
ARTICLE REVIEW

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

Azmawati Mohammed Nawil¹, Norfazilah Ahmad¹, Siti Norbayah Yusof¹, Nurmawati Ahmad¹, Zaleha Md Nor¹, Juhaida Mohd Noor¹, Hasanain 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 Nawil, 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 countries¹. 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.² 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.³ 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.

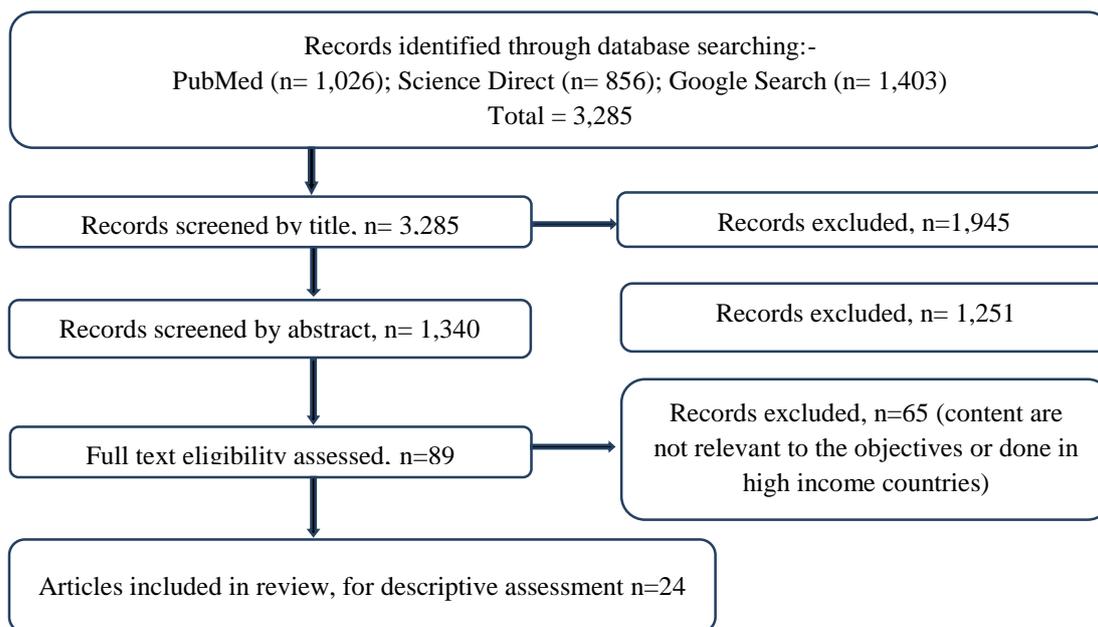


Figure 1 Flow of article search

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;⁴ ii) Steffen et al. and Zhang et al. used “close contact”;^{5,6} iii) Fortunato and Sant’anna did among “children exposed to TB patients”;⁷ and iv) Crampin et al. studied the spouses of tuberculosis patients.⁸ 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”.⁹⁻¹⁵ “Household contacts” definitions in the other 13 studies varied considerably. Some described household based on location, such as a common eating or sleeping area^{16, 17} while some studies stipulated a minimum duration of exposure or degree of proximity.^{18, 19} 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

Author & Year	Place	Year of study	Nature of index case	Index cases	Nature of contact	Degree of contact	Duration of contact	Contact investigated	Contacts investigation method	Criteria for TST positive	Positive screening test	Confirmatory test	Active TB detection rate (%)
Thanh et al. (2014)	Vietnam	2010	SS (+) PTB	1091	Adult & children	Household	3 months from diagnosis of the index case.	4118	Sputum smear examination	NA	20 / 374 (5.3%)	NA	27 / 4118 (0.7%)
Jones-López et al. (2014)	Brazil	2008 – 2012	SS (+) PTB	124	Adult & children	Sharing meals ≥5 days/week Household	3 months from diagnosis of the index case.	731	TST	≥10 mm	488 / 681 (71.7%)	NA	NA
Ma et al. (2014)	Uganda	2002 – 2008	SS (+) PTB	NA	Adult & children	Household	7 consecutive days during the 3 months prior to diagnosis of index case	1318	TST	≥10 mm ≥5 mm for children <5 y.o. & HIV+	1068 / 1210 (88.3%)	CXR & sputum smear	NA
Jia et al. (2014)	China	2008	SS (+) PTB	1575	Adult & children	Household	2 weeks after case diagnosed	3355	Sputum smear & CXR (all contacts)	NA	92 (2.7%)	NA	92 / 3355 (2.7%)
Singh et al. (2012)	India	2006 – 2010	SS (+) & SS (-) but CXR (+)	470	Adult & children	NA	NA	789	TST	≥10mm	476 / 667 (71.4%)	Sputum smear & culture	NA
Thind et al. (2012)	South Africa	2009 – 2010	SS (+) PTB	732	Adult & children	Sleep & eat together	NA	3573	Sputum smear & culture (symptomatic only)	NA	< 5 years: 34 / 320 (10.6%) ≥ 5 years: 93 / 637 (14.6%)	NA	< 5 years: 34 / 361 (9.4%) ≥ 5 years: 93 / 3029 (3.1%)
Rutherford et al. (2012)	Indonesia	NA	SS (+) PTB	210	Children (6/12 –9 y.o.)	Children	3 months from diagnosis of the index case.	320	TST	≥10mm	145 / 302 (48%)	CXR	NA
Crampin et al. (2011)	Malawi	2002 – 200	SS (+) PTB	805	Spouse	Lived in the same household/	Since onset of cough of	264	IGRA (QFT-GIT) Combined test (either or both tests positive) TST	≥10mm	152 / 299 (50.8%) 180 / 304 (59.2%)	CXR & sputum smear &	

		5				sleeping in the same room/ nursing the patient	index case				Prospective (active intervention): 81 / 117 (69.2%) Prospective (no intervention): 71 / 97 (73.2%)	culture	1.1%
Zhang et al. (2011)	China	2007	SS (+) PTB	5255	Adult & children	Consistent cough for ≥ 3 weeks	NA	13310	Sputum smear (symptomatic only)	NA	90 / 13310 (0.7%)	NA	90 / 13310 (0.7%)
Fortuna and Sant'anna (2011)	Angola	2007 – 2009	PTB	NA	Children (<5 y.o.)	Household	NA	124	TST and CXR	≥ 10 mm - nonBCG vaccinated ≥ 15 mm - BCG-vaccinated <2 years ≥ 10 mm	70 / 124 (56.5%)	NA	70 / 124 (56.5%)
Del Corral et al. (2009)	Columbia	2005 – 2006	SS (+) & CXR (+)	433	Adult & children	Household	Spent time regularly (weekly) / a month prior to diagnosis of index case	2060	TST IGRA		331 / 502 (65.9%) 1311 / 1977 (66.3%)	CXR & sputum smear & culture or gastric aspirate (child)	37 / 2052 (1.8%) 26 / 1977 (1.3%)
Lienhardt et al. (2010)	Senegal	2004 – 2006	SS (+) PTB	206	Adult & children	Physical proximity of the household member to the index case at night-time:	3 months from diagnosis of the index case.	2679	TST IGRA (ELISPOT) Combined test (either or both tests positive) Combined test (both tests positive)	≥ 10 mm	1591 / 2458 (64.7%) 544 / 952 (57.1%) 706 / 893 (79.1%) 436 / 893 (48.8%)	CXR & sputum smear & culture or gastric lavage	39 / 3332 (1.2%) 17 / 1183 (1.4%) 17 / 1526 (1.1%) 14 / 950 (1.5%)
Khan et al. (2014)	Pakistan	2012 – 2013	SS (+) PTB	135	Adult & children	Household & share meals	NA	750	Sputum smear (symptomatic only)	NA	88 / 165 (53.3%)	NA	88 / 750 (11.7%)
Nguyen et al. (2009)	Laos	2006	SS (+) PTB	72	Adult & children	Share the same meal or the same bed, or live in the same room	From the onset of the disease to the beginning of the directly observed therapy (DOT).	317	TST Sputum smear	≥ 10 mm at 48–72 hrs	Children: 46 / 148 (31.1%) Adult: NA Children: 0 Adult: 3 / 167 (1.8%)	CXR	NA
Hill et al. (2008)	West Africa	2002 – 2004	SS (+) PTB	317	Adult & children	Same compound /sharing meals/ identifying a common household head	6 months	2313	TST IGRA (ELISPOT) Combined test (either or both tests positive)	≥ 10 mm	843 / 2230 (37.8%) 649 / 1736 (37.4%) 835 / 1648 (50.7%)	CXR & sputum smear & culture	14 / 843 (1.7%) 11 / 649 (1.7%) 15 / 835 (1.8%)
Sinfield et al. (2006)	Central Africa	2003 – 2005	SS (+) PTB	161	Adult & children (≤ 5 y.o.)	Household / same room	NA	195	TST	≥ 10 mm (≥ 5 mm if HIV +)	88 / 195 (45.1%)	CXR & sputum smear	44 / 195 (22.6%)

Tuberculosis in Low and Middle Income Countries

Singh et al. (2005)	India	200 5	SS (+) & SS (-) of PTB	200	≤5 y.o.	Household	NA	281	TST	≥10mm	95 / 281 (33.8%)	CXR & gastric lavage	9 / 281 (3.2%)
Pai et al. (2009)	India	200 6 – 200 7	SS (+) PTB	54	NA	NA	NA	250	TST	≥10mm	115 (46%)	NA	NA
Lewins ohn et al. (2008)	Uganda	199 5 – 199 9 & 200 2 – 200 6	SS (+) & SS (-) but CXR (+)	NA	Adult & childre n	NA	NA	1267	TST	≥5mm	943 / 1267 (74.4%)	NA	NA
Bakir et al. (2008)	Turkey	200 2 – 200 4	SS (+) PTB	443	Childre n (≤16 y.o.)	Household	NA	908	TST		550 (60.6%)	CXR & sputum smear & culture or gastric lavage	12 / 722 (1.7%)
									IGRA (ELISAPOT)		381 (42.0%)		11 / 536 (2.1%)

NA: not available; SS (+): sputum smear positive; SS (-): sputum smear-negative; CXR: chest x-ray; y.o.: years old ; ≤ : less than; ≥ : more than.

Definition of tuberculosis contact is important as it gives the general who should be included or excluded in the screening or contact tracing, activity of which has been proven as an important way of curbing the infectious disease. One interesting study by—which evaluated a program called the Fidelis (Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB) project.⁶ The project is an active case finding through symptom screening and sputum microscopy of symptomatic close contacts in 35 counties in Shandong province, China. The study suggests that future active case finding projects should provide clear operational guidelines with adequate training and TB close contacts definition should include close contact outside household.

It is important to note that molecular epidemiology for contact investigation revealed that especially in high-prevalence countries, substantial transmission of *Mycobacterium tuberculosis* may occur outside households.^{20, 21} Students and workmates tend to be in relatively closer settings thus had a higher risk of transmitting TB.²² Thus, contact investigations should not focus exclusively on the household and depend on the circumstances.

Decision on How to Prioritize Contacts

Contact tracing is an important part of tuberculosis (TB) prevention and control in low incidence countries.^{3, 23} It aims primarily to identify individuals with latent or active TB who have been in contact with patients with infectious TB so that appropriate preventive or curative treatment can be given.²⁴ If the first notified or index case is one of primary tuberculosis, contact tracing is done to locate the source case; and if the index case has smear positive post-primary or reactivation tuberculosis, the concern is that other contacts may have been infected by the index case, although a source case may still be sought.²⁵

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.²⁶ 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 or live 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.^{14, 15, 27} Some studies focusing in the PTB group with HIV positive.^{8, 15}

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.^{28, 29}

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.^{3, 23} 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).^{27, 30, 31} Higher yield is seen if screening among those contacts who are: i) index case with positive sputum culture;^{14, 15} ii) symptomatic (of any TB symptoms);³² iii) children less than 5 years old;^{14, 15} iv) children with

malnutrition;¹⁵ v) spouses;⁸ vi) absence of BCG scar¹⁵ and vii) smoking/ exposure to smoking.^{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

Characteristics	Yield of Screening (Active TB Detection)			
Household Contact	Thanh et al. (2014); 0.7 %	Jia et al. (2014); 2.7 %	Del Corral et al. (2009); 1.3 – 1.8 %	Lienhardt et al. (2010); 1.1 – 1.5 %
Index sputum positive	Singh et al. (2005) (OR: 3.20)		Sinfield et al. (2006) (OR 2.15)	
+ Symptomatic	Khan et al. (2010); 11.7%			
Children :	Thind et al. (2012)	Sinfield et al. (2006)	Singh et al. (2005)	Khan et al. (2010)
< 5 years old	9.4%	(≤ 5 yo) 22.6%	(< 2 yo; OR: 6.65)	(Significantly higher risk among ≤ 12 yo; OR: 3.3)
≥ 5 years old	3.1%	(especially if index case is their mothers)		
≤ 16 years old	Bakir et al. (2008); 1.7 – 2.1 %			
Malnutrition	Singh et al. (2005); (OR: 3.97)			
Spouses	Crampin et al. (2011) 71.0 % among the spouses positive			
Absence of BCG Scar	Singh et al. (2005); (OR: 2.07)			
Smoking/ exposure to smoking	Singh et al. (2005); (OR:2.68)		Khan et al. (2010) ; (OR: 36.41)	

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 used 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 ≥10 mm, except for three study that also specified ≥5 mm of induration in children less than 5 years old or HIV-infected individuals, and one study has additional category of ≥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 contacts⁷. 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.³³

A study found that the commercial serological test had poor sensitivity and specificity and suggests no utility for detection of pulmonary tuberculosis.³⁴ TST was found to be more sensitive tool than 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.³⁵ Another found that IGRA has value as prognostic marker of tuberculosis disease development, compared to TST.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

(QFT-GIT), and TST followed by IGRA confirmation (QFT-GIT/TST) and found that TST was the most cost-effective strategy.⁵ 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.^{9,36} 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.³

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.¹² 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.³

Treatment for TB Contact

In most of the article not much of the treatment towards the contact were discussed. From 24 articles, only 11 mentioned regarding recommendation of treatment towards contact. Most of the article recommended chemoprophylaxis therapy to children close contact.^{7, 9, 10, 12, 16, 31, 36-38} Isoniazide Preventive Therapy (IPT) is recommended for children that is having latent TB infection (positive TST in the absence of TB disease).¹⁶ It also should be given regardless the child's BCG vaccination status.³¹ Priority of treatment was given to children contact especially child that is less than 5 years old,³⁷ malnourished and unvaccinated,^{15,31} close contact with active multidrug resistant TB (MDR-TB)¹⁰ and contact that having HIV infection.⁷

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.⁷ Children with active TB disease were treated as recommended by 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.¹² 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.⁹ 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).²⁸ 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.³⁹

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.

REFERENCES

1. World Health Organization. Tuberculosis. Fact Sheet No.104. 2012. Geneva: World Health Organization.
2. World Health Organization. Global Tuberculosis Control: Who Report 2011.2011. Geneva: World Health Organization.
3. World Health Organization. Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low-and Middle-Income Countries. 2012. Geneva: World Health Organization.
4. Tulu B, Dida N, Kassa Y et al. Smear Positive Pulmonary Tuberculosis and Its Risk Factors among Tuberculosis Suspect in South East Ethiopia; A Hospital Based Cross-Sectional Study. *BMC Research Notes*.2014;7(1):285.
5. Steffen RE, Caetano R, Pinto M et al. Cost-Effectiveness of Quantiferon®-Tb Gold-in-Tube Versus Tuberculin Skin Testing for Contact Screening and Treatment of Latent Tuberculosis Infection in Brazil. *PLoS One* 2013;8(4):e59546.
6. Zhang X, Wei X, Zou G et al. Evaluation of Active Tuberculosis Case Finding through Symptom Screening and Sputum Microscopy of Close Contacts in Shandong, China. *Trop Med Int Health*. 2011;16(12):1511-17.
7. Fortunato I, Sant'anna C. Screening and Follow-up of Children Exposed to Tuberculosis Cases, Luanda, Angola. *Int J Tuberc Lung Dis*. 2011;15 (10):1359-1361.
8. Crampin A, Kasimba S, Mwaungulu N et al. Married to M. Tuberculosis: Risk of Infection and Disease in Spouses of Smear-Positive Tuberculosis Patients. *Trop Med Int Health*. 2011;16(7):811-18.
9. Bakir M, Millington KA, Soysal A et al. Prognostic Value of a T-Cell-Based, Interferon- Γ Biomarker in Children with Tuberculosis Contact. *Ann Intern Med*. 2008;149 (11):777-86.
10. Becerra MC, Franke MF, Appleton SC et al. Tuberculosis in Children Exposed at Home to Multidrug-Resistant Tuberculosis. *The Pediatric Infect Dis J*. 2013;32(2):115-19.
11. Lewinsohn DA, Zalwango S, Stein CM et al. Whole Blood Interferon-Gamma Responses to Mycobacterium Tuberculosis Antigens in Young Household Contacts of Persons with Tuberculosis in Uganda. *PLoS One*. 2008;3(10):e3407.
12. Mandalakas AM, Hesselning AC, Gie RP et al. Modelling the Cost-Effectiveness of Strategies to Prevent Tuberculosis in Child Contacts in a High-Burden Setting. *Thorax*. 2013;68(3):247-55.
13. Pai M, Dendukuri N, Wang L et al. Improving the Estimation of Tuberculosis Infection Prevalence Using T-Cell-Based Assay and Mixture Models. *The international journal of tuberculosis and lung disease: Int J Tuberc Lung Dis*. 2008;12(8):895.
14. Sinfield R, Nyirenda M, Haves S et al. Risk Factors for Tb Infection and Disease in Young Childhood Contacts in Malawi. *Ann Trop Paediatr*. 2006;26(3):205-13.
15. Singh M, Mynak M, Kumar L et al. Prevalence and Risk Factors for Transmission of Infection among Children in Household Contact with Adults Having Pulmonary Tuberculosis. *Arch Dis Child*. 2005;90(6):624-28.
16. Nguyen TH, Odermatt P, Slesak G et al. Risk of Latent Tuberculosis Infection in Children Living in Households with Tuberculosis Patients: A Cross Sectional Survey in Remote Northern Lao People's Democratic Republic. *BMC Infect Dis*. 2009;9(1):96.
17. Thind D, Charalambous S, Tongman A et al. An Evaluation of 'Ribolola': A Household Tuberculosis Contact Tracing Programme in North West Province, South Africa. *Int J Tuberc Lung Dis*. 2012;16(12): 1643-48.
18. Jones-López EC, Kim S, Fregona G et al. Importance of Cough and M. Tuberculosis Strain Type as Risks for Increased Transmission within Households. *PLoS One*. 2014;9(7):e100984.
19. Ma N, Zalwango S, Malone LL et al. Clinical and Epidemiological Characteristics of Individuals Resistant to M. Tuberculosis Infection in a Longitudinal TB Household Contact

Tuberculosis in Low and Middle Income Countries

- Study in Kampala, Uganda. *BMC Infect Dis.* 2014;14(1):352.
20. Kranzer K, Houben, RM, Glynn JR et al. Yield of Hiv-Associated Tuberculosis During Intensified Case Finding in Resource-Limited Settings: A Systematic Review and Meta-Analysis. *Lancet Infect Dis.* 2010;10(2):93-102.
 21. Van Der Spuy G, Warren R, Van Helden P. The Role of Molecular Epidemiology in Low-Income, High-Burden Countries. *Int J Tuberc Lung Dis.* 2009;13(4):419-20.
 22. Wu N, Lin Y, Dai Z. Age and Sex Distribution Trend of New Smear Positive TB Patients in Fujian Province (2005–2007). *Chinese Primary Care.* 2009;23:55-56.
 23. Lönnroth K, Jaramillo E, Williams B et al. Tuberculosis: The Role of Risk Factors and Social Determinants. Equity, Social determinants and Public Health Programmes. 2010. Geneva: World Health Organization.
 24. Morrison J, Pai M, Hopewell PC. 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. *Lancet Infect Dis.* 2008;8(6):359-368.
 25. Fair E, Morrison J, Pai M et al. Hopewell P. Review and Policy Recommendations for Investigation of Contacts of Persons with Infectious Tuberculosis in High Incidence Areas. Draft for Stop TB Department. 2009. Geneva: World Health Organization.
 26. Australasian Contact Tracing Manual. 4th Ed. 2010. Darlinghurst, NSW: Australasian Society for HIV Medicine.
 27. Thanh THT, Dinh SN, Nguyen NV et al. A Household Survey on Screening Practices of Household Contacts of Smear Positive Tuberculosis Patients in Vietnam. *BMC Public Health.* 2014;14(1):713.
 28. World Health Organization. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2014. Geneva: World Health Organization.
 29. TB-Care-I. International Standards for Tuberculosis Care. 3rd Ed. 2014. The Hague: United States Agency for International Development (USAID).
 30. Jia Z, Cheng S, Ma Y et al. Tuberculosis Burden in China: A High Prevalence of Pulmonary Tuberculosis in Household Contacts with and without Symptoms. *BMC Infect Dis.* 2014;14(1):64.
 31. Del Corral H, Paris SC, Marín ND et al. Ifn γ Response to Mycobacterium Tuberculosis, Risk of Infection and Disease in Household Contacts of Tuberculosis Patients in Colombia. *PLoS One.* 2009;4(12): e8257.
 32. Khan T, Ahmed Z, Zafar M et al. Active Case Finding of Sputum Positive Pulmonary Tuberculosis in Household Contacts of Tuberculosis Patients in Karachi, Pakistan. *J Assoc Chest Physicians.* 2014;2(1):25.
 33. Liu E, Cheng S, Wang X et al. A Systematic Review of the Investigation and Management of Close Contacts of Tuberculosis in China. *J Public Health.* 2010;2 (4):461-66.
 34. Singh S, Singh J, Kumar S et al. Poor Performance of Serological Tests in the Diagnosis of Pulmonary Tuberculosis: Evidence from a Contact Tracing Field Study. *PLoS One.* 2012;7(7):e40213.
 35. Pai M, Joshi R, Dogra S et al. T-Cell Assay Conversions and Reversions among Household Contacts of Tuberculosis Patients in Rural India. *Int J Tuberc Lung Dis.* 2009;13(1):84.
 36. Hill PC, Jackson-Sillah DJ, Fox A et al. Incidence of Tuberculosis and the Predictive Value of Elispot and Mantoux Tests in Gambian Case Contacts. *PLoS One.* 2008;(1):e1379.
 37. Lienhardt C, Fielding K, Hane AA et al. Evaluation of the Prognostic Value of Ifn- γ Release Assay and Tuberculin Skin Test in Household Contacts of Infectious Tuberculosis Cases in Senegal. *PLoS One.* 2010;5(5):e10508.
 38. Rutherford M, Hill P, Maharani W et al. Risk Factors for Mycobacterium Tuberculosis Infection in Indonesian Children Living with a Sputum Smear-Positive Case. *Int J Tuberc Lung Dis.* 2012;16(12):1594-99.
 39. Van Halsema CL, Fielding KL, Chihota VN et al. Tuberculosis Outcomes and Drug Susceptibility in Individuals Exposed to Isoniazid Preventive Therapy in a High HIV Prevalence Setting. *Aids.* 2010;24(7):1051-55.