Tuberculosis Contact Tracing in Low and Middle Income Countries: A Systematic Review

Azmawati Mohammed Nawi1, Norfazilah Ahmad1, Siti Norbayah Yusof1, Nurmawati Ahmad1, Zaleha Md Nor1, Juhaida Mohd Noor1, Hasanan Faisal Ghazi2, Mohammad Saffree Jeffee3 and Mohd Rohaizat Hassan1

1 Department of Community Health, Faculty of Medicine, University Kebangsaan Malaysia Medical Centre.
2 Community Medicine Unit, International Medical School, Management and Science University, Selangor, Malaysia.
3 Department of Community Medicine, Faculty of Medicine & Health Science, Universiti Malaysia Sabah, Kota Kinabalu Sabah Malaysia.

*For reprint and all correspondence: Azmawati Mohammed Nawi, Department of Community Health, Faculty of Medicine, UKM Medical Centre. Email: azmawati@ppukm.ukm.edu.my

ABSTRACT

Received 28 December 2017
Accepted 21 March 2018

Introduction Tuberculosis (TB) is a major global health challenge especially in low- and middle-income countries reflects improper, delayed or missed diagnosis. Contact screening should be utilized both as an efficient and effective targeted approach to intensify TB case finding.

Methods Through a comprehensive systematic literature review of online database, this paper aims at providing an insight into the current practice of TB contact screening and to provide evidence based practice for formulation of appropriate policies in low- and middle-income countries. There are 24 articles included in this review from studies published from 2005 to 2014.

Results Findings in literature varies substantially. Generally, contact screening is better intensified with clear operational guidelines, adequate training, include close contact outside household as appropriate and follow up at least for 1 year. Prioritizing high risk close contacts is helpful in resource limited setting. Tuberculin skin test is still of value as screening tool and intensified case finding must be accompanied with effective management protocol. Prophylaxis treatment is recommended especially for children especially less than 5 years old, unvaccinated, malnourished, living with person having HIV and close contact with MDR-TB.

Conclusions Policy recommendations in improving TB management must incorporate complementary strategies to enhance case finding, effective management protocol for follow up or prophylaxis treatment, training for public health capacity and concerted dedication from various stakeholders.

Keywords Tuberculosis - contact tracing - screening - systematic review - low and middle income countries.
INTRODUCTION

Tuberculosis (TB) is among the world’s leading infectious causes of death, ranked second only to HIV/AIDS in mortality due to a single infectious agent. While TB has largely been controlled in the developed world, control efforts have been less successful in low and middle income countries. Tuberculosis (TB) remains a major global health challenge, affecting 8.8 million people each year, most of who live in low- and middle-income countries. Thus, TB still remains a major global public health threat.

The WHO has not issued clear guidance on how to conduct contact investigation or how to prioritize contacts except to say in children 5 years of age and persons with HIV infection who should be considered high-priority groups for tracing. In Malaysia there are no detailed guidelines on how to prioritize high risk groups and what screening approaches to be employed. The procedures have not been standardized at a national level and largely dependent on local understanding and practice based upon the clinical practice guideline.

Therefore, a systematic review is needed to better understand the current practice and yield of active TB cases of contact investigations and to provide evidence base for formulation of appropriate policies in Malaysia by taking exemplary approach from patients with TB in household and non-household settings in low and middle income countries and in various risk groups. Specifically, it sought to answer the following questions: i) what is the definition of TB contact? ii) who should be prioritised during contact TB screening? iii) what is the choice of effective method for TB contact investigation? iv) who should be prioritised to get TB chemoprophylaxis?

METHODS

We conducted the search using PubMed, Science Direct and Google Scholar using the terms: “tuberculosis”, “Mycobacterium tuberculosis” and “contact”, “contact tracing”, “contact screen”, “disease transmission”, “household contact”, “case finding” or “case detection”. To ensure that the review will be of recent 10 years, the search includes all studies from 1 January 2005 up to October 1, 2014. All titles and abstracts were assessed for inclusion according to the following agreed criteria. We included all accessible English language studies, original article that reported on any of the study objectives either among children or adults or both and were done in the low and middle income countries. We excluded editorials, conference abstracts, systematic reviews and meta-analysis articles.

The articles downloaded by the search engines were screened three times, first on the title, second on the abstract and lastly the whole full-text article to check on the relevance of the topic and suitability to be included in this review according to the objectives of this study. At each review step, only the articles that are considered relevant to these study objectives were subjected to the next step, while those that irrelevant are excluded. At the third step, each full-text article was reviewed independently by two reviewers to determine eligibility for inclusion into this systematic review. Disagreements were resolved by consensus. Figure 1 shows the flow of the article search.

Figure 1 Flow of article search
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RESULTS AND DISCUSSION

Definition and Nature of Contacts

Most of the study claim their study population as among the “household contacts” of confirmed tuberculosis patients (index cases) except: i) Tulu et al. which was a cross-sectional study among population; ii) Steffen et al. and Zhang et al. used “close contact” ; iii) Fortunato and Sant’anna did among “children exposed to TB patients” ; iv) Crampin et al. studied the spouses of tuberculosis patients. Among the 20 studies of “household contact” (Table 1), 7 of them do not have a specific or definitive operational definition other than as “living in the same house”. “Household contacts” definitions in the other 13 studies varied considerably. Some described household based on location, such as a common eating or sleeping area while some studies stipulated a minimum duration of exposure or degree of proximity. Generally, “household contacts” are individuals that shared the same house with the index case for a period of at least 3 months leading up to the time of diagnosis of the index case.

Table 1 Summary of studies been reviewed for TB contact investigation among household

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Place</th>
<th>Yea r of stud y</th>
<th>Nature of index case</th>
<th>Index cases</th>
<th>Nature of contact</th>
<th>Degree of contact</th>
<th>Duration of contact</th>
<th>Contac t investigated</th>
<th>Contacts investigation method</th>
<th>Criteria for TST positive</th>
<th>Positive screening test</th>
<th>Confirmatory test</th>
<th>Active TB detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thanh et al. (2014)</td>
<td>Vietnam</td>
<td>2010</td>
<td>SS (+) PTB</td>
<td>1091</td>
<td>Adult &amp; children</td>
<td>Household</td>
<td>3 months from diagnosis of index case</td>
<td>6118</td>
<td>Spum smear examination</td>
<td>NA</td>
<td>20 / 374 (5.3%)</td>
<td>NA</td>
<td>27 / 4118 (0.7%)</td>
</tr>
<tr>
<td>Jones-López et al. (2014)</td>
<td>Brazil</td>
<td>2008-2012</td>
<td>SS (+) PTB</td>
<td>124</td>
<td>Adult &amp; children</td>
<td>Sleeping under the same roof ≥5 days/week / sharing meals ≥5 days/week</td>
<td>Household</td>
<td>3 months from diagnosis of the index case</td>
<td>731</td>
<td>TST</td>
<td>&gt;10 mm</td>
<td>488 / 681 (71.7%)</td>
<td>NA</td>
</tr>
<tr>
<td>Ma et al. (2014)</td>
<td>Uganda</td>
<td>2008-2010</td>
<td>SS (+) PTB</td>
<td>NA</td>
<td>Adult &amp; children</td>
<td>House hold</td>
<td>7 consecutive days during the 3 months prior to diagnosis of index case</td>
<td>1318</td>
<td>TST</td>
<td>&gt;10 mm</td>
<td>1068 / 1210 (88.3%)</td>
<td>NA</td>
<td>92 / 3355 (2.7%)</td>
</tr>
<tr>
<td>Jia et al. (2014)</td>
<td>China</td>
<td>2008</td>
<td>SS (+) PTB</td>
<td>1575</td>
<td>Adult &amp; children</td>
<td>Household</td>
<td>2 weeks after case diagnosed</td>
<td>3355</td>
<td>Sputum smear &amp; CXR (all contacts)</td>
<td>TST</td>
<td>&gt;10mm</td>
<td>476 / 667 (71.4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Singh et al. (2012)</td>
<td>India</td>
<td>2008-2010</td>
<td>SS (+) &amp; SS (-) but CXR (+)</td>
<td>470</td>
<td>Adult &amp; children</td>
<td>NA</td>
<td>Contact</td>
<td>789</td>
<td>TST</td>
<td>&gt;10mm</td>
<td>225 / 789 (28.5%)</td>
<td>154 / 789 (19.5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Thind et al. (2012)</td>
<td>South Africa</td>
<td>2008-2010</td>
<td>SS (+) PTB</td>
<td>732</td>
<td>Adult &amp; children</td>
<td>Sleep &amp; eat together</td>
<td>NA</td>
<td>3573</td>
<td>NA</td>
<td>&lt; 5 years: 34 / 320 (10.6%)</td>
<td>&lt; 5 years: 93 / 637 (14.6%)</td>
<td>NA</td>
<td>&lt; 5 years: 34 / 361 (9.4%)</td>
</tr>
<tr>
<td>Rutherford et al. (2012)</td>
<td>Indonesia</td>
<td>2010</td>
<td>SS (+) PTB</td>
<td>210</td>
<td>Childrenchildren</td>
<td>3 months from diagnosis of the index case</td>
<td>320</td>
<td>TST</td>
<td>&gt;10mm</td>
<td>152 / 299 (50.8%)</td>
<td>NA</td>
<td>180 / 304 (59.2%)</td>
<td></td>
</tr>
<tr>
<td>Crampin et al. (2011)</td>
<td>Malawi</td>
<td>2008</td>
<td>SS (+) PTB</td>
<td>805</td>
<td>Spouse</td>
<td>Lived in the same household</td>
<td>NA</td>
<td>264</td>
<td>TST</td>
<td>&gt;10mm</td>
<td>152 / 214 (71.0%)</td>
<td>NA</td>
<td>Sputum smear &amp; culture</td>
</tr>
</tbody>
</table>
| Author et al. (year) | Country | Sample Size | Age Group | Duration of Symptoms | Method of Diagnosis | Prospective Test | Culture Sputum | Culture ...
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al. (2011)</td>
<td>China</td>
<td>5255</td>
<td>Adult &amp; child</td>
<td>Consistent cough for ≥3 weeks</td>
<td>NA</td>
<td>13310</td>
<td>Sputum smear (symptomatic only)</td>
<td>NA</td>
</tr>
<tr>
<td>Fortuna to and Sant'anna (2011)</td>
<td>Angola</td>
<td>124</td>
<td>Childre n (&lt;5 y.o.)</td>
<td>Household</td>
<td>NA</td>
<td>70 / 124</td>
<td>TST and CXR</td>
<td>70 / 124</td>
</tr>
<tr>
<td>Del Corral et al. (2009)</td>
<td>Colombia</td>
<td>433</td>
<td>Adult &amp; children</td>
<td>Household</td>
<td>2060</td>
<td>TST</td>
<td>331 / 502</td>
<td>65.9%</td>
</tr>
<tr>
<td>Lienhart et al. (2010)</td>
<td>Senegal</td>
<td>206</td>
<td>Adult &amp; children</td>
<td>Physical proximity of the household member to the index case at night-time:</td>
<td>3 months from diagnosis of index case.</td>
<td>2679</td>
<td>TST</td>
<td>1591 / 2458</td>
</tr>
<tr>
<td>Khan et al. (2014)</td>
<td>Pakistan</td>
<td>135</td>
<td>Adult &amp; children</td>
<td>Household &amp; share meals</td>
<td>NA</td>
<td>750</td>
<td>Sputum smear (symptomatic only)</td>
<td>NA</td>
</tr>
<tr>
<td>Nguyen et al. (2009)</td>
<td>Laos</td>
<td>72</td>
<td>Adult &amp; children</td>
<td>Share the same meal or the same bed, or live in the same room</td>
<td>NA</td>
<td>317</td>
<td>TST</td>
<td>1596 / 278 (56.5%)</td>
</tr>
<tr>
<td>Hill et al. (2008)</td>
<td>West Africa</td>
<td>317</td>
<td>Adult &amp; children</td>
<td>Same compound /sharing meals/ identifying a common household head</td>
<td>6 months</td>
<td>2313</td>
<td>TST</td>
<td>843 / 2230 (37.8%)</td>
</tr>
<tr>
<td>Sinfield et al. (2006)</td>
<td>Central Africa</td>
<td>161</td>
<td>Adult &amp; children ≤5 y.o.)</td>
<td>Household / same room</td>
<td>NA</td>
<td>195</td>
<td>TST</td>
<td>88 / 195 (45.1%)</td>
</tr>
</tbody>
</table>
Contact tracing is the process of identifying the relevant contacts of a person with an infectious disease (the index patient) and ensuring they are aware of their exposure. To use time and resources wisely, the contact tracing should be focused on the high-priority contacts, the contacts that are most at risk for developing TB infection or TB disease. A TB contact is considered if either shares the same meal or the same bed in the same house (Table 1). The degree of contact however varied in each study either weekly, monthly, 3 month or 6 month. Some of the studies stratified their contacts by age but the classification of children was inconsistent. Children were classified as either below 15 or 5 years old. Some studies focusing in the PTB group with HIV positive.

The World Health Organization, the International Standards for Tuberculosis Care and the International Union Against Tuberculosis and Lung Disease recommend as a minimum; a) screening households and close contacts of smear positive pulmonary tuberculosis cases to detect new TB cases; b) for children under five years of age and for all people with HIV without symptoms suggestive of TB.

The prioritization of appropriate target populations of TB contact tracing is critical prerequisites for rational active case-finding activities. A decision to conduct such activities should be based on the setting-specific and further cost-effectiveness analysis research need to be done for better outcome. In this review however, it is possible to summarise that the yield for screening among household contact was range 0.7 to 2.7 percent depending on the screening tool (either TST or IGRA)(see Table 2). Higher yield is seen if screening among those contacts who are: i) children with positive sputum culture; ii) symptomatic (of any TB symptoms); iii) children less than 5 years old; iv) children with...
malnutrition;\textsuperscript{15} v) spouses;\textsuperscript{8} vi) absence of BCG scar\textsuperscript{43} and vii) smoking/ exposure to smoking.\textsuperscript{15, 32} Thus, TB contact screening should be focusing on the high risk group to increase its effectiveness.

**Table 2: Summary of Yield of TB Contact Screening from the Review**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Yield of Screening (Active TB Detection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household Contact</td>
<td></td>
</tr>
<tr>
<td>For all children, (\leq 16 \text{ yo})</td>
<td>Jia et al. (2014); 0.7%</td>
</tr>
<tr>
<td>+ Symptomatic</td>
<td>Singh et al. (2005)</td>
</tr>
<tr>
<td>Children:</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years old</td>
<td>Thanh et al. (2014); 2.7%</td>
</tr>
<tr>
<td>≥ 5 years old</td>
<td>Singh et al. (2005)</td>
</tr>
<tr>
<td>≤ 16 years old</td>
<td>11.7%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Singh et al. (2005)</td>
</tr>
<tr>
<td>Spouses</td>
<td>71.0% among the spouses positive</td>
</tr>
<tr>
<td>Absence of BCG</td>
<td></td>
</tr>
<tr>
<td>Smoking/ exposure to smoking</td>
<td>Singh et al. (2005); (OR2.68)</td>
</tr>
</tbody>
</table>

**Investigation Methods of TB Contact**

All articles were assessed for investigation methods for TB contact and 20 studies were found relevant (Table 1). The methods used in investigation of TB contact were varied across the studies assessed. Of the 20 published studies, 15 studies used Tuberculin skin test (TST) for TB contact investigation. Among these, four used TST as an independent screening strategy. Only one study administered chest radiograph (CXR) and TST simultaneously to screen TB contacts, and the other compared TST with sputum examination (one study), serology (one study) and Interferon-gamma release assays (IGRA) (eight studies). While most of the studies used sputum examination for confirmatory testing, there were six studies using sputum examination for TB contact investigation, with three used this method independently, one simultaneously with CXR, one compared with TST (as mentioned above) and the other one compared with CXR.

Generally the TST was considered as positive in most of the related studies at the cut off induration \(\geq 10\) mm, except for a study that also specified \(\geq 5\) mm of induration in children less than 5 years old or HIV-infected individuals, and one study has additional category of \(\geq 15\) mm for those BCG-vaccinated within previous 2 years. While the more sensitive 6 mm increment has been suggested, the 10 mm increment cut-off is more specific and recommended by the American Thoracic Society (ATS) and the US Centre for Disease Control (CDC).

Yield for active TB in studies reviewed were range from 0.7 to 56.5%. The highest yield of 56.5% was a study that investigated the lowest number of contacts with a total of 124 and among children <5 years old only. Seventy active TB cases were found among these 124 contacts.\textsuperscript{7} However there might be sampling bias as most of children were brought for hospital care when they were symptomatic and those asymptomatic remained not investigated. As compared to other studies that performed TB contact investigation using larger sample size, the yield for active TB was much lower. These findings were concurrent with a systematic review done in China with yields for active TB ranged from 0 to 6.9% in household contacts.\textsuperscript{35}

A study found that the commercial serological test had poor sensitivity and specificity and suggests no utility for detection of pulmonary tuberculosis.\textsuperscript{34} TST was found to be more sensitive tool then serological test. On the other hand, IGRA have features that are advantageous compared with TST for serial testing; i.e. they are highly specific and are therefore unaffected by prior BCG vaccination; they can be repeated without concern with boosting, there is no need for a baseline two-step testing protocol; and the testing protocol requires only one visit. IGRA could therefore potentially provide a more accurate estimate of the annual risk of TB infection (ARTI) in specific populations.\textsuperscript{35} Another found that IGRA has value as prognostic marker of tuberculosis disease development, compared to TST.\textsuperscript{31}

Steffan et al. conducted a cost-effectiveness analysis from the health system perspective, comparing three different strategies for screening and treating LTBI: TST alone, IGRA
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(QFT-GIT), and TST followed by IGRA confirmation (QFT-GIT/TST) and found that TST was the most cost-effective strategy. However this was based on model assumption that only 10% of subjects submitted to TST do not return for reading and not considered costs for repeated TST in case of lost reading and for diagnosing TST conversion. Furthermore two prospective studies showed that TB contacts with positive IGRA results have a similar incidence rate of active tuberculosis with TST positive contacts. Therefore as according to WHO recommendation, depending on the epidemiological circumstances and resources, TST or IGRA for LTBI may be used as part of the clinical evaluation of the TB contacts in low- and middle-income countries.

On the other hand, in most TB high-burden settings, screening TB contact without testing for tuberculosis infection is found to be the most cost-effective strategy in 0–2-year-old children and the preferred strategy in 3–5-year-old children. This is concurrent with recommendation by WHO that children < 5 years of age and people living with HIV, for whom isoniazid preventive treatment is recommended without testing for LTBI.

Treatment for TB Contact

In most of the article not much of the treatment towards the contact ware discussed. From 24 articles, only 11 mentioned regarding recommendation of treatment towards contact. Most of the article recommended chemoprophylaxis therapy to children close contact. Isoniazide Preventive Therapy (IPT) is recommended for children that is having latent TB infection (positive TST in the absence of TB disease). It also should be given regardless the child’s BCG vaccination status. Priority of treatment was given to children contact especially child that is less than 5 years old, malnourished and unvaccinated close contact with active multidrug resistant TB (MDR-TB) and contact that have HIV infection.

Diagnosis of active TB was established from the contacts using the Brazilian Ministry of Health (MOH) scoring system based on clinical examination, CXR, TST, epidemiological data and nutritional status. Children with active TB disease were treated as per the Angolan MOH. TB-infected children who is asymptomatic with normal CXR and TST induration ≥10 mm (vaccinated for BCG more than 2 years) or TST induration ≥15 mm (vaccinated for BCG less than 2 years) will received Isoniazide Preventive Therapy (IPT) of 5 mg/kg/day for 6 months.

However from 11 studies that mentioned regarding the treatment for the contacts, only 3 studies have the results of the chemoprophylaxis. Isoniazid preventive therapy (IPT) substantially decreases rates of TB progression, morbidity and mortality among close contacts of infectious TB cases. Contact tracing and IPT delivery in young children exposed to TB in high-burden countries is highly cost-effective intervention. Lack of testing capacity should not be a barrier to IPT delivery.

A study done in Istanbul, Turkey comparing screening method using TST and IGRA, found that a positive IGRA is a useful and valid marker of latent tuberculosis infection because it predicts the subsequent development of active tuberculosis. This suggests that contacts diagnosed with latent tuberculosis infection on the basis of IGRA could benefit from preventive therapy.

Preventive therapy is indicated for an asymptomatic contact or a contact in whom TB disease has been excluded if the contact is less than 5 years of age or who is living with HIV (regardless of age). Preventive therapy for young children with TB infection who have not yet developed TB disease will greatly reduce the likelihood of TB disease developing during childhood. The preventive therapy regimen usually recommended is isoniazid 10 mg/kg (7-15 mg/kg) daily for 6 months, hence the name isoniazid preventive therapy (IPT). Follow-up should be carried out at least every 2 months until treatment is complete. There is no risk of isoniazid resistance developing in children receiving IPT, even if the diagnosis of active TB is missed.

What This Study Add and Its Limitation

In low and middle countries, despite the tendency of high prevalence of TB cases, need to use time and resources wisely and efficiently, contact investigation may need prioritization focusing on close contacts that are at high risk of developing disease if infected. Despite the issue with TST, this cheaper screening tool is found in this review still useful especially in limited resources setting, provided a standard operational guideline of what is considered positive test is defined.

As for prophylaxis treatment, it is recommended as it does reduce the rates of TB progression, morbidity and mortality among close contacts. The priority of IPT were towards children especially less than 5 years old, unvaccinated, malnourished, living with person having HIV and close contact with MDR-TB. Lack of testing capacity should not be barrier to IPT. From this review, future research should be on scaling-up of intensified case finding with development of standardised screening algorithms, efficient systems to ensure that people newly diagnosed with tuberculosis receive adequate treatment and evaluation for improved efficiency.

This study however poses its own limitations due to the descriptive nature of the analysis. However, it does highlights in recent literature with regards to TB contact tracing...
program in the low and middle income countries and the gaps for future studies.

CONCLUSION
TB management need to be improve by considering evidence of the standardized screening program, incorporate complementary strategies to enhance case finding, cost-effectiveness of various contact tracing strategies, training for public health capacity and concerted dedication from various stakeholders to ensure that the disease is sufficiently and properly managed towards achieving Sustainable Developmental Goal (SDG) 2030.

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