Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis

Janina Morrison, Madhukar Pai, Philip C Hopewell

Investigation of people exposed to cases of infectious tuberculosis (contact investigation) is key to tuberculosis control in countries with low tuberculosis incidence. However, in countries in which the incidence of tuberculosis is high, contact investigation is not commonly done. Increasing concerns about the failure to meet case-detection targets and about the spread of drug-resistant *Mycobacterium tuberculosis* have prompted a reassessment of the potential benefits of contact investigation. We did a systematic review to determine the yield of household contact investigation. The yield for all tuberculosis (bacteriologically confirmed and clinically diagnosed) was 4·5% (95% CI 4·3–4·8, I^2=95·5%) of contacts investigated; for cases with bacteriological confirmation the yield was 2·3% (95% CI 2·1–2·5, I^2=96·6%). Latent tuberculosis infection was found in 51·4% (95% CI 50·6–52·2, I^2=99·4%) of contacts investigated. The substantial heterogeneity in all analyses indicated high variability among studies that was not accounted for by subgroup analyses. These results suggest that contact investigation merits serious consideration as a means to improve early case detection and decrease transmission of *M tuberculosis* in high-incidence areas.

Lancet Infect Dis 2008; 8: 359–68

Published Online
April 30, 2008
DOI:10.1016/S1473-3099(08)70071-9

Francis J Curry National Tuberculosis Center, Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California—San Francisco, San Francisco, California, USA (J Morrison MD, P C Hopewell MD); **and Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada** (M Pai MD)

Correspondence to:
Dr Philip C Hopewell, Pulmonary and Critical Care Medicine, Room 5K1, San Francisco General Hospital, San Francisco, CA 94110, USA
phopewell@medsfgh.ucsf.edu

Introduction

Mycobacterium tuberculosis is a prototypical airborne pathogen that is transmitted, almost exclusively, from person to person via shared air.[1] Several factors related to the source case, the organism, the environment, and the people who are exposed to the source case determine whether transmission will occur and establish a new infection, but, generally, *M tuberculosis* is not highly infectious.[2] Nevertheless, people who are in close contact with an individual who has an infectious form of tuberculosis are at increased risk of acquiring the infection and, once infected, of progressing to active tuberculosis infection.[3] Consequently, the identification and assessment of people who have been in contact with individuals who have pulmonary tuberculosis—hereafter referred to as contact investigation—is a recommended component of tuberculosis control programmes in many low-incidence areas.[4] Contact investigation identifies both the relatively small number of people who already have active tuberculosis and those with tuberculosis infection but without active tuberculosis (latent tuberculosis infection [LTBI]) who may be candidates for treatment. There are several international guidelines for contact investigations in high-incidence countries that recommend isoniazid prophylaxis for exposed children aged under 5 years who do not have active disease,[5–8] and advocate case finding in settings where HIV-infected people are concentrated.[9] However, in high-incidence areas, contact investigation for tuberculosis among close contacts is generally accorded a low priority, in part because of the workload imposed by active cases, who are the first priority for treatment in any tuberculosis control programme. Furthermore, the use of contact investigation for LTBI is limited because the diagnostic criteria for LTBI in low-income country settings has not been standardised, and because treatment of LTBI is not usually provided, except for children under 5 years of age.[10]

Despite expanded international efforts to control the spread of tuberculosis through WHO's directly observed short-course treatment (DOTS) strategy, the percentage of cases found globally has fallen short of WHO's target to detect 70% of new smear-positive cases by 2005.[11] Furthermore, with 9 million new cases of tuberculosis in 2004—an 8% increase from 2000—the transmission of *M tuberculosis* continues unchecked through many low-income and middle-income countries, particularly in settings with high HIV prevalence.[11] The emergence of extensively drug-resistant tuberculosis has also served to increase concerns with regard to transmission and propagation of drug-resistant organisms in areas with high tuberculosis or high HIV prevalence.[12,13] As a means of improving case detection in high-prevalence communities, and, potentially, as a means of interrupting the transmission of drug-resistant organisms, we have previously suggested that active contact investigation should be practiced more widely.[14] Furthermore, contact investigation may be used increasingly to identify candidates for treatment of LTBI, especially in areas of high HIV prevalence. However, the potential contribution of contact investigation to case detection and identification of people at increased risk of tuberculosis has not been systematically examined.

Our aim was to review the evidence on the yield of household contact investigations in low-income and middle-income countries. Many of these countries share the dilemma of whether implementation of contact investigations should be pursued. This review will collate data from similar settings to provide information that can be used to estimate the benefit of such interventions

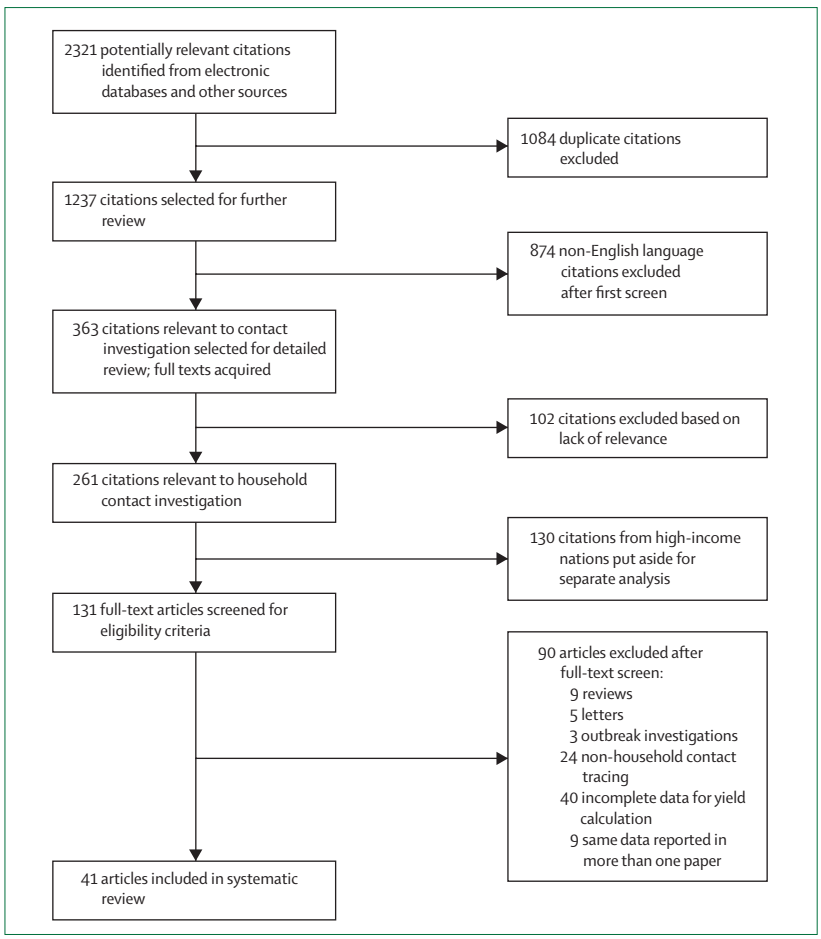

Figure 1: **Flow diagram for study selection**

See Online for webappendix

in settings of high tuberculosis prevalence. Ultimately, the information can be used to guide the development of policies and procedures for tuberculosis control programmes in low-income and middle-income countries.

Methods

Search strategy

We first searched the literature for available systematic and narrative reviews that assessed the yield of household contact investigation for cases of active tuberculosis and LTBI. No systematic reviews were found. One narrative review of contact investigation in high-incidence countries assessed studies of household contact investigation but did not pool data on yield.[10] This review reported a wide range of yields for cases of active tuberculosis among household contacts and concluded that contact investigation in high-incidence countries is most justified among children who are contacts of individuals with sputum-smear-positive tuberculosis.[10]

Our search strategy then aimed to identify all studies that assessed the number of cases of active tuberculosis or LTBI found when contact investigation was done in households of people with active pulmonary tuberculosis (index cases). We reviewed all published articles that reported the yield of household contact-investigation efforts, including cross-sectional and prospective studies. We restricted the language of the publications reviewed to English.

We searched four electronic databases for primary studies: PubMed, BIOSIS, Embase, and Web of Science. Searches in BIOSIS, Embase, and Web of Science included published reports through December, 2004. The PubMed search was extended to December, 2005. The search terms included "tuberculosis", "*Mycobacterium tuberculosis*", "contact tracing", "contact investigation", and "household contact". The complete search strategy is detailed in the webappendix.

We supplemented this search with several additional search strategies to identify relevant articles not found in electronic databases. We hand-searched the indices of *The International Journal of Tuberculosis and Lung Disease* (1997 to 2005) and *The Indian Journal of Tuberculosis* (1953 to 2004). We reviewed the reference lists of primary studies, reviews, and editorials. We contacted selected authors of the papers included and requested a complete list of their publications, and reviewed personal databases for relevant citations.

We excluded the following studies: (1) abstracts, editorials, case studies, outbreak reports; (2) contact-investigation studies reporting yield for contacts other than household (eg, casual contacts); (3) studies in which the number of contacts screened (ie, denominator) was not reported; and (4) studies using molecular epidemiology in which only contacts with active tuberculosis were included, therefore providing no denominator for calculating yield.

Initial review of studies

The initial database created from the electronic searches was compiled and all duplicate citations were eliminated. Two reviewers (JM and MP) screened these citations by title and abstract review to capture relevant studies. Disagreements between the reviewers were resolved by consensus. This database was then screened again to include only primary articles, and the full text of each citation was obtained and reviewed. Studies were eligible for inclusion if they reported the yield of household contact investigations for active tuberculosis or LTBI, including the number of household contacts assessed and number of active cases found, or, for studies reporting LTBI, the number of contacts found to be infected.

The relevant citations were classified, according to World Bank definitions, by whether the studies had been done in low-income, middle-income, or high-income countries.[15] Because the community incidence of tuberculosis was not reported in most of the studies reviewed, we also used the World Bank income classification system as a proxy for incidence. For the purposes of this review, only those studies from

low-income and middle-income settings were included for data extraction. The studies from high-income settings will be reported in a separate review. In instances in which publications were found to have reported the same cohort of index cases and contacts at several timepoints, the most recent publication was used and all others were excluded.

Data extraction

A data extraction form was developed in consultation with experts in the area of contact investigation, and was designed and pilot tested by two reviewers (JM and MP). Five of the 41 studies were reviewed by both reviewers and an inter-rater agreement of 100% was obtained for the data from these studies. The remainder of data extraction was then completed by one reviewer (JM). The data extracted included the following information: study design, description of index cases, description of household contacts, and outcomes among contacts including bacteriologically confirmed tuberculosis (sputum-smear microscopy and/or culture positivity), clinical and radiological diagnoses of tuberculosis, and LTBI. The definition of household in each study indicated the conditions of the community investigated and therefore varied between studies. For the purposes of this review, we used the definition of household set out in each paper to determine the contacts who qualified as household contacts. Close contacts not specified as household contacts were not included in this analysis.

For confirmed tuberculosis among contacts, the process of diagnosis in all studies began with assessment of symptoms among household contacts. The symptoms for which contacts were screened varied little between the studies and included cough, fevers, night sweats, weight loss, and haemoptysis in all studies. The process of diagnosis for confirmed tuberculosis then proceeded to sputum studies (smear and/or culture) for those with symptoms. A case of confirmed tuberculosis was defined as a person with smear or culture positive for *M tuberculosis*. If possible, cases of infection by mycobacteria other than tuberculosis were excluded. Cases of smear-positive but culture-negative disease were excluded, but a few studies included smear-positive cases for which cultures were not done. These cases were included in our analysis. The yield of confirmed tuberculosis among contacts was defined as the percentage of contacts assessed and found to have confirmed tuberculosis.

For clinical and radiological diagnoses of active tuberculosis among contacts, the process of diagnosis for each reviewed study included assessment of symptoms, followed by chest radiograph and sputum studies among those with symptoms. A diagnosis of clinical and radiological active tuberculosis was defined as a person with symptoms and a chest radiograph showing findings characteristic of tuberculosis (eg, opacities, cavitation, or, in children aged <5 years, hilar or mediastinal adenopathy). Pathological diagnoses were not reported in any of the included studies. The yield for all active tuberculosis among contacts was defined as the percentage of contacts assessed that either met the clinical and radiological criteria for active tuberculosis or had bacteriological confirmation.

For LTBI, the process of diagnosis for each reviewed study included the use of a tuberculin skin test (TST) and exclusion of active tuberculosis through symptom and sputum assessment for those who had a positive test. Those who had been previously treated for tuberculosis were also excluded from the analysis. In all but one study[16] the Mantoux method was used. History of BCG vaccination was not reported in most studies. A case of LTBI was defined in most studies as an individual with TST induration greater than 10 mm after 48–72 h in whom active tuberculosis was excluded. The remainder

	Year of study	Country	Index cases	Contacts investigated*	Contacts with active tuberculosis† (% yield)	Contacts with confirmed active tuberculosis‡ (% yield)
Afonja et al[28]	1973	Nigeria	33	288	38 (13·19%)	..
Aluoch et al[29]	1978	Kenya	124	628	3 (0·48%)	3 (0·48%)
Aluoch et al[30]	1982	Kenya	78	419	7 (1·67%)	7 (1·67%)
Andrews et al[31]	1960	India	191	693	48 (6·93%)	29 (4·18%)
Aziz et al[32]	1985	Pakistan	78	434	40 (9·22%)	10 (2·30%)
Bayona et al[33]	2003	Peru	192	945	72 (7·62%)	72 (7·62%)
Becerra et al[34]	2005	Peru	191	1094	10 (0·91%)	10 (0·91%)
Claessens et al[35]	2002	Malawi	770	2766	56 (2·02%)	56 (2·02%)
Devadatta et al[18]	1970	India	291	875	74 (8·46%)	29 (3·31%)
Egsmose et al[36]	1965	Kenya	125	775	89 (11·48%)	11 (1·42%)
Espinal et al[37]	2000	Dominican Republic	174	802	46 (5·74%)	23 (2·87%)
Gilpin et al[16]	1987	South Africa	67	132	4 (3·03%)	4 (3·03%)
Guwatudde et al[37]	2003	Uganda	302	1206	76 (6·30%)	40 (3·32%)
Kamat et al[38]	1966	India	..	773	70 (9·06%)	22 (2·85%)
Klausner et al[39]	1993	Zaire	169	1213	54 (4·45%)	54 (4·45%)
Kritski et al[40]	1996	Brazil	64	218	17 (7·80%)	17 (7·80%)
Kumar et al[41]	1984	India	50	312	17 (5·45%)	8 (2·56%)
Lemos et al[42]	2004	Brazil	69	282	10 (3·55%)	..
Narain et al[43]	1966	India	341	1442	32 (2·22%)	4 (0·28%)
Nsanzumuhire et al[44]	1981	Kenya	66	251	6 (2·39%)	6 (2·39%)
Nunn et al[45]	1994	Kenya	82	357	21 (5·88%)	..
Saunders et al[46]	1984	South Africa	806	3047	166 (5·45%)	..
Suggaravetsiri et al[47]	2003	Thailand	499	1200	58 (4·83%)	13 (1·08%)
Teixeira et al[48]	2001	Brazil	78	408	17 (4·17%)	17 (4·17%)
Wares et al[49]	2000	Nepal	668	2298	14 (0·61%)	14 (0·61%)
WHO[20]	1961	Kenya	74	398	40 (10·05%)	12 (3·02%)
Zachariah et al[50]	2003	Malawi	189	985	9 (0·91%)	2 (0·20%)

*The assessment involved questioning for symptoms, followed by chest radiograph and sputum analysis if symptoms were present. †All active tuberculosis includes all cases with findings on chest radiograph consistent with active tuberculosis and cases with a positive sputum smear and/or positive culture for *M tuberculosis*. ‡Confirmed tuberculosis includes all cases with either a positive sputum smear or culture for *M tuberculosis*.

Table 1: **Yield of contact investigations for all active tuberculosis (confirmed tuberculosis and clinical/radiological diagnoses) and bacteriologically confirmed tuberculosis**

	Year of study	Country	Index cases	Contacts investigated*	Contacts with LTBI† (% yield)
Andrews et al[31]	1960	India	191	647	286 (44·20%)
Aziz et al[32]	1985	Pakistan	78	434	244 (56·22%)
Devadatta et al[18]	1970	India	291	875	618 (70·63%)
Elliot et al[51]	1993	Zambia	71	307	150 (48·85%)
Espinal et al[17]	2000	Dominican Republic	174	802	571 (71·20%)
Gilpin et al[16]	1987	South Africa	67	86	24 (27·91%)
Guwatudde et al[37]	2003	Uganda	302	1206	801 (66·42%)
Hill et al[23]	2004	Gambia	130	735	300 (40·82%)
Kamat et al[38]	1966	India	..	186	80 (43·01%)
Klausner et al[39]	1993	Zaire	169	1213	749 (61·75%)
Kritski et al[40]	1996	Brazil	64	186	173 (93·01%)
Lemos et al[42]	2004	Brazil	69	269	172 (63·94%)
Lienhardt et al[52]	2003	Gambia	315	2870	1165 (40·59%)
Lutong et al[19]	2000	China	76	646	266 (41·18%)
Narain et al[43]	1966	India	341	1442	473 (32·80%)
Rathi et al[53]	2002	Pakistan	77	385	190 (49·35%)
Suggaravetsiri et al[47]	2003	Thailand	499	1192	663 (55·62%)
Teixeira et al[48]	2001	Brazil	78	364	145 (39·83%)
WHO[20]	1961	Kenya	74	398	251 (63·07%)

*The screening process involved the placement of a tuberculin skin test (TST) with purified protein derivative and reading the results after 48–72 h. †LTBI was defined as a TST reaction of >10 mm in most studies; see text for other cut-offs used.

Table 2: **Yield of contact investigations for LTBI**

of studies reported outcomes for greater than 5 mm (three studies),[17–19] greater than 8 mm (one study),[20] and greater than 15 mm (two studies).[21,22] One study used the Heaf test and defined a positive reaction as grade 3 or higher when read 4–7 days after administration.[16] For the purposes of data extraction, a case of LTBI was defined as an individual with TST induration greater than 10 mm (or, if 10 mm was not used, the publication cut-off was used) and in whom active tuberculosis had been excluded. Yield for LTBI was defined as the percentage of contacts assessed who met the criteria. One of the included studies reported the outcomes for a test other than TST (purified protein derivative ELISPOT), but TST was also reported and used to give the yield for LTBI.[23]

Data collation and meta-analysis

For each study, the yield of contact investigation for all active tuberculosis, confirmed tuberculosis, and LTBI was calculated. Meta-analysis of the yield data was done using Meta-DiSc software (version 1·4).[24] Because the yield data are simple proportions, we used methods appropriate for pooling rates and proportions.[25] A meta-analysis was done with studies weighted by the number of contacts screened in each study to pool (summarise) yields for active tuberculosis and LTBI across studies. To account for the expected between-study variability, we corrected for over-dispersion (to simulate a random-effects meta-analysis).[26]

	All active tuberculosis					Confirmed tuberculosis				
	Studies	Pooled % yield (95% CI)	Heterogeneity		References	Studies	Pooled % yield (95% CI)	Heterogeneity		References
			p	I^2				p	I^2	
Geographic region										
Africa	13	4·6% (4·2–5·0%)	<0·001	95·7%	16,20,28–30,35–37, 39,44–46,50	10	2·2% (1·9–2·6%)	<0·001	88·8%	16,20,29,30,35–37,39, 44,50
Asia	8	4·2% (3·8–4·7%)	<0·001	96·7%	18,31,32,38,41,43,47,49	8	1·6% (1·3–1·9%)	<0·001	92·0%	18,31,32,38,41,43,47, 49
Americas	6	4·6% (4·0–5·3%)	<0·001	93·2%	17,33,34,40,42,48	5	4·0% (3·4–4·7%)	<0·001	94·6%	17,33,34,40,48
National income status*										
Low-income economy	18	4·3% (4·0–4·6%)	<0·001	96·6%	18,20,28–32,35–39,41, 43–45,49,50	16	2·0% (1·8–2·2%)	<0·001	90·9%	18,20,29–32,35–39,41, 43,44,49,50
Middle-income economy	9	4·9% (4·5–5·4%)	<0·001	89·6%	16,17,33,34,40,42,46–48	7	3·3% (2·8–3·8%)	<0·001	94·2%	16,17,33,34,40,47,48
Year										
Pre-1980	8	6·7% (6·1–7·4%)	<0·001	96·7%	18,20,28,29,31,36,38,43	7	2·0% (1·6–2·4%)	<0·001	91·4%	18,20,29,31,36,38,43
1980 and later	19	3·8% (3·5–4·1%)	<0·001	94·4%	16,17,30,32–35,37,39–42, 44–50	16	2·3% (2·1–2·6%)	<0·001	92·8%	16,17,30,32–35,37, 39–42,47–50
HIV status of index case										
HIV negative	4	5·1% (4·2–6·1%)	0·449	24·4%	17,39,45,47	2	..	..	..	39,47
HIV positive	4	4·9% (3·8–6·2%)	0·493	0%	17,39,45,47	2	..	..	..	39,47
Sputum smear status of index case										
Positive sputum smear	12	4·0% (3·6–4·4%)	<0·001	92·9%	16,20,32,35,37,39,41,45, 47–50	10	2·3% (2·0–2·6%)	<0·001	88·0%	16,20,32,35,37,39, 47–50

Definitions used for all active and confirmed tuberculosis are the same as in tables 1–3. *Defined by the World Bank income groups, classified according to 2004 gross national annual income per head: low income, <US$825; middle income, US$825–10 066. ..=too few studies for meta-analysis.

Table 3: **Pooled yields among subgroups for all active and confirmed tuberculosis**

The presence of heterogeneity across studies was assessed by the conventional chi-squared test for heterogeneity and by calculating the I^2 statistic.[27] This heterogeneity may indicate differences in community incidence of tuberculosis, index-case characteristics, or contact characteristics. To investigate sources of heterogeneity, we supplemented simple pooling of all yield data with pre-specified subgroup analyses. We stratified study results by the geography of the study setting (Africa, Asia, and the Americas), World Bank income classification (low income, gross national income per head <US$825 per year; middle income, $825–10 066 per year), year of study publication (before 1980, 1980 and later), sputum-smear status of the index case, HIV status of the index case, and age of household contacts. The age of the index case and HIV status of contacts were also considered, but there were insufficient studies with these outcomes to warrant analysis.

Results

The study selection process is shown in figure 1. We identified 1237 unique citations from all literature searches, and of these 41 publications were eligible for inclusion. The median number of index cases in each study was 103 (range 32–806, IQR 70·5–201·5; webtable). Of the 41 studies, 27 reported the yield of all active tuberculosis (clinical/radiological diagnoses with or without bacteriological confirmation; table 1). 23 studies reported the yield of bacteriologically confirmed active tuberculosis. 19 studies reported the yield of LTBI (table 2). The median number of contacts screened in each study was 523·5 (range 56–3046, IQR 286·25–1012·25) for active tuberculosis, and 384 (range 32–2870, IQR 186–768·5) for LTBI. Only four studies reported the incidence of multiple tuberculosis cases in the household contacts of one index case.[21,33,41,54] In these studies, 25–56% of the households had more than one contact with tuberculosis. The remaining studies did not report on the household breakdown of the secondary cases, and no studies described the household breakdown of LTBI cases.

The 41 studies were done in 17 countries: 20 (49%) were done in Africa, 12 (29%) in Asia, and nine (22%) in Central or South America. By the World Bank classification system, 26 (63%) studies were from 11 low-income nations, and 15 (37%) were from seven middle-income nations. Eight (20%) of the studies reviewed were published before 1980 and 33 (80%) were published in 1980 or later. 17 studies reported outcomes for all contacts (children and adults combined) of sputum-smear-positive index cases. Of these 17 studies, 12 reported yield for active tuberculosis, ten for confirmed tuberculosis, and 12 for LTBI. Six studies reported results of contact investigations stratified by the HIV status of the index case: four reported active tuberculosis, two reported confirmed tuberculosis, and five reported LTBI (table 3). 23 studies reported outcomes for children

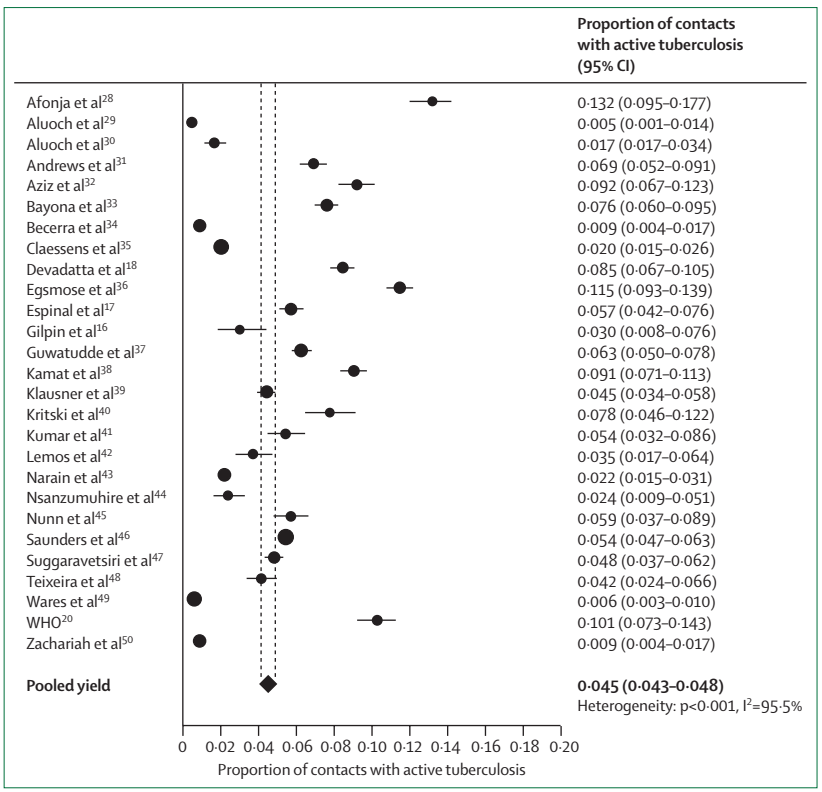

***Figure 2*: Forest plot of the yield of contact investigations for all active tuberculosis (confirmed and clinical/radiological diagnoses)**
Symbol size is proportional to sample size of study.

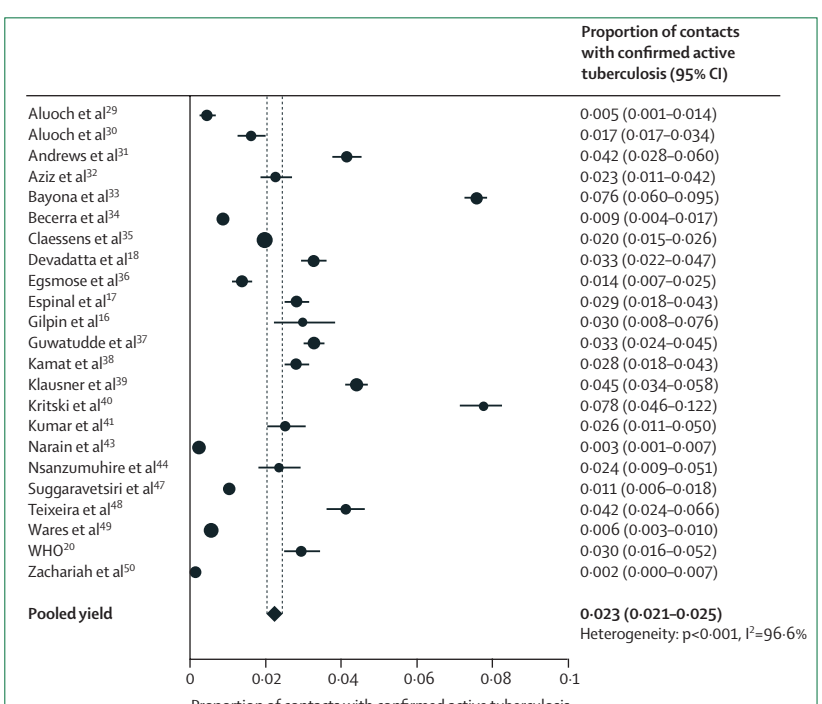

***Figure 3*: Forest plot of the yield of contact investigations for confirmed tuberculosis**
Confirmed tuberculosis includes all cases with either a positive sputum smear or culture for *M tuberculosis*. Symbol size is proportional to sample size of study.

See Online for webtable

separately (see webtable), and 18 of these reported outcomes for children aged under 5 years. One study reported on contact investigation of adult contacts of child index cases.[55] This study was not included in the pooled analysis.

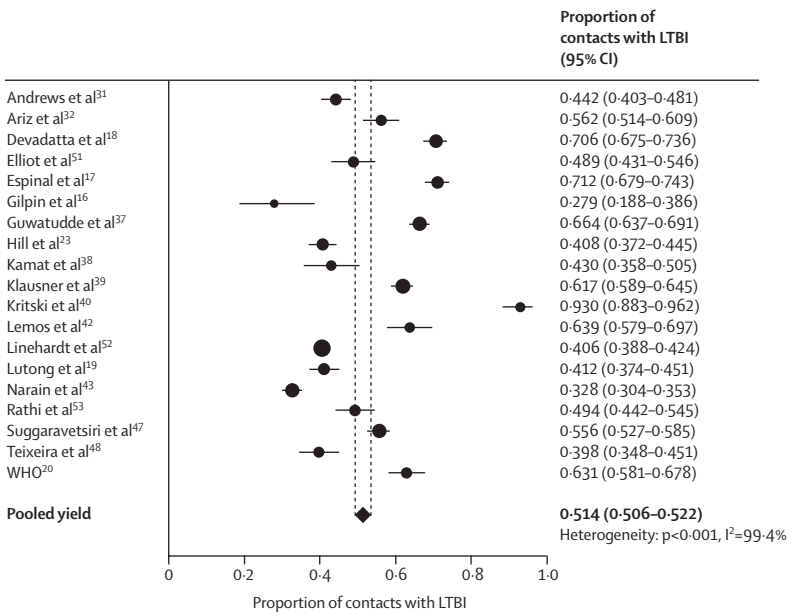

***Figure 4*: Forest plot of the yield of contact investigations for LTBI**
Symbol size is proportional to sample size of study.

	Studies	Pooled % yield (95% CI)	Heterogeneity		References
			p	I²	
Geographic region					
Africa	7	50·5% (49·3–51·7%)	<0·001	98·4%	16,20,23,37,39,51,52
Asia	8	48·6% (47·3–49·9%)	<0·001	98·1%	18,19,31,32,38,43,47,53
Americas	4	65·5% (63·1–67·8%)	<0·001	98·4%	17,40,42,48
National income status*					
Low-income economy	12	49·6% (48·7–50·6%)	<0·001	98·4%	18,20,23,31,32,37–39, 43,51–53
Middle-income economy	7	56·8% (55·2–58·5%)	<0·001	98·2%	16,17,19,40,42,47,48
Year					
Pre-1980	5	48·1% (46·5–49·8%)	<0·001	98·9%	18,20,31,38,43
1980 and later	14	52·5% (51·5–53·4%)	<0·001	98·2%	16,17,19,23,32,37,39,40, 42,47,48,51–53
HIV status of index case					
HIV negative	5	63·1% (61·1–65·0%)	<0·001	95·3%	17,39,47,48,51
HIV positive	5	52·0% (49·5–54·6%)	<0·001	92·9%	17,39,47,48,51
Sputum smear status of index case					
Positive sputum smear	12	51·8% (50.9–52·8%)	<0·001	98·0%	16,17,19,20,23,32,37,39, 47,48,52,53

Definitions used for LTBI are the same as in tables 1–3. *Defined by the World Bank income groups, classified according to 2004 gross national annual income per head: low income, <US$825; middle income, US$825–10 066.

***Table 4:* Pooled yields among subgroups for LTBI**

Table 1 and figure 2 show the results of the 27 studies that reported yield for all active tuberculosis (with or without bacteriological confirmation) among all household contacts. The pooled yield was 4·5% (95% CI 4·3–4·8). The pooled yield of the 23 studies reporting the yield for confirmed tuberculosis among all household contacts was 2·3% (95% CI 2·1–2·5; table 1, figure 3). Table 2 and figure 4 show the results of the 19 studies reporting the yield for LTBI. The pooled yield was 51·4% (95% CI 50·6–52·2). All the above meta-analyses had substantial statistical heterogeneity. In the one study that screened only adult contacts of child index cases the yield for all active disease was 16·1%.[55]

Of the subgroups examined, the groups sorted by geographical region, national income status, year of publication, and HIV status of the index case had insufficient numbers to warrant comparative analysis. The pooled yields for these subgroups are reported in table 3 and table 4. The subgroup of studies reporting outcomes for contacts of sputum-smear-positive index cases included more than ten studies (table 3 and table 4), but there were not enough studies reporting outcomes for sputum-smear-negative index cases to warrant comparison. There was substantial heterogeneity ($p<0·001$, $I^2>85\%$) in all but a few analyses. One exception was the subgroups sorted by HIV status of the index case, but these subgroups contained data from only four studies and were therefore also inappropriate for comparison. Results for the studies reporting subgroup outcomes sorted by the age of the contacts are reported in table 5 and table 6. There was significant statistical heterogeneity in all subgroups (table 6).

Discussion

Transmission of *M tuberculosis* from an infectious source case to people with whom they share air is governed by several factors, among which are the closeness of contact and duration of exposure. Studies have generally shown a gradation in the indicators of transmission (active tuberculosis and LTBI) by closeness and duration of contact with the infectious source.[61] Thus, household contacts are a particularly high-risk population for LTBI and for active tuberculosis.[61] Assessment of people who are likely to have recently acquired infection with *M tuberculosis* is important because of the risk such people have of progressing to active tuberculosis soon after infection has occurred, generally within 1–2 years. In many areas of low tuberculosis incidence, contact investigation with emphasis on household contacts is an integral part of tuberculosis control, contributing to case finding and to prevention of tuberculosis by treatment of LTBI. According to the US Centers for Disease Control and Prevention, contact investigation is one of the highest priority activities in tuberculosis control, and had an important role in bringing about the 44% decrease in the incidence of tuberculosis in the USA between 1993 and 2004.[4] However, whether the use of contact investigations

	Yield (%) for active tuberculosis				Yield (%) for LTBI			
	Child contacts			Adult contacts (>15 years)	Child contacts			Adult contacts (>15 years)
	<5 years	5–14 years	<15 years		<5 years	5–14 years	<15 years	
Almeida et al[56]	..	..	..	..	36·7%	53·3%	47·5%	..
Andrews et al[31]	9·2%	3·0%	5·5%	8·3%	16·2%	53·6%	38·8%	52·4%
Bayona et al[33]	..	..	1·5%	10·1%	..	..	..	..
Beyers et al[22]	8·9%	..	..	..	41·8%	..	..	..
Devadatta et al[18]	19·7%	6·9%	11·1%	5·7%	24·1%	..	..	70·6%
Espinal et al[17]	..	..	7·0%	4·7%	48·9%	60·7%	56·3%	83·1%
Gilpin et al[16]	..	..	..	3·0%	..	..	27·9%	..
Guwatudde et al[37]	11·0%	..	..	..	..	..	..	..
Kamat et al[38]	24·8%	9·2%	15·2%	5·9%	..	..	..	..
Klausner et al[39]	2·6%	6·2%	4·8%	4·0%	45·9%	54·7%	51·3%	75·5%
Kumar et al[41]	3·5%	..	..	7·1%	..	..	..	..
Lienhardt et al[57]	..	..	..	..	25·8%	..	..	..
Madico et al[58]	..	..	..	..	..	..	55·4%	..
Narain et al[43]	..	..	..	..	5·8%	26·6%	18·5%	50·2%
Nunn et al[45]	12·7%	4·8%	7·3%	5·8%	27·2%	..	..	..
Rathi et al[53]	..	..	..	..	23·3%	52·0%	39·3%	54·8%
Salazar-Vergara et al[59]	3·9%	2·9%	3·3%	..	51·3%	76·9%	69·2%	..
Saunders et al[46]	11·2%	..	..	..	..	..	..	..
Schaaf et al[21]	11·2%	..	..	..	52·8%	..	..	..
Singh et al[60]	3·2%	..	..	..	33·8%	..	..	..
Teixeira et al[48]	..	..	..	..	..	..	31·0%	46·4%
Topley et al[54]	..	..	..	..	28·4%	..	..	..
Zachariah et al[50]	1·7%	..	..	..	..	..	..	..

Table 5: **Yields for all active tuberculosis and LTBI among household contacts, by age**

applies to high-prevalence settings is not clear. Although close contacts are certainly a high-risk group for tuberculosis transmission,[62] most secondary cases in any high-prevalence community will still arise outside close-contact investigations for any given source case.[63] Also, in high-incidence countries, contact investigation has historically been viewed as an expensive, low priority endeavour. Although the International Standards for Tuberculosis Care recommend contact investigation as a public-health standard,[14] the overwhelming emphasis in most low-income and middle-income countries is, appropriately, on detection and treatment of patients with active tuberculosis.

During the past decade, many countries have committed more resources towards tuberculosis control efforts with an emphasis on implementation of the DOTS strategy. Since 2000, the number of countries implementing the DOTS strategy has increased from 119 to 182, with a parallel increase in the number of identified cases of tuberculosis and cases in which treatment is completed.[64] Unfortunately, there has not been a decrease in the incidence of tuberculosis globally. With the growing prevalence of co-infection with *M tuberculosis* and HIV, the current control strategy that stresses treatment of disease alone may not be enough to have an impact on the transmission of *M tuberculosis* and on the incidence of tuberculosis in low-income and middle-income countries.[65] Consequently, contact investigation both as a means of case finding and to identify high-priority candidates for treatment of LTBI may prove to be important interventions,

	Total studies (n)	Pooled yield (95% CI)	Heterogeneity		References
			p	I^2	
Active tuberculosis					
Child contacts					
<5 years	13	8·5% (7·4–9·7%)	<0·001	88·8%	18,21,22,31,37–39, 41,45,46,50,59,60
5–14 years	6	6·0% (4·7–7·5%)	0·064	43·5%	18,31,38,39,45,59
<15 years	8	7·0% (6·0–8·0%)	<0·001	88·3%	17,18,31,33,38,39,45,59
Adult contacts (>15 years)	9	6·5% (5·7–7·4%)	<0·001	70·1%	16–18,31,33,38,39,41,45
LTBI					
Child contacts					
<5 years	14	30·4% (28·6–32·3%)	<0·001	94·4%	17,18,21,22,31,39,43,45, 53,54,56,57,59,60
5–14 years	7	47·9% (45·5–50·4%)	<0·001	96·0%	17,31,39,43,53,56,59
<15 years	10	40·4% (38·7–42·2%)	<0·001	97·8%	16,17,31,39,44,48,53,56, 58,59
Adult contacts (>15 years)	7	64·6% (62·9–66·2%)	<0·001	98·7%	17,18,31,39,43,48,53

Table 6: **Pooled data for all active tuberculosis and LTBI among household contacts, by age**

even in low-income settings, when pursued as part of a comprehensive tuberculosis control programme.

This systematic review presents pooled data on the yield of household contact investigation from a large number of studies in low-income and middle-income countries with the aim of providing the evidence base for formulation of appropriate policies. We also aim to clarify the best targets for contact-tracing activities in settings in which resources are limited.

Unfortunately, the pooled analysis of all studies showed substantial heterogeneity across studies. The high level of heterogeneity seems to indicate that there is not a yield around which all the studies can be pooled. This limits the ability to compare pooled yields among subgroups and calls into question the ability of pooled results from these studies to predict outcomes in other low or middle-income settings. Nevertheless, the yields among household contacts were high enough for a tuberculosis control intervention to warrant serious consideration.

The pooled yield among household contacts was 4·5% for all active tuberculosis, 2·3% for confirmed tuberculosis, and 51·4% for LTBI. These are remarkably high yields for a tuberculosis control intervention. However, less than half of the cases of active tuberculosis have bacteriological evidence to confirm the diagnosis. Assuming that there was an attempt to confirm a microbiological diagnosis, this finding could either be interpreted as a consequence of over-diagnosis or as being consistent with early diagnosis before the bacillary population has reached the threshold of detection.

With regard to the age subgroups, analyses showed that the yields of both active tuberculosis and LTBI vary with age. However, direct comparison of the pooled yields was not appropriate because of the high heterogeneity within each subgroup analysis. The variation among age-groups for active tuberculosis is consistent with evidence that young age is a risk factor for tuberculosis.[37] However, because of the difficulty in diagnosing tuberculosis in children, there may be a tendency towards over-diagnosis in children in contact with an infectious case. The variation among age-groups for LTBI may be explained by the limited years of exposure to tuberculosis that children have had compared with adults, resulting in lower yields of LTBI among the youngest children and the highest among adults. Neither the subgroup analysis by age or by any other index case characteristic were able to account for the heterogeneity in the comparisons of all studies.

This systematic review has several strengths. The comprehensive search strategy enabled us to review articles from multiple databases covering the period 1955–2005, and yielded more studies than any previous review. The systematic nature of the review resulted in inclusion of studies from a large number of countries in several geographical areas. Moreover, two reviewers independently and reproducibly completed screening, study selection, and data extraction. An additional strength was the ability to divide the studies on the basis of the economic status of the country in which each study was done, giving us a unique picture of *M tuberculosis* transmission in low-income and middle-income countries.

This review also has limitations. Although our search strategy was systematic, we were not able to include non-English-language papers, thereby limiting the scope of included studies. Additionally, in almost all reported studies, community incidence of tuberculosis was not reported. We therefore could not compare outcomes among household contacts with the overall community incidence of tuberculosis. Since incidence could not be used, we used the World Bank income classification system to examine contact investigation in low-income and middle-income nations as a proxy for high-incidence areas. Had it been available, incidence would have been a more appropriate measure on which to group studies to guide tuberculosis control efforts.

As in any systematic review, publication bias was a concern. However, existing methods such as funnel plots and regression asymmetry tests for publication bias were designed for meta-analysis of randomised controlled trials. To our knowledge, they cannot be used to detect publication bias in meta-analysis of diagnostic studies or rates.[66]

The pooled data were also limited by the variability in diagnostic criteria among studies, although, for active tuberculosis, this was minimised by the separate analysis of bacteriologically confirmed and clinical/radiological diagnoses. The pooling of data for LTBI among contacts was also limited by the lack of diagnostic standards for LTBI, especially in the setting of high HIV prevalence and high incidence of BCG vaccination. Unfortunately, there were not enough studies reporting HIV or BCG status of the contacts for subgroup analysis to minimise this limitation. Some cases of mycobacterial infection other than tuberculosis may have been included in the analysis, although this was minimised by the exclusion of smear-positive but culture-negative cases. The pooled data were also limited by the fact that most studies did not report clustering among contacts, though the few studies that did report clustering showed it to be common within household contacts. In general, the outcome data had uniformly high heterogeneity, even with subgroup analyses, limiting the confidence with which pooled data can be used to predict yields in a given community. However, to some extent, the analyses were helpful in exploring reasons for heterogeneity. The lack of molecular epidemiology data limited the ability to establish transmission links between index cases and contacts. Finally, this meta-analysis took into account only a limited number of index and contact characteristics, and ignored the many other individual characteristics that are known to influence household transmission.

Conclusions

Overall, this systematic review and meta-analysis provides information on the yield of household contact investigations

in high-incidence areas that may be used to determine the benefit of investing resources in this activity. The yield of household contact investigations for active tuberculosis is high throughout low-income and middle-income countries. Contact investigation for active tuberculosis among children under 5 years results in the highest yield of any subgroup. The evidence for targeting this age-group is consistent with the current recommendation by WHO and the International Union Against Tuberculosis and Lung Disease to provide contact investigation and treatment of LTBI for children under 5 years who are household contacts in low-income countries.[7] This finding may be especially salient for those nations that are unable to implement full-scale contact investigation but that could target high-risk populations such as young children. Finally, the high yield of LTBI among household contacts is a telling glimpse at the pervasiveness of this epidemic and the need for expansion of control efforts in the future. An important step in the consideration of household contact investigation in high-incidence areas is a determination of policies for treatment of LTBI. This may be necessary to realise the full value of contact investigations and to have a substantial impact on the transmission of tuberculosis in these settings.

This review raises several important questions that warrant exploration through further research. Because of the resources needed to pursue contact investigation in high-incidence areas, further assessment of the projected impact of household contact-tracing investigation on community incidence of tuberculosis, possibly through computer modelling, is warranted. Epidemiological studies need to follow the community impact of contact investigation interventions over time. It will also be essential to consider the implementation of contact investigation policy, which, even in high-income countries, faces the hurdles of non-adherence and incomplete follow-up for close contacts. Additionally, to determine the use of contact investigation in these resource-poor settings, cost-effectiveness analyses will be essential.

Very little information exists on the results of contact investigations in cases of drug-resistant tuberculosis. In low-income and middle-income countries, there are few data on the prevalence of drug resistance, and testing for drug susceptibility in individual patients is rare. However, in situations in which drug resistance in the index case is known, contact investigation could be a cost-effective method for early identification of secondary cases and prevention of further propagation of drug resistance. The available information suggests that contacts of drug-resistant cases who themselves are found to have tuberculosis usually have drug-resistant organisms as well, but the data are very limited.[21,28,40,48]

Search strategy and selection criteria

These are described in the Methods section.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This work was supported in part by the US Agency for International Development through the Tuberculosis Coalition for Technical Assistance. MP is a recipient of the Canadian Institutes of Health Research (CIHR) New Investigator Award. PCH receives research support from the US National Institutes of Health and the Centers for Disease Control and Prevention.

References

1 Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, Shivpuri DN. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. *Am Rev Respir Dis* 1962; **85:** 511–25.

2 Styblo K. Epidemiology of tuberculosis. Selected papers. The Hague: Royal Netherlands Tuberculosis Association, 1991.

3 Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc* 1975; **50:** 90–106.

4 Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR Recomm Rep* 2005; **54:** 1–81.

5 Harries AD, Maher D. TB/HIV: a clinical manual. Geneva: World Health Organization, 1996.

6 Rieder HL. Interventions for TB control and elimination. Paris: International Union Against Tuberculosis and Lung Disease, 2002.

7 Enarson D, Arnadottir T, Trebucq A. Management of tuberculosis: a guide for low income countries, 5th edn. Paris: International Union Against Tuberculosis and Lung Disease, 2000.

8 Stop TB Partnership, Child TB Subgroup, WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371. http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf (accessed Feb 6, 2008).

9 Maher D, Floyd K, Raviglione M. A strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296. http://whqlibdoc.who.int/hq/2002/WHO_CDS_TB_2002.296.pdf (accessed Feb 6, 2008).

10 Rieder HL. Contacts of tuberculosis patients in high-incidence countries. *Int J Tuberc Lung Dis* 2003; **7** (suppl 3)**:** S333–36.

11 WHO. Global tuberculosis control: surveillance, planning, financing. WHO report 2006. Geneva: World Health Organization, 2006.

12 Raviglione M. XDR-TB: entering the post-antibiotic era? *Int J Tuberc Lung Dis* 2006; **10:** 1185–87.

13 Van Rie A, Enarson D. XDR tuberculosis: an indicator of public-health negligence. *Lancet* 2006; **368:** 1554–56.

14 Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. International standards for tuberculosis care. *Lancet Infect Dis* 2006; **6:** 710–25.

15 World Bank. Data and statistics. Country classification. http://go.worldbank.org/K2CKM78CC0 (accessed March 27, 2008).

16 Gilpin TP, Hammond M. Active case-finding for the whole community or for tuberculosis contacts only? *S Afr Med J* 1987; **72:** 260–62.

17 Espinal MA, Peréz EN, Baéz J, et al. Infectiousness of *Mycobacterium tuberculosis* in HIV-1-infected patients with tuberculosis: a prospective study. *Lancet* 2000; **355:** 275–80.

18 Devadatta S, Dawson JJY, Fox W, et al. Attack rate of tuberculosis in a 5-year period among close family contacts of tuberculous patients under domiciliary treatment with isoniazid plus PAS or isoniazid alone. *Bull World Health Organ* 1970; **42:** 337–51.

19 Lutong L, Bei Z. Association of prevalence of tuberculin reactions with closeness of contact among household contacts of new smear-positive pulmonary tuberculosis patients. *Int J Tuberc Lung Dis* 2000; **4:** 275–77.

20 WHO Tuberculosis Chemotherapy Centre. An investigation of household contacts of open cases of pulmonary tuberculosis amongst the Kikuyu in Kiambu, Kenya. *Bull World Health Organ* 1961; **25:** 831–50.

21 Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics* 2002; **109:** 765–71.

22 Beyers N, Gie RP, Schaaf HS, et al. A prospective evaluation of children under the age of 5 years living in the same household as adults with recently diagnosed pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997; **1:** 38–43.

23 Hill PC, Brookes RH, Fox A, et al. Large-scale evaluation of enzyme-linked immunospot assay and skin test for diagnosis of *Mycobacterium tuberculosis* infection against a gradient of exposure in The Gambia. *Clin Infect Dis* 2004; **38:** 966–73.

24 Zamora J, Abraira V. Meta-DiSc for windows: a software package for the meta-analysis of diagnostic tests. http://www.hrc.es/investigacion/metadisc_en.htm (accessed Feb 6, 2008).

25 Glasziou P, Irwig L, Bain C, Colditz G. Systematic reviews in health care. A practical guide. Cambridge: Cambridge University Press, 2001: 67–73.

26 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

27 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

28 Afonja AO, Labode MO, Edet EG. Early yield of pulmonary tuberculosis among household contacts of known cases of open pulmonary tuberculosis in Lagos. *East Afr Med J* 1973; **50:** 136–39.

29 Aluoch JA, Karuga WK, Nsanzumuhire H, et al. A second study of the use of community leaders in case-finding for pulmonary tuberculosis in Kenya. *Tubercle* 1978; **59:** 233–43.

30 Aluoch JA, Edwards EA, Stott H. A fourth study of case-finding methods for pulmonary tuberculosis in Kenya. *Trans R Soc Trop Med Hyg* 1982; **76:** 679–91.

31 Andrews RH, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan CV, Velu S. Prevalence of tuberculosis among close family contacts of tuberculous patients in South India, and influence of segregation of the patient on early attack rate. *Bull World Health Organ* 1960; **23:** 463–510.

32 Aziz A, Ishaq M, Akhwand R. Infection risk of sputum positive tuberculosis patients to their family contacts with and without chemotherapy. *J Pak Med Assoc* 1985; **35:** 249–52.

33 Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, Becerra MC. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2003; **7** (suppl 3)**:** S501–09.

34 Becerra MC, Pachao-Torreblanca IF, Bayona J, et al. Expanding tuberculosis case detection by screening household contacts. *Public Health Rep* 2005; **120:** 271–77.

35 Claessens NJM, Gausi FF, Meijnen S, Weismuller MM, Salaniponi FM, Harries AD. High frequency of tuberculosis in households of index TB patients. *Int J Tuberc Lung Dis* 2002; **6:** 266–69.

36 Egsmose T, Ang'Awa JO, Poti SJ. The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. *Bull World Health Organ* 1965; **33:** 419–33.

37 Guwatudde D, Nakakeeto M, Jones-Lopez EC, et al. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. *Am J Epidemiol* 2003; **158:** 887–98.

38 Kamat SR, Dawson JJ, Devadatta S, et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. *Bull World Health Organ* 1966; **34:** 517–32.

39 Klausner JD, Ryder RW, Baende E, et al. *Mycobacterium tuberculosis* in household contacts of human immunodeficiency virus type 1-seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. *J Infect Dis* 1993; **168:** 106–11.

40 Kritski AL, Marques MJ, Rabahi MF, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 1996; **153:** 331–35.

41 Kumar RA, Saran M, Verma BL, Srivastava RN. Pulmonary tuberculosis among contacts of patients with tuberculosis in an urban Indian population. *J Epidemiol Community Health* 1984; **38:** 253–58.

42 Lemos AC, Matos ED, Pedral-Sampaio DB, Netto EM. Risk of tuberculosis among household contacts in Salvador, Bahia. *Braz J Infect Dis* 2004; **8:** 424–30.

43 Narain R, Nair SS, Rao GR, Chandrasekhar P. Distribution of tuberculous infection and disease among households in a rural community. *Bull World Health Organ* 1966; **34:** 639–54.

44 Nsanzumuhire H, Aluoch JA, Karuga WK. A third study of case-finding methods for pulmonary tuberculosis in Kenya, including the use of community leaders. *Tubercle* 1981; **62:** 79–94.

45 Nunn P, Mungai M, Nyamwaya J, et al. The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. *Tuber Lung Dis* 1994; **75:** 25–32.

46 Saunders LD, Irwig LM, Wilson TD. Tuberculosis management in Soweto. *S Afr Med J* 1984; **66:** 330–33.

47 Suggaravetsiri P, Yanai H, Chongsuvivatwong V, Naimpasan O, Akarasewi P. Integrated counseling and screening for tuberculosis and HIV among household contacts of tuberculosis patients in an endemic areas of HIV infection: Chiang Rai, Thailand. *Int J Tuberc Lung Dis* 2003; **7** (suppl 3)**:** S424–31.

48 Teixeira L, Perkins MD, Johnson JL, et al. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2001; **5:** 321–28.

49 Wares DF, Akhtar M, Singh S, Luitel H. Is TB contact screening relevant in a developing country setting? Experiences from eastern Nepal, 1996–1998. *Int J Tuberc Lung Dis* 2000; **4:** 920–24.

50 Zachariah R, Spielmann MP, Harries AD, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district of Malawi. *Int J Tuberc Lung Dis* 2003; **7:** 1033–39.

51 Elliott AM, Hayes RJ, Halwiindi B, et al. The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. *AIDS* 1993; **7:** 981–87.

52 Lienhardt C, Fielding K, Sillah J, et al. Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in the Gambia. *Am J Respir Crit Care Med* 2003; **168:** 488–55.

53 Rathi SK, Akhtar S, Rahbar MH, Azam SI. Prevalence and risk factors associated with tuberculin skin test positivity among household contacts of smear-positive pulmonary tuberculosis cases in Umerkot, Pakistan. *Int J Tuberc Lung Dis* 2002; **6:** 851–57.

54 Topley JM, Maher D, Mbewe LN. Transmission of tuberculosis to contacts of sputum positive adults in Malawi. *Arch Dis Child* 1996; **74:** 140–43.

55 Eckhoff CT. Evaluation of a clinical index among adult contacts of children with tuberculosis in rural Haiti. *Int J Tuberc Lung Dis* 2000; **4:** 1143–48.

56 Almeida LM, Barbieri MA, da Paixao AC, Cuevas LE. Use of purified protein derivative to assess the risk of infection in children in close contact with adults with tuberculosis in a population with high Calmette-Guerin bacillus coverage. *Pediatr Infect Dis J* 2001; **20:** 1061–65.

57 Lienhardt C, Sillah J, Fielding K, et al. Risk factors for tuberculosis infection in children in contact with infectious tuberculosis cases in the Gambia, West Africa. *Pediatrics* 2003; **111:** e608–14.

58 Madico G, Gilman RH, Checkley W, et al. Community infection ratio as an indicator for tuberculosis control. *Lancet* 1995; **345:** 416–19.

59 Salazar-Vergara RM, Sia IG, Tupasi TE, et al. Tuberculosis infection and disease in children living in households of Filipino patients with tuberculosis: a preliminary report. *Int J Tuberc Lung Dis* 2003; **7** (suppl 3)**:** S494–500.

60 Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. *Arch Dis Child* 2005; **90:** 624–28.

61 Etkind S. Contact tracing follow-up in high and low prevalence countries. In: Reichman L, ed. Tuberculosis: a comprehensive international approach, 2nd edn. New York: Mercel Dekker, 2000: 377–400.

62 Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. *Tuber Lung Dis* 1992; **73:** 73–76.

63 Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985; **14:** 32–38.

64 World Health Organization. WHO report 2006. Global tuberculosis control: surveillance, planning, financing. http://www.who.int/hiv/topics/tb/TB2006.ppt (accessed March 27, 2008).

65 Brewer TF, Heymann SJ. To control and beyond: moving towards eliminating the global tuberculosis threat. *J Epidemiol Community Health* 2004; **58:** 822–25.

66 Tatsioni A, Zarin DA, Aronson N, et al. Challenges in systematic reviews of diagnostic technologies. *Ann Intern Med* 2005; **142:** 1048–55.