Yield of Contact Investigations in Households of Patients With Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis

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Contact investigations among individuals living with drug-susceptible tuberculosis patients (source cases) have shown a high yield of tuberculosis disease and latent tuberculosis, but the yield of such investigations in households of drug-resistant tuberculosis source cases is unknown. In this systematic review and meta-analysis, we found 25 studies that evaluated a median of 111 (interquartile range, 21–302) household contacts of drug-resistant tuberculosis source cases. The pooled yield was 7.8% (95% CI, 5.6%–10.0%) for active tuberculosis and 47.2% (95% CI, 30.0%–61.4%) for latent tuberculosis, although there was significant statistical heterogeneity ($P < .0001$). More than 50% of secondary cases with drug susceptibility test results were concordant with those of the source case. Among studies that followed household members, the majority of secondary cases were detected within 1 year of the source case's diagnosis. Household contact investigation around drug-resistant tuberculosis patients is a high-yield intervention for detection of drug-resistant tuberculosis and prevention of ongoing transmission.

Keywords. tuberculosis; contact; drug resistance; transmission.

Drug-resistant tuberculosis is a global epidemic and is a particular threat to persons infected with human immunodeficiency virus (HIV). In 2011, there were an estimated 630 000 cases of multidrug-resistant (MDR) tuberculosis (ie, tuberculosis resistant to at least isoniazid and rifampin) worldwide, representing 5.3% of all tuberculosis cases [1]. The 2-year regimen for MDR tuberculosis is toxic and costly, and average cure rates are only 60%–70% [2–5]. Extensively drug-resistant (XDR) tuberculosis—defined as MDR tuberculosis with additional resistance to a fluoroquinolone and a second-line injectable antituberculosis agent—was first described in 2005 and has since been identified in 77 countries worldwide [6]. The emergence of XDR tuberculosis is of great concern because few treatment options remain against such highly resistant strains, and outcomes for patients with XDR tuberculosis are substantially poorer than outcomes for MDR tuberculosis [7–13]. Thus, prevention of new MDR and XDR tuberculosis cases is paramount to curb these epidemics.

Persons who live with a tuberculosis patient are at high risk for tuberculosis infection and disease due to prolonged, intense exposure to source cases [14, 15]. Thus, a well-established method for preventing tuberculosis cases is the household contact investigation, which seeks to detect and treat active cases earlier and identify latently infected individuals who would benefit from chemoprophylaxis. Contact investigations are a key component of tuberculosis programs [16]. This approach is used widely and effectively in low-burden settings, but rarely in high-incidence settings due in part to financial and human resource constraints [16].

The yield of a household contact investigation can be measured by the proportion of patients with active tuberculosis detected, as well as the proportion of latently infected persons detected. A review of household

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contact investigations of tuberculosis source cases (both drug-susceptible and drug-resistant) in low- and middle-income countries found that 4.5% of household contacts were diagnosed with active tuberculosis [17]. A more recent review of contact investigations of tuberculosis source cases (not limited to household contacts) found, in low- and middle-income countries, that the prevalence of active tuberculosis among contacts of MDR or XDR tuberculosis source cases (3.4%) was similar to the overall prevalence of active tuberculosis among contacts of all tuberculosis source cases (3.1%) [18].

It is unclear, however, whether the yield of contact investigation specifically in the households of drug-resistant tuberculosis source cases is similar to that of investigations around drug-susceptible source cases. A greater understanding of the anticipated yield from investment in these activities can provide an evidence base to assist tuberculosis programs in incorporating them into routine activities as these expand access to drug-resistant tuberculosis treatment. We conducted a systematic review and meta-analysis of contact investigations among household contacts of drug-resistant tuberculosis source cases, and compared infection and disease rates in children and adults in the household.

METHODS

Search Strategy

We first searched the literature for available systematic and narrative reviews of the yield of contact investigations conducted specifically in the households of drug-resistant tuberculosis patients. None were found.

Our search strategy then aimed to identify all studies that assessed the rate of active or latent tuberculosis among contacts of drug-resistant tuberculosis patients. We reviewed all published articles that discussed results of contact investigations. We did not restrict the language of the publications reviewed.

We searched 7 electronic databases for primary studies published through December 2011: PubMed, Embase, LILACS, IMSEAR, IMEMR, WPRIM, and AIM. The search terms included *tuberculosis*, *resistan**, *contact*, *outbreak*, and *transmission*. The complete search strategy is detailed in Supplementary Appendix 1.

To identify relevant articles not found through our search, we also reviewed the reference lists of primary studies and review articles for additional references.

Initial Review of Studies

We compiled an initial database from the electronic searches and removed duplicate citations. Two reviewers (A. W. T., C. M. Y.) screened these citations by reviewing the title and abstract to capture relevant studies. Studies were eligible for inclusion if they included contact investigation of drug-resistant tuberculosis source cases. Outbreak investigations were included. We also hand-searched the references of reviews of contact investigations to evaluate whether these references met inclusion criteria.

Full text was obtained for relevant citations and reviewed by 2 reviewers (A. W. T., C. M. Y.) to determine eligibility for inclusion. We resolved disagreements between the reviewers by consensus. Studies were excluded for the following reasons: contact investigation was not performed, <5 household contacts were evaluated, contact investigation was restricted to a facility or institution, household contacts were not reported separately from nonhousehold contacts, contacts of drug-resistant source cases were not reported separately from contacts of drug-susceptible source cases, total number of evaluated household contacts was not reported, no original data were reported, either the cohort or dataset was identical to that of another included report, or the full text of the report could not be obtained. For studies in which household contact investigation results were contained within a larger dataset and not presented separately, and which were published after 2000, we contacted the authors requesting the disaggregated data. We also contacted authors of studies in which results were not stratified by adult and pediatric age groups. Articles in German, Japanese, Polish, Romanian, Russian, and Serbian were evaluated with the aid of translators who were trained on inclusion criteria and data extraction.

Data Collection

We designed a data extraction form (Supplementary Appendix 2), which 2 reviewers (N. S. S., C. M. Y.) piloted. These 2 reviewers extracted data from all of the studies included, and disagreements were resolved by consensus. The data elements extracted from each study comprised the yield of each contact investigation, including number of source cases, drug resistance category of source case isolates (eg, isoniazid monoresistant, MDR), number of evaluated contacts, duration of follow-up for contacts, number of active cases detected among contacts (secondary cases), and number of latently infected individuals detected among contacts. Among secondary cases, we also extracted the following data elements: results of tuberculin skin testing (TST), smear, culture, drug susceptibility testing (DST), and genotyping. Where possible, data for contacts were disaggregated by pediatric and adult age groups, and active cases detected at baseline and within 1, 2, and 3 years were indicated.

Definitions

The source case was defined as the tuberculosis case that led to investigation of a household. For data extraction, we used the definition of active tuberculosis reported by each study, including both clinical and bacteriologically confirmed diagnoses. We also used the definition of household contact and of TST positivity reported by each study. A secondary case was defined as a case of active tuberculosis in a household contact. Secondary

cases and source cases were classified as having concordant drug resistance patterns if both had isolates in the same resistance category, based on drugs tested in each study (eg, isoniazid monoresistant tuberculosis, MDR tuberculosis, XDR tuberculosis). Secondary cases and source cases were considered genotypically concordant according to the criteria used to compare isolates in each study. We used each study's definition of latent tuberculosis where latent tuberculosis diagnosis was specified; where latent tuberculosis diagnosis was not specified, we deduced that contacts with positive TST results but without active tuberculosis disease had latent tuberculosis. We used the definitions of child and adult in each study if age-stratified data were presented. When contacting authors requesting data disaggregated by age group, we defined the pediatric age range as 0–14 years.

Data Analysis

We computed the proportion of active tuberculosis disease and latent tuberculosis among household contacts for all studies and estimated 95% confidence intervals (CIs) using Wilson's method, which can be applied to studies even with 0% transmission rates [19–21]. We estimated overall proportions by meta-analysis using a random effects model, given the high heterogeneity of the risk of transmission observed across studies. Studies were weighted by the inverse variance of the corresponding transmission risks. Overall yield was also calculated among prespecified subgroups, stratified by drug resistance category of the index case (MDR tuberculosis vs mono- or polyresistant tuberculosis), tuberculosis disease burden (high vs low, based on World Health Organization categories), and age (children aged 0–14 years vs adults). Heterogeneity was measured using the I^2 statistic and tested by Q-statistic [22]. Analysis was performed using SAS and S-plus software.

RESULTS

We identified 3188 unique citations through the literature search, of which 25 studies were eligible for inclusion (Figure 1). For 12 of these, data extraction relied on additional unpublished information provided to us by the authors.

The included studies evaluated a median of 111 household contacts (interquartile range [IQR], 21–302) and a median of 26 (IQR, 2–87) drug-resistant source cases (Table 1). Eighteen studies included MDR tuberculosis source cases, 2 of which also included XDR tuberculosis source cases. Six studies included monoresistant tuberculosis source cases (mostly to isoniazid, although source cases with isolates with monoresistance to pyrazinamide, rifampicin, and streptomycin were also reported), and 4 studies included source cases with other drug resistance patterns.

All included studies reported the number of active tuberculosis cases among the household contacts (Table 1 and Figure 2) with an overall pooled yield of 7.8% (95% CI, 5.6%–10.0%). Latent tuberculosis was reported or could be calculated based on TST results in 14 studies (Table 2 and Figure 3). The overall proportion of household contacts with latent tuberculosis was 47.2% (95% CI, 30.0%–61.4%). There was significant statistical heterogeneity in the pooled measures ($P < .0001$, $I^2 = 94.9\%$ for active tuberculosis disease; $P < .0001$, $I^2 = 96.0\%$ for latent tuberculosis).

Among the 16 studies with only MDR tuberculosis source cases, the overall proportion of household contacts with active tuberculosis disease was 6.5% (95% CI, 4.6%–8.4%, $I^2 = 87.2\%$). Among the 7 studies with only mono- or polyresistant tuberculosis source cases, it was 11.6% (95% CI, 2.7%–20.4%, $I^2 = 97.7\%$). Latent tuberculosis was reported or calculated in 9 studies that included only MDR tuberculosis source cases, with an overall yield of 50.7% (95% CI, 41.5%–59.9%, $I^2 = 78.4\%$). Among 3 studies with mono- or polyresistant tuberculosis source cases, the yield of latent tuberculosis among household contacts was 41.5% (95% CI, 8.19%–74.8%, $I^2 = 94.7\%$).

The overall proportion of household contacts with active tuberculosis disease was 8.7% (95% CI, 6.08%–11.2%, $I^2 = 95.6\%$) among 12 studies from high-burden tuberculosis settings and 6.3% (95% CI, 2.4%–10.1%, $I^2 = 79.7\%$) among 13 studies from low-burden settings ($P = .316$). Latent tuberculosis among household contacts was reported or could be calculated from 5 studies in high-burden settings and 9 studies in low-burden settings, with overall yields of 52.5% (95% CI, 33.8%–71.2%, $I^2 = 95.8\%$) and 44.1% (95% CI, 24.9%–63.4%, $I^2 = 94.2\%$), respectively.

Five studies evaluated only pediatric household contacts, 1 study evaluated only adult household contacts, 13 studies evaluated both, and 6 studies did not report age for evaluated household contacts. Of the studies that evaluated both pediatric and adult contacts, it was possible to calculate the yield of active tuberculosis cases for the 2 age groups separately in 11 studies (Table 3). Overall, 4.0% (95% CI, 1.5%–6.5%, $I^2 = 80.1\%$) of pediatric contacts and 4.9% (95% CI, 2.7%–7.0%, $I^2 = 82.3\%$) of adult contacts had active tuberculosis disease ($P = .631$). Among 5 studies in which latent tuberculosis was reported or could be calculated for both children and adults, 27.3% (95% CI, 3.9%–50.6%, $I^2 = 88.5\%$) of pediatric contacts and 51.9% (95% CI, 25.6%–78.2%, $I^2 = 93.1\%$) of adult contacts had latent tuberculosis.

DST results of secondary cases were reported in 17 studies. In 1 of these studies, only secondary cases with drug resistance patterns and genotypes concordant with their source cases were reported [34]. Of the remaining 16 studies, 15 reported that >50% of secondary cases with DST results were drug-

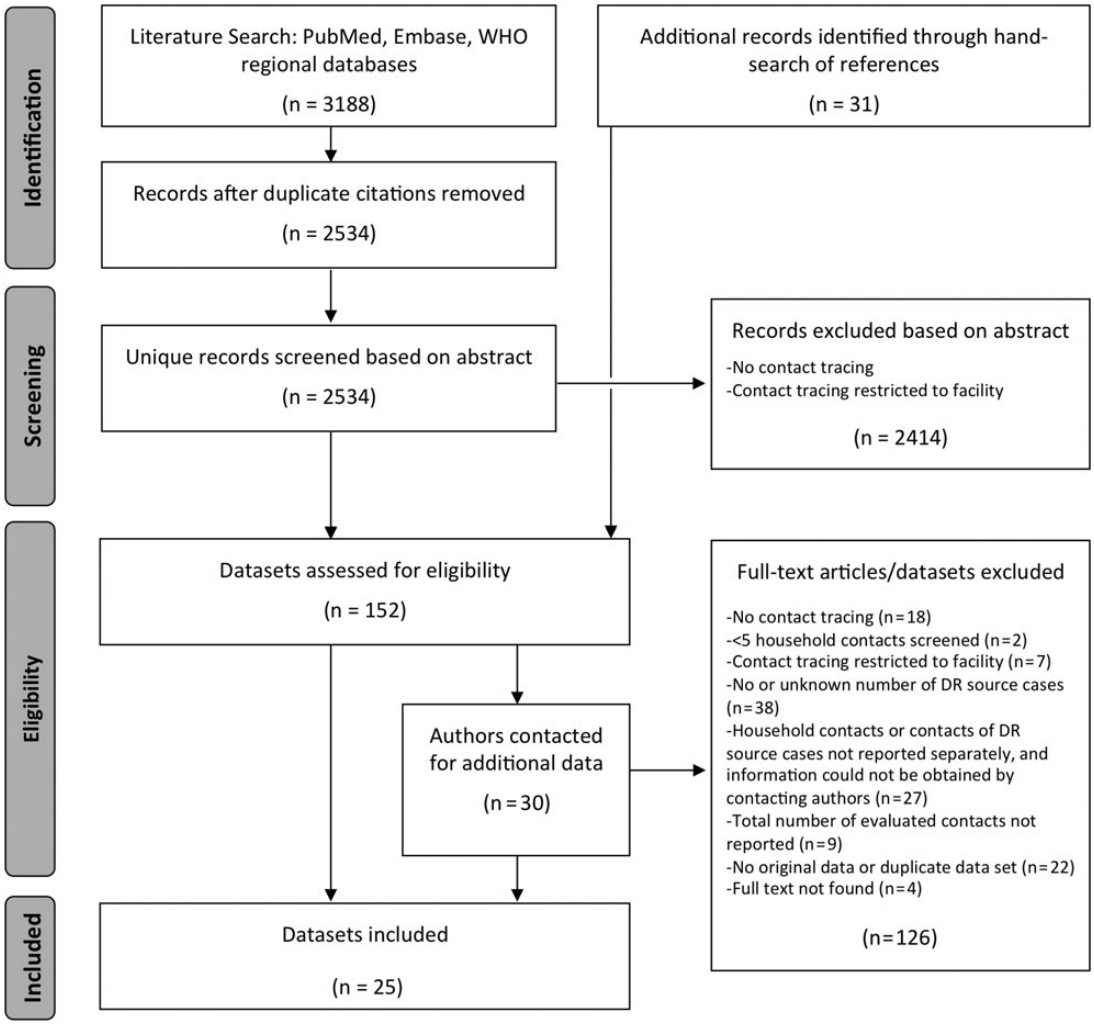

Figure 1. Flow diagram for study selection. Abbreviations: DR, drug-resistant; WHO, World Health Organization.

resistant tuberculosis (Table 1), and 14 reported that >50% of secondary cases with DST results had drug resistance categories that were concordant with that of the source case (Table 4). In 7 of the 8 studies that reported genotyping results for secondary cases, at least 75% of secondary cases analyzed had strains whose genotypes were concordant with that of the source case (Table 4).

In 7 studies, household contacts were followed up for >1 year, and it was possible to determine the number of secondary cases detected within 1, 2, or 3 years of baseline evaluation (Figure 4). Five studies reported detecting >50% of secondary cases within 1 year of baseline evaluation, and all 6 studies that followed household contacts for >2 years reported detecting >50% of secondary cases within 2 years of baseline evaluation.

DISCUSSION

In this systematic review and meta-analysis, we evaluated the pooled yield of household contact investigation for drug-resistant tuberculosis source cases and found a high overall yield for active tuberculosis cases (7.8%) and latent tuberculosis (47.2%). In almost all of the studies that reported DST and genotyping results, the majority of secondary cases had DST and/or genotyping results concordant with that of the source case. In 5 of the 7 (71%) studies that followed household contacts for >1 year, the majority of secondary cases were detected within 1 year of the source case's diagnosis. Together, these findings support the growing epidemiologic evidence for the high yield of household contact investigation of drug-resistant tuberculosis source cases, particularly within the first year after diagnosis.

Table 1. Yield of Secondary Cases of Active Tuberculosis in 25 Included Studies

Author(s)	Location	Year(s) of Enrollment	Drug-Resistant Tuberculosis Source Cases, No.	Source Case Drug Resistance Category	Household Contacts Evaluated for Active Tuberculosis, No.	Active Secondary Cases, No. (%)	Drug-Resistant Secondary Cases Among Secondary Cases With DST, No. (%)
CDC [23]	Federated States of Micronesia	2007–2009	5	MDR	163	16 (10)	3/3 (100)
Agerton et al [24]	US	1992–1997	12	MDR	21	3 (14)	3/3 (100)
Bayona et al [25]	Peru	1997–1999	92	MDR	464	38 (8)	9/9 (100)
Becerra et al [26]	Peru	1996–2003	693	MDR, XDR	4503	359 (8)	173/186 (93)
Grandjean et al [27]	Peru	2005–2008	358	MDR	2112	108 (5)	44/50 (88)
Huang et al [28]	Taiwan	2005–2007	19	MDR	78	0 (0)	NA
Johnson et al [29]	US	1997	2	Mono, MDR	12	0 (0)	NA
Kritski et al [30]	Brazil	1988–1992	64	Poly, MDR	218	17 (8)	10/13 (77)
Mehta et al [31]	US	1996–2002	4	Poly	26	1 (4)	1/1 (100)
Miramontes et al [32]	US	2007	2	MDR	9	1 (11)	
Mokaddas et al [33]	Kuwait	2000–2003	1	Mono	9	1 (11)	1/1 (100)
Neely et al [34]	UK	1995–2000	87	Mono	129	26 (20)	26/26 (100)
Perri et al [35]	US	2003–2009	16	Mono	73	0 (0)	NA
Pineiro Perez et al [36]	Spain	Unknown	1	MDR	9	0 (0)	NA
Tuberculosis Research Centre [37]	India	1968–1983	209	Mono	779	188 (24)	4/22 (18)
Reichler et al [38]	US Virgin Islands	1997–1998	1	MDR	7	0 (0)	NA
Salazar-Vergara et al [39]	Philippines	2001	44	MDR	111	3 (3)	1/1 (100)
Schaaf et al [40]	South Africa	1994–2000	73	MDR	125	29 (23)	4/4 (100)
Singla et al [41]	India	2005–2008	58	MDR	302	16 (5)	2/3 (67)
Snider et al [42]	US	Unknown	180	Mono, Poly	601	4 (1)	2/3 (67)
Steiner et al [43]	US	1969	1	Poly	23	6 (26)	3/3 (100)
Teixeira et al [44]	Brazil	1994–1998	26	MDR	157	9 (6)	5/6 (83)
van Zyl et al [45]	South Africa	1996–2003	55	MDR	55	16 (29)	
Vella et al [46]	South Africa	2005–2008	508	MDR, XDR	1766	73 (4)	53/55 (96)
Younossian et al [47]	Switzerland	2003	2	MDR	13	0 (0)	NA

Abbreviations: CDC, Centers for Disease Control and Prevention; DST, drug susceptibility testing; MDR, multidrug-resistant tuberculosis; Mono, monoresistant tuberculosis (any type); NA, not applicable; Poly, polyresistant tuberculosis; XDR, extensively drug-resistant tuberculosis.

Emerging data suggest that drug-resistant tuberculosis cases are primarily occurring as a result of transmission of a tuberculosis strain that is already drug resistant ("primary transmission") [3, 6]. Although it was initially believed that the mutations that caused drug resistance in tuberculosis would exert a fitness cost, rendering drug-resistant strains less able to cause new cases [48], transmission of drug-resistant tuberculosis strains has been well documented [49–52]. The high concordance between source case and secondary case strain resistance patterns and genotypes observed in this review are further evidence of the transmissibility of drug-resistant tuberculosis strains. Furthermore, the yields of both tuberculosis disease and latent tuberculosis among household contacts in this review were higher than those observed in a systematic review of household contact investigations that was not limited to drug-resistant tuberculosis source cases [17] and another review of all types of contact investigations [18]. This supports the conclusion that the households of both types of source cases merit systematic contact investigation.

Our study found higher yields of household contact investigation for both active tuberculosis disease and latent tuberculosis in high-burden settings as compared to low-burden tuberculosis settings (8.65% vs 6.27% contacts with active tuberculosis disease; 52.5% vs 44.1% contacts with latent tuberculosis), but these differences were not statistically significant. The difference may be attributable in part to community transmission in high-burden settings. Studies from South Africa have shown that although transmission is occurring in households,

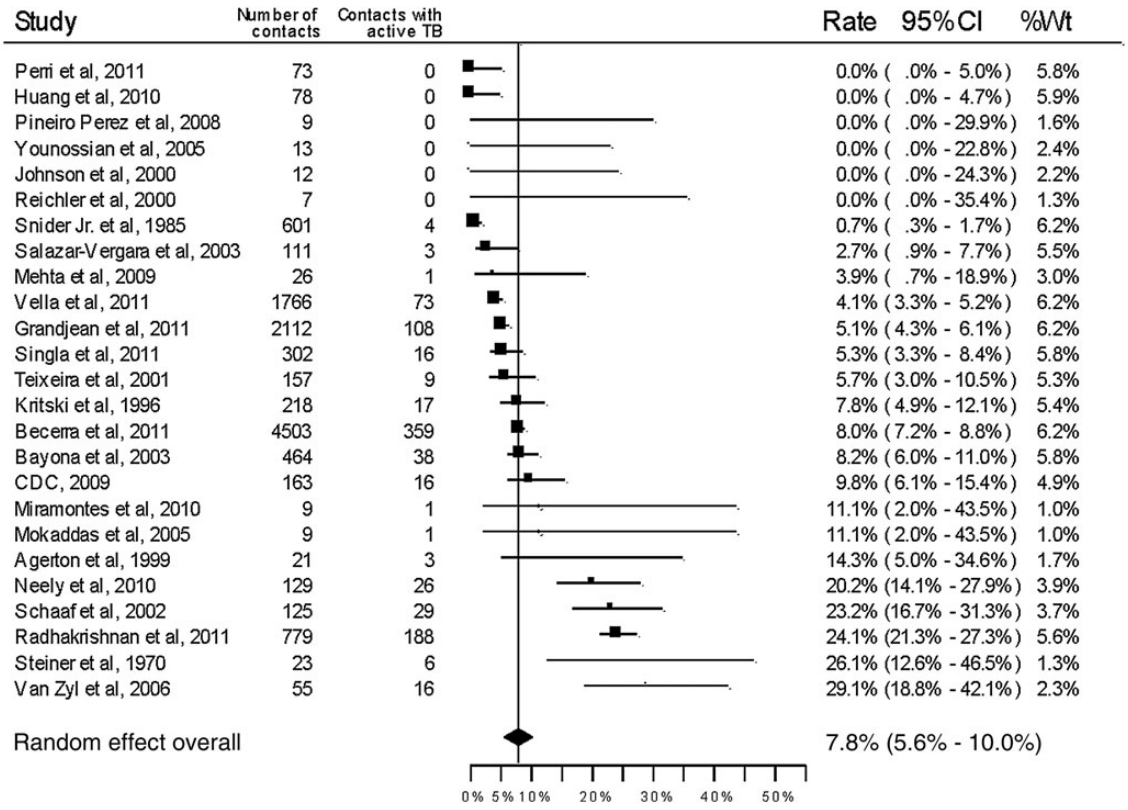

Figure 2. Forest plot for secondary cases of active tuberculosis among household contacts of drug-resistant tuberculosis source cases. Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; TB, tuberculosis; Wt, weight.

community transmission may account for up to 50% of drug-resistant tuberculosis cases [46, 53]. Community transmission may also explain the proportion of secondary cases with discordant DST and genotyping results observed in our study

Table 2. Yield of Latent Tuberculosis Detected in 14 Studies[a]

Author(s)	Location	Year(s) of Enrollment	Household Contacts Evaluated for Latent Tuberculosis, No.	Latent Tuberculosis Among Household Contacts, No. (%)
CDC [23]	Federated States of Micronesia	2007–2009	163	104 (64)
Agerton et al [24]	US	1992–1997	21	13 (62)
Huang et al [28]	Taiwan	2005–2007	78	36 (46)
Johnson et al [29]	US	1997	12	0 (0)
Kritski et al [30]	Brazil	1988–1992	218	173 (79)
Mehta et al [31]	US	1996–2002	26	9 (38)
Neely et al [34]	UK	1995–2000	129	23(18)
Pineiro Perez et al [36]	Spain	Unknown	9	5 (56)
Reichler et al [38]	US Virgin Islands	1997–1998	7	4 (57)
Salazar-Vergara et al [39]	Philippines	2001	111	65 (59)
Schaaf et al [40]	South Africa	1994–2000	125	64 (51)
Steiner et al [43]	US	1969	23	17 (74)
van Zyl et al [45]	South Africa	1996–2003	55	14 (25)
Younossian et al [47]	Switzerland	2003	9	4 (44)

Abbreviation: CDC, Centers for Disease Control and Prevention.

[a] Studies that reported a diagnosis of latent tuberculosis or where it could be calculated from data on tuberculin skin testing and clinical status of contacts.

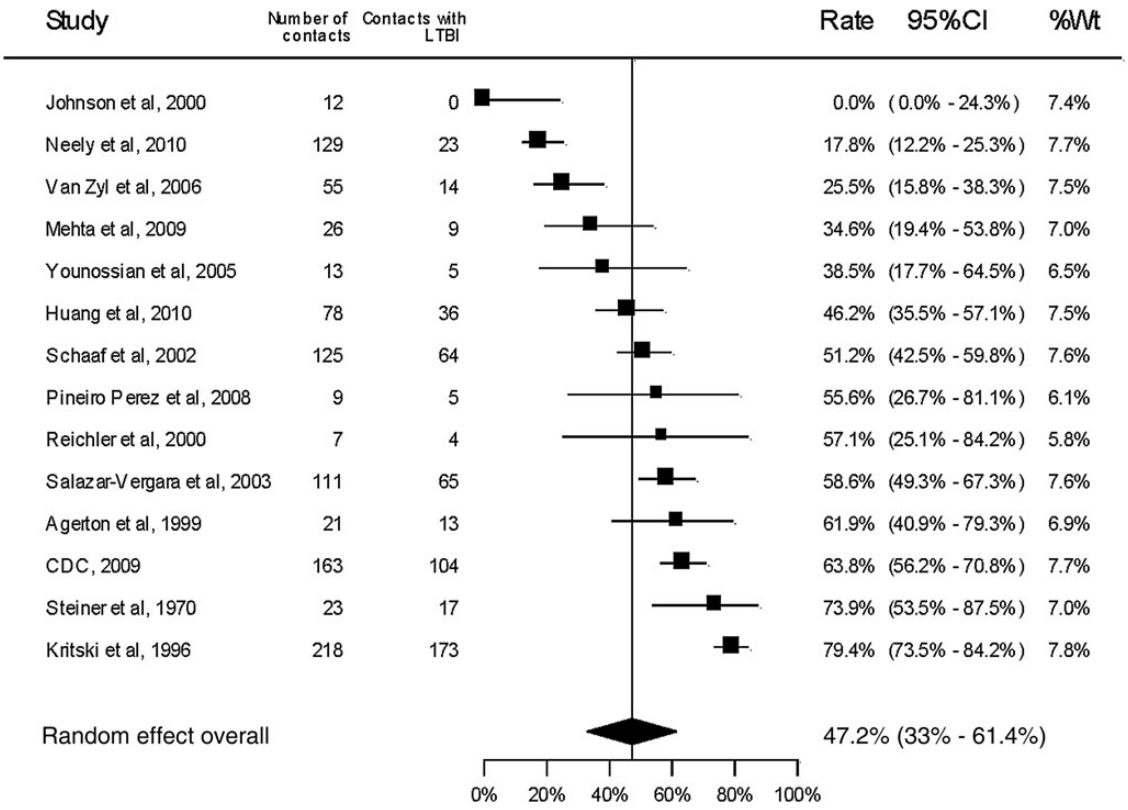

Figure 3. Forest plot for secondary cases of latent tuberculosis infection among household contacts of drug-resistant tuberculosis source cases. Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; LTBI, latent tuberculosis; Wt, weight.

(Table 4). The difference between yields of household contact investigations in high- and low-burden settings may also be attributable to resource limitations in high-burden settings that may delay diagnosis and initiation of effective drug-resistant tuberculosis therapy and, therefore, contribute to prolonged infectious periods. For patients with XDR tuberculosis, this is

Table 3. Yield of Active and Latent Tuberculosis Among Household Contacts by Age Group

			Household Contacts Evaluated, No.		Active Secondary Cases, No. (%)		Latent Tuberculosis, No. (%)	
Author(s)	Location	Year(s) of Enrollment	Child	Adult	Child	Adult	Child	Adult
CDC [23]	Federated States of Micronesia	2007–2009	60	103	9 (15)	7 (7)	20 (33)	84 (82)
Bayona et al [25]	Peru	1997–1999	118	343	3 (3)	35 (10)		
Becerra et al [26]	Peru	1996–2003	1272	3041	70 (6)	237 (8)		
Grandjean et al [27]	Peru	2005–2008	524	1567	14 (3)	94 (6)		
Huang et al [28]	Taiwan	2005–2007	16	62	0 (0)	0 (0)	5 (31)	31 (50)
Johnson et al [29]	US	1997	8	4	0 (0)	0 (0)	0 (0)	0 (0)
Mehta et al [31]	US	1996–2002	4	17	1 (25)	0 (0)	0 (0)	7 (41)
Miramontes et al [32]	US	2007	2	7	1 (50)	0 (0)		
Perri et al [35]	US	2003–2009	10	63	0 (0)	0 (0)		
Tuberculosis Research Centre [37]	India	1968–1983	405	374	4 (1)	18 (5)		
Steiner et al [43]	US	1969	17	6	5 (29)	1 (17)	12 (71)	5 (83)

Abbreviation: CDC, Centers for Disease Control and Prevention.

Table 4. Frequency of Concordance Between Source and Secondary Case Isolates by Resistance Category and Genotype

Author(s)	Location	Year(s) of Enrollment	Cases With Concordant Resistance Category Among Cases With DST, No. (%)	Cases With Concordant Genotype Among Cases With Genotype, No. (%)
CDC [23]	Federated States of Micronesia	2007–2009	3/3 (100)	3/3 (100)
Agerton et al [24]	US	1992–1997	3/3 (100)	3/3 (100)
Bayona et al [25]	Peru	1997–1999	9/9 (100)	. . .
Becerra et al [26]	Peru	1996–2003	164/186 (88)	. . .
Grandjean et al [27]	Peru	2005–2008	36/50 (72)	. . .
Kritski et al [30]	Brazil	1988–1992	8/13 (62)	. . .
Mehta et al [31]	US	1996–2002	1/1 (100)	0/1 (0)
Mokaddas et al [33]	Kuwait	2000–2003	1/1 (100)	1/1 (100)
Tuberculosis Research Centre [37]	India	1968–1983	4/22 (18)	. . .
Salazar-Vergara et al [39]	Philippines	2001	0/1 (0)	. . .
Schaaf et al [40]	South Africa	1994–2000	4/4 (100)	3/4 (75)
Singla et al [41]	India	2005–2008	2/3 (67)	. . .
Snider et al [42]	US	Unknown	2/3 (67)	. . .
Steiner et al [43]	US	1969	3/3 (100)	. . .
Teixeira et al [44]	Brazil	1994–1998	5/6 (83)	6/6 (100)
Vella et al [46]	South Africa	2005–2008	33/55 (60)	. . .

Cells with missing data indicate that genotyping was not performed or not available for these studies.

Abbreviations: CDC, Centers for Disease Control and Prevention; DST, drug susceptibility testing.

further exacerbated by extremely limited laboratory capacity globally for second-line drug susceptibility testing [54] and the paucity of effective treatment options. However, the increasing availability of rapid phenotypic and genotypic tests for diagnosis of drug-resistant tuberculosis offers great promise for improving case detection, initiating earlier treatment and averting further transmission of drug-resistant tuberculosis in community and congregate settings [55, 56].

The yields of active and latent tuberculosis among pediatric household contacts of drug-resistant tuberculosis in our study were comparable to those observed for drug-susceptible tuberculosis [17]. Although this population is known to be at high risk for disease progression, little is known about the disease burden among children, who likely represent a large pool of exposed, undiagnosed, and untreated latent infections. In one of the largest studies to date of pediatric MDR tuberculosis

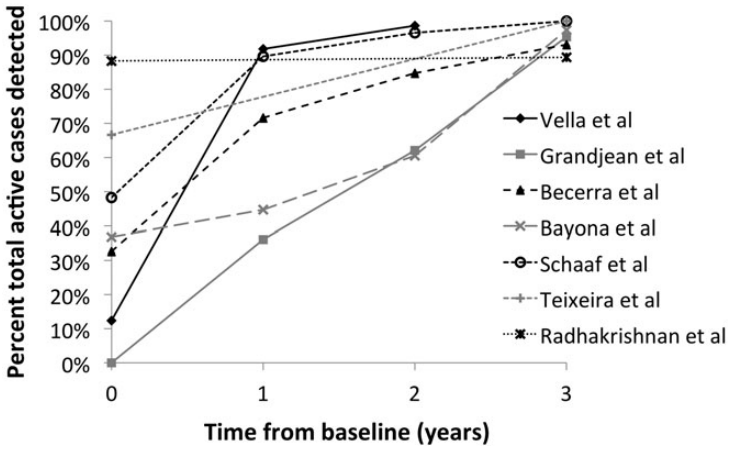

Figure 4. Yield for active tuberculosis disease over time among household contacts of drug-resistant tuberculosis source cases.

contacts, tuberculosis prevalence among children who were MDR tuberculosis household contacts was nearly 30 times higher than among children in the general population [57]. The majority of secondary cases had MDR tuberculosis, suggesting transmission in the home. Greater efforts to strengthen contact investigation for children, together with studies on safe and effective chemoprophylaxis, are urgently needed.

There are limitations to this study. First, we were unable to systematically assess the impact of HIV on risk of active tuberculosis disease and latent tuberculosis in household contacts given the limited data reported on this important variable in most studies. HIV is known to increase the risk of progression to active tuberculosis disease [58, 59], so it is likely to have an important effect on secondary case rates observed in high- vs low-HIV prevalence settings. Second, direct comparisons between yields of household contact investigations for drug-susceptible and drug-resistant source cases must be interpreted with caution as testing practices for drug resistance are likely to vary in each country, subjecting drug-resistant source cases to ascertainment bias. Source cases who are sicker or who are infectious for longer periods may have exposed household contacts for a longer time, thus increasing the potential for transmission. With scale-up of simpler, rapid diagnostic tests for drug-resistant tuberculosis, exposure periods and secondary case rates would be expected to decline. Although high-quality treatment for drug-resistant tuberculosis is not yet widely accessible, in some programs where it is available, staff may make greater efforts to identify and screen contacts of drug-resistant tuberculosis source cases, resulting in ascertainment bias among contacts. Third, genotyping of source and secondary cases was not consistently available in all studies included in our analysis, especially those from high-burden tuberculosis settings. Our ability to determine whether transmission occurred in the household or community was thus limited.

All systematic reviews are subject to the possibility of publication bias. A strength of our study is the inclusion of non-English-language papers that expanded the number of included studies and increased the robustness and generalizability of our findings. Likewise, in any meta-analysis, heterogeneity of the included studies is inevitable, and the heterogeneity across studies included in our meta-analysis was very large even in the subgroups. Although heterogeneity was accounted for using a random-effects model, we were unable to determine factors that might have resulted in such a large heterogeneity.

Despite these limitations, our study provides a systematic review and pooled estimates of yield from household contact investigation of drug-resistant tuberculosis source cases. Individuals who live with patients with any form of tuberculosis are at high risk for developing disease or latent infection. Globally, household contact investigation is an underutilized strategy against tuberculosis. As programs are expanding access to drug-resistant tuberculosis treatment and early diagnosis, there is strong evidence to support the prompt implementation of systematic contact investigation in the households of drug-resistant tuberculosis patients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. N. S. S., M. C. B., and C. M. Y. conceived of and designed the study. C. M. Y. and A. W. T. conducted the literature search and review of articles. N. S. S., C. M. Y., and A. W. T. extracted and cleaned data. M. H. conducted data analysis and data interpretation. All authors contributed to drafting and critical review of the final version of the manuscript. N. S. S. had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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