementation. Different approaches to contact investigation, in particular use of an active versus a passive approach, have not been evaluated. Moreover, different screening and clinical evaluation algorithms have not been compared.

There is limited information on approaches to and the value of contact investigation in settings with a high prevalence of HIV infection, including testing of contacts as part of routine evaluation. Undertaking contact investigations in such settings would require overcoming significant operational and technical barriers. The current recommendation is to test new cases of TB for HIV. Ideally, contacts in settings with a high prevalence of HIV infection should also be tested. It is clear that treatment of LTBI in people with HIV infection reduces their risk for TB, but it has not been established whether treatment of contacts with HIV infection, regardless of whether they have been infected, is beneficial. Both operational investigations and clinical trials will be necessary to answer these questions.

There is also insufficient information on the yield of contact investigations when the index case has TB caused by drug-resistant *M. tuberculosis*. Systematic investigation of contacts of known or suspected cases of MDR-TB and XDR-TB may be effective for reducing transmission of drug-resistant strains of *M. tuberculosis* in a community, although this is not proven. In addition, contact investigation may reduce morbidity and mortality by shortening the time to diagnosis and initiation of effective treatment. There has been little systematic investigation of the epidemiology of MDR-TB and XDR-TB, and the potential role of transmission to adults and children who are household contacts has not been well quantified. Operational investigations, clinical trials and mathematical modelling will be necessary to prove this presumed benefit.

More generally, the use of any of the treatment regimens for LTBI in high-incidence, low-income settings in the framework of contact investigation requires further investigation. Smieja et al. (41) in 1999 systematically reviewed 11 randomized controlled clinical trials of isoniazid preventive therapy for 6–12 months and found that treatment resulted in a relative risk for active TB of 0.40 (95% confidence interval, 0.31–0.52) over 2 years or longer. Only two of these studies, however, were conducted in high-burden, low-income countries, and many other factors, such as feasibility, drug availability and cost, must be considered before recommending routine treatment for LTBI as a component of contact investigation in such settings.

Although interferon-gamma release assays, now commonly used in high-income areas, are currently too costly for routine use in high-burden settings, they may prove valuable for identifying LTBI in places where coverage with bacillus Calmette-Guérin is high, if or when the price drops (42). Use of this category of tests should be evaluated under programme conditions in high-burden settings to determine their performance, practicality and feasibility in contact investigations.

There is little information on the long-term benefits of treating LTBI in children, and long-term follow-up is needed. This will require a link between data on exposure and the development of active TB, which should be incorporated into national TB programme databases.

8.
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ANNEX 1. SUMMARY OF SYSTEMATIC REVIEW OF THE EVIDENCE FOR CONTACT INVESTIGATION IN LOW- AND MIDDLE-INCOME COUNTRIES [1]

Fox G, Barry S, Britton W, Marks G, University of Sydney, Australia

BACKGROUND

Contact investigation for early case detection of tuberculosis (TB) is a priority in many low-middle income settings (1). The aim of this review was to synthesize the published evidence on the diagnostic yield of contact investigation in low–middle-income settings.

METHODS

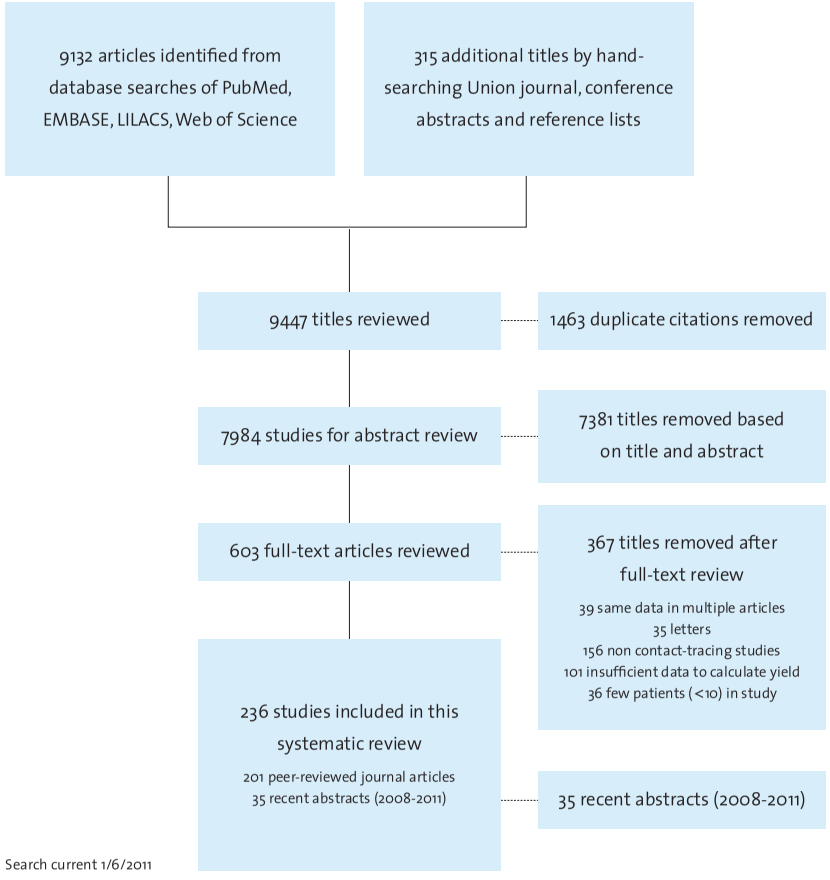
A search was conducted in PubMed, Web of Science, EMBASE and LILACS with prespecified search terms, including 'tuberculosis', 'contact' and 'screening'. Additionally, the *International Journal of Tuberculosis and Lung Diseases* and conference abstracts were searched. All titles identified up to 1 June 2011 were reviewed independently by two reviewers. Duplicates were removed, and the abstracts were reviewed by two reviewers. The reviewers obtained the full texts of relevant abstracts and extracted data into a Microsoft Access database. The data extracted included the study setting, the numbers of contacts and index patients screened, the numbers of cases of TB and microbiologically proven TB identified, the numbers of people screened and diagnosed with latent TB infection (LTBI), information about subgroups of index patients (smear-positive, smear-negative, human immunodeficiency virus [HIV]-positive, multi-drug-resistant [MDR]-TB- or extremely drug-resistant [XDR]-TB-positive) and information about contact subgroups (HIV-positive, children < 5 years, household contacts and close contacts). Data were extracted for incident cases and co-prevalent cases of TB, defined as cases diagnosed within the first 3 months after diagnosis of the index patient or, when this information was not available, at the baseline investigation. Only studies conducted in low–middle-income countries were analysed.

RESULTS

The flowchart of articles extracted is shown in Figure A1. There was significant heterogeneity in the published literature, and the definitions of cases of TB and the case detection methods used varied considerably. We identified only one randomized controlled trial of contact investigation (2). The other studies were descriptive, few of which had comparison groups of unaffected individuals.

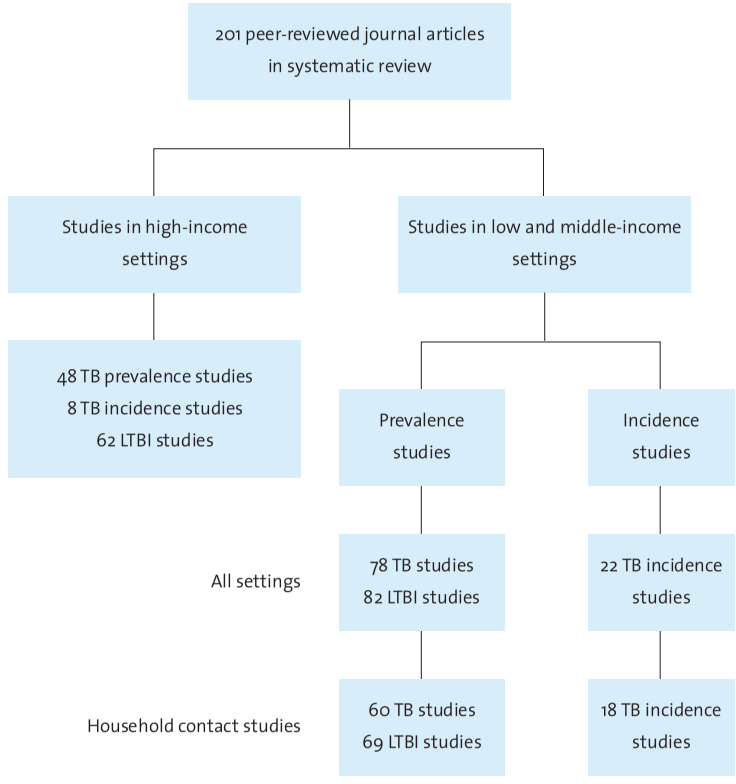
[1] available on http://www.ncbi.nlm.nih.gov/pubmed/22936710

Figure A1. Studies included in the systematic review by Fox G, Barry S and Marks G



Search current 1/6/2011

Number of studies included in systematic review



Co-prevalent TB and LTBI

The overall yield of co-prevalent TB was 3.1% (95% confidence interval [CI], 2.3–4.2), with a yield of 3.6% (95% CI, 2.6–5.1) in household contacts and 3.6% (95% CI,2.5–5.1) in close contacts. In most studies, the close contacts were household members. The yield of co-prevalent, microbiologically proven TB was 0.9% (95% CI, 0.6–1.3) overall, 1.0% (95% CI, 0.6–1.6) among close contacts and 0.9% (95% CI, 0.6–1.4) among household contacts. The prevalence of LTBI was 45.9% (95% CI, 41.3–50.6), 49.0% (95% CI, 44.5–53.5) in close contacts and 48.3% (95% CI, 44.0–52.7) in household contacts.

Incident TB

The yield of incident disease overall each year during the first 5 years was: year 1, 1.2% (95% CI, 0.6–2.3); year 2, 0.3% (95% CI, 0.2–0.7); year 3, 0.6%; year 4, 0.7% (95% CI, 0.6–0.8); year 5, 0.6%. Among household contacts, the annual incidence was: year 1, 1.6% (95% CI, 0.8–3.3); year 2, 0.4% (95% CI, 0.2–0.9); year 3, 0.6%; year 4, 0.7% (95% CI, 0.6–0.8); year 5, 0.6%.

Co-prevalent TB and LTBI in subgroups

The co-prevalence of TB among household contacts was 4.1% (95% CI, 2.6–6.4) for those of smear-positive index patients, 5.5% (95% CI, 2.5–11.7) for those of patients with MDR-TB or XDR-TB and 5.4% (95% CI, 2.2–12.4) for those of HIV-positive patients. Similarly, for LTBI, the prevalence among household contacts was 47.8% (95% CI, 42.7–53.0) for those of smear-positive patients, 61.2% (95% CI, 34.8–72.3) for those of patients with MDR-TB or XDR-TB and 45.5% (95% CI, 37.9–53.3) for those of HIV-positive patients.

The co-prevalence of disease in household members was 13.2% (95% CI, 7.4–22.6) in those < 5 years and 7.7% (95% CI, 1.7–28.6) in those aged 5–14 years and 28.4% (95% CI, 9.8–59.2) in household contacts living with HIV. The prevalence of LTBI in these groups was 30.0% (95% CI, 23.4–37.5) in household members < 5 years, 44.0% (95% CI, 30.8–58.0) in those aged 5–14 years and 41.2% (95% CI, 23.9–61.1) in household contacts living with HIV.

CONCLUSIONS

The evidence on which this review is based has significant weaknesses, largely due to the heterogeneity of the studies included. First, the different rates of TB in the general population have a significant impact upon the prevalence of disease and infection in contacts. Much of the variation can be explained by differences in the definitions and inclusion criteria for index cases and contacts (household contacts, close contacts), the diagnostic tests used to establish disease in contacts (culture, smear or clinical and radiological criteria), the cut-offs for tuberculin skin testing (5 mm versus ≥ 10 mm), the diagnostic algorithms applied and the specific age stratification for children. Furthermore, some studies

did not separately report co-prevalent and incident cases, and studies differed in whether they included contacts with previously known tuberculosis in their outcomes. There is a clear need for more robust evidence on the effectiveness and cost–effectiveness of contact investigation.

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ANNEX 2. SYSTEMATIC REVIEW OF TUBERCULOSIS CONTACT INVESTIGATION IN LOW- AND MIDDLE-INCOME COUNTRIES: AN UPDATE

Fair E, Miller C, Cattamanchi A, Morrison J, Hopewell P, Curry International Tuberculosis Center, University of California, San Francisco, California, USA

RATIONALE

The identification and evaluation of persons in close contact with an infectious tuberculosis (TB) patient (contact investigation) has been viewed as an expensive, low-priority endeavour in low- and middle-income countries. Increasing concern about failure to meet case detection targets, with the spread of *Mycobacterium tuberculosis* to vulnerable people such as children and people with HIV infection and with the transmission of drug-resistant *M. tuberculosis*, have, however, prompted reassessment of the potential benefits of contact investigation. The goal of this review was to update a systematic review by Morrison et al. published in 2008 (1), that included studies through 2005. In particular, we were interested in examining studies that included information on the drug susceptibility of the index case strain and on the HIV status of the index case and contacts.

METHODS

We conducted a systematic review and meta-analysis to determine the yield of household contact investigation. Two electronic databases (PubMed and Embase) were searched for primary studies from January 2006 through August 2011 with the same search terms as in the previous review: 'tuberculosis', *'Mycobacterium tuberculosis'*, 'contact tracing', 'contact investigation' and 'household contact.' The aim of the search strategy was to identify all studies that evaluated the number of cases of active TB or latent tuberculosis infection (LTBI) found when contact investigation was conducted among household members of people with active pulmonary TB (index cases). All published articles on the yield of household contact investigation, including cross-sectional and prospective studies, were included. The language of the publications reviewed was restricted to English.

RESULTS

Nineteen papers were included in the overall analysis. The yield for all TB (bacteriologically confirmed and clinically diagnosed) was 4.51% of contacts investigated; for cases with bacteriological confirmation, the yield was 2.24%. LTBI was found in 50.54% of contacts investigated. For HIV-positive index cases, the yield was 9.41% of contacts investigated; for index cases with multi-drug-resistant (MDR)-TB, the yield was 3.44%.

CONCLUSIONS

The overall results of contact investigations conducted in the past 5.5 years are essentially the same as those found in the earlier review, but the studies provide more information on transmission from HIV-infected index cases and patients with MDR-TB. These findings suggest that contact investigation may improve early case detection and decrease transmission of *M. tuberculosis* in high-incidence areas. In addition, there should be a focus on evaluating contacts of HIV-positive index cases and on contacts of persons with MDR-TB.

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ANNEX 3. SAMPLE FORMS FOR CONTACT INVESTIGATIONS

These forms were designed for contact investigations and are examples of the comprehensive data collection instruments that may be used.

FORM 1. INDEX CASE INTERVIEW AND CHART REVIEW: HOUSEHOLD ROSTER AND CLINICAL DATA

TB index case

ID _____ Registry number (For example: 7101/K/11/201)

Surname _____

First name _____

Interview date __ __ / __ __ / __ __ __ __ (Date the index case is interviewed)
(D D / M M / Y Y Y Y)

Clinic name _____

District TB coordinator _____

TB contact investigator _____

Was the patient screened for TB in the household?* ☐ Yes
☐ No

Demographic information

Date of birth __ __ / __ __ / __ __ __ __ (Date patient was born; if unknown, estimate)
(D D / M M / Y Y Y Y)

Gender ☐ Male ☐ Female

Address Ward _____

Street _____

House number _____

Ten cell leader _____

Telephone number _____

Occupation ☐ Teacher ☐ Health care worker
☐ Correctional employee ☐ Farmer
☐ Petty trader ☐ Other
☐ Not employed in past 24 months
☐ Other, specify _____

Household contacts

Please list the household contacts for this patient:

Name	Gender	Age

Current episode of TB

Have you had a cough? ☐ Yes ☐ No

If yes, how long have you had a cough? ☐ < 1 week ☐ 1–3 weeks ☐ 3 weeks – 1 year ☐ > 1 year

Are you coughing up blood or blood-stained sputum? ☐ Yes ☐ No

If yes, for how long? (in weeks) _____

Have you had a fever? ☐ Yes ☐ No

If yes, for how long? (in weeks) _____

Have you had noticeable weight loss? (≥ 3 kg loss in a month) ☐ Yes ☐ No

Have you been sweating at night for 3 or more weeks in the last 4 weeks? ☐ Yes ☐ No

Have you noticed any swelling and/or lumps on your neck, arm pits, or groin? ☐ Yes ☐ No

Prior episode of TB

Have you ever been told before that you had TB? ☐ Yes ☐ No

If so, did you take all the medication you were given? ☐ Yes ☐ No

Do you have contact with anyone with TB? ☐ Yes ☐ No

If so, is that person a household contact or a non-household contact?
☐ Household
☐ Non-household

Tuberculosis patient chart review

What type of TB patient is this? ☐ New ☐ Treatment after default ☐ Relapse ☐ Failure ☐ Transfer-in ☐ Unknown

What is this patient's HIV status? ☐ Reactive (positive) ☐ Non-reactive (negative) ☐ Unknown ☐ Not tested

Was a chest X-ray done? ☐ Yes ☐ No ☐ Unknown

If a chest x-ray was done, on what date? __ __ / __ __ / __ __ __ __
(D D / M M / Y Y Y Y)

If a chest x-ray was done, what was the result? ☐ Cavitary ☐ Abnormal, no cavitary ☐ Normal ☐ Unknown

Was an acid-fast bacilli (AFB) sputum smear examination done? ☐ Yes ☐ No ☐ Unknown

If an AFB sputum smear examination was done,
on what date? __ __ / __ __ / __ __ __ __
(D D / M M / Y Y Y Y)

If an AFB sputum smear examination was done, what was the result? ☐ AFB positive ☐ AFB negative ☐ Unknown

Does the patient have extrapulmonary TB? ☐ Yes ☐ No

Was the patient a resident of a correctional facility at the time of diagnosis? ☐ Yes ☐ No

FORM 2. HOUSEHOLD TB CONTACT SCREENING FORM

Contact and index case information

Index case ID _____ (Registry #, e.g. 7101/K/11/201)

Index case surname _____

Index case first name _____

Contact number _____ (Example: _01, _02, _10)

Contact surname _____

Contact first vame _____

Contact date of birth __ __ / __ __ / __ __ __ __ (Date contact was born; if unknown, estimate) (D D / M M / Y Y Y Y)

Contact gender ☐ Male
☐ Female

What is your relation to the index case? ☐ Husband or wife
☐ Child
☐ Other relative
☐ Not related

GPS coordinates of house _____

_____

Date of this household interview __ __ / __ __ / __ __ __ __
(D D / M M / Y Y Y Y)

Which household visit is this? ☐ 1st
☐ 2nd
☐ 3rd
☐ 4th

Index case ID _____

Contact number _____

Note to TB contact investigators

- Fill in the top part of the last sheet of paper on this form, and give it to this household contact.
- If this contact answers 'Yes' to any of the symptom screening questions, or the contact is HIV-positive or a child under 5 years of age:
  - Tell this contact that she or he should go to the health clinic for evaluation.
  - Tell this contact to present the sheet of paper to the clinic at the time of evaluation.
  - Inform the district TB coordiantor that he or she will be coming in for evaluation.

- If this contact answers 'No' to all symptom screening questions:
  - Tell this contact to go to the clinic for evaluation if she or he develops any of these symptoms in the future.
  - Tell the contact to bring the sheet of paper to the clinic if she or he does go to the clinic to get evaluated.

TB symptom screening

Do you have a cough ☐ Yes ☐ No

If yes, how long have you had a cough? ☐ < 1 week ☐ 1–3 weeks ☐ 3 weeks – 1 year ☐ > 1 year

Are you coughing up blood or blood-stained sputum? ☐ Yes ☐ No

If yes, for how long? (in weeks) _____

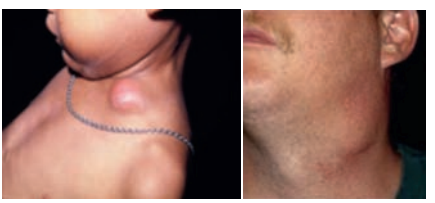
Have you had a fever? ☐ Yes ☐ No

If yes, for how long? (in weeks) _____

Have you had noticeable weight loss? (≥ 3 kg loss in a month) ☐ Yes ☐ No

Have you been sweating at night for 3 or more weeks in the last 4 weeks? ☐ Yes ☐ No

Have you noticed any swelling and/or lumps on your neck, arm pits, or groin? ☐ Yes ☐ No



Medical history

Have you ever been told before that you had TB? ☐ Yes ☐ No

Have you ever been tested for HIV? ☐ Yes ☐ No

If yes, are you HIV-positive? ☐ Yes, HIV-positive ☐ No, HIV-negative ☐ HIV result unknown

If yes, what medications are you taking? (ask for medication card) _____

Do you have any other underlying medical conditions? ☐ Yes
☐ No

If yes, please list them _____

Level of exposure to index case

How much time in one day do you spend in the same room as the index case?
☐ All the time
☐ Only at night
☐ Only during the day

Do you share a bed with the index case? ☐ Yes
☐ No

Do you sleep in the same room as the index case? ☐ Yes
☐ No

How long have you lived in the same house as the index case? _____ years
If less than 1 year, _____ months

TB contact investigator findings

Is the investigator referring this contact for clinical evaluation? ☐ Yes
☐ No

Bring this sheet with you to the clinic for evaluation.

Contact information: to be filled in by the Tb contact investigator at the time of household screening

Index case ID _____ (Registry #, e.g. 7101/K/11/201)

Index case surname _____

Index case first name _____

Contact number _____ (Example: _01, _02, _10)

Contact surname _____

Contact first name _____

Medical examination results: to be filled at the clinic by the clinician or district TB coordinator if the contact is being evaluated for TB

Date of clinical examination __ __ / __ __ / __ __ __ __
(D D / M M / Y Y Y Y)

Chest X-ray reading ☐ Normal
☐ Abnormal (report results)
☐ Unknown
☐ Not done

Smear results ☐ Positive
☐ Negative
☐ Unknown
☐ Not done

Outcome of medical evaluation ☐ Treatment for TB started
☐ Treatment not started, awaiting laboratory results

If TB treatment started, please give TB registry number of this patient: _____
(For example: 7101/K/11/201)

FORM 3. HOUSEHOLD TB CONTACT ROSTER

Index case ID _____ (Registry #, e.g. 7101/K/11/201)

Index case name _____

Address Ward _____

Street _____

House number _____

Ten cell leader _____

Telephone number _____

TB contact investigator _____

Date of first household visit __ __ / __ __ / __ __ __ __

(D D / M M / Y Y Y Y)

Roster of household contacts

Contact no.	Contact name (first name, surname)	Age	Sex (M, F)
_01			
_02			
_03			
_04			
_05			
_06			
_07			
_08			
_09			
_10			
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_25			

World Health Organization

Stop TB Department
World Health Organization
20 avenue Appia, 1211 Geneva 27, Switzerland

Web site: www.who.int/tb
Information Resource Centre HTM/STB: tbdocs@who.int