ARTICLE REVIEW

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

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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[1]. 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.

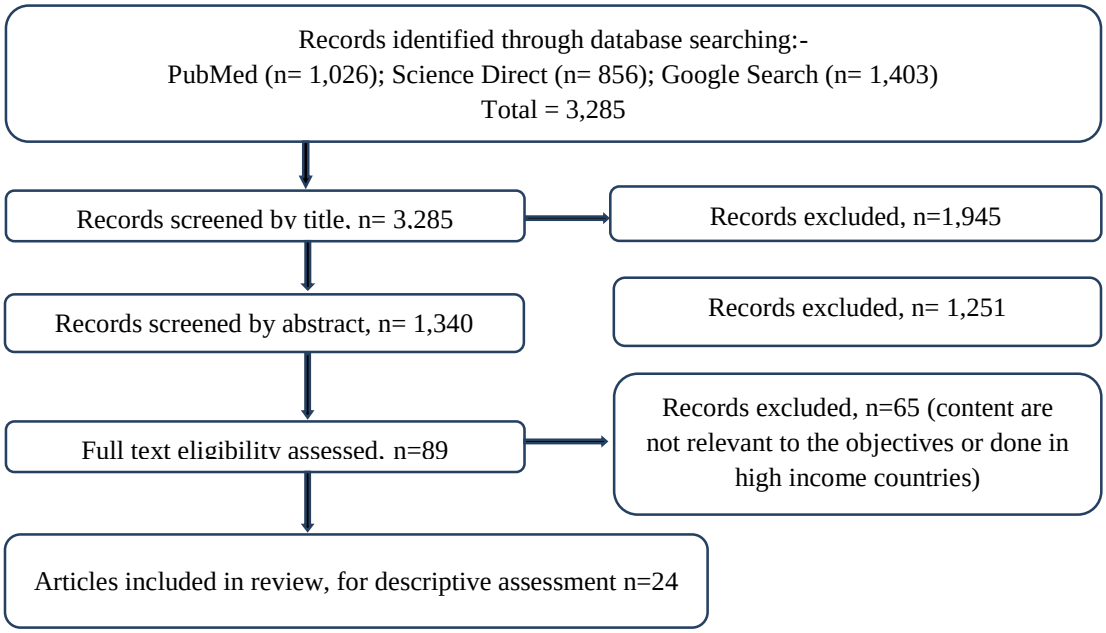

Figure 1 Flow of article search

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 investi-gated	Contacts investi-gation method	Criteria for TST positive	Positive screening test	Confir-matory 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 examinati-on	NA	20 / 374 (5.3%)	NA	27 / 4118 (0.7%)
Jones-López et al. (2014)	Brazil	2008 – 2012	SS (+) PTB	124	Adult & children	Sleeping under the same roof ≥5 days / week / sharing meals ≥5 days/week	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 Serology: IgM IgA IgG	⩾10mm	476 / 667 (71.4%) 225 / 789 (28.5%) 154 / 789 (19.5%) 185 / 789 (23.4%)	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 (sympto-matic 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)	Indo-nesia	NA	SS (+) PTB	210	Children (6/12 –9 y.o.)	Children	3 months from diagnosis of the index case.	320	TST IGRA (QFT-GIT) Combined test (either or both tests positive)	⩾10mm	145 / 302 (48%) 152 / 299 (50.8%) 180 / 304 (59.2%)	CXR	NA
Crampin et al. (2011)	Malawi	2002 – 200	SS (+) PTB	805	Spouse	Lived in the same household/	Since onset of cough of	264	TST	⩾10mm	152 / 214 (71.0%)	CXR & sputum smear &	

		5				sleeping in the same room/ nursing the patient	index case				Prospec-tive (active interventio n): 81 / 117 (69.2%) Prospectiv e (no interventio n): 71 / 97 (73.2%)	culture	1.1% 2.4%
Zhang et al. (2011)	China	200 7	SS (+) PTB	5255	Adult & childre n	Consistent cough for ≥3 weeks	NA	13310	Sputum smear (symptom-matic only)	NA	90 / 13310 (0.7%)	NA	90 / 13310 (0.7%)
Fortuna to and Sant'an na (2011)	Angola	200 7 – 200 9	PTB	NA	Childre n (<5 y.o.)	Household	NA	124	TST and CXR	⩾10 mm - nonBCG vaccinated ⩾15 mm - BCG-vaccinated <2 years	70 / 124 (56.5%)	NA	70 / 124 (56.5%)
Del Corral et al. (2009)	Columbi a	200 5 – 200 6	SS (+) & CXR (+)	433	Adult & childre n	Household	Spent time regularly (weekly) / a month prior to diagnosi s of index case	2060	TST IGRA	⩾10mm	331 / 502 (65.9%) 1311 / 1977 (66.3%)	CXR & sputum smear & culture or gastric aspirate (child)	37 / 2052 (1.8%) 26 / 1977 (1.3%)
Lienhar dt et al. (2010)	Senegal	200 4 – 200 6	SS (+) PTB	206	Adult & childre n	Physical proximity of the household member to the index case at night-time:	3 months from diagnosi s of the index case.	2679	TST IGRA (ELISPOT) Combined test (either or both tests positive) Combined test (both tests positive)	⩾10mm	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	201 2 – 201 3	SS (+) PTB	135	Adult & childre n	Household & share meals	NA	750	Sputum smear (symptom atic only)	NA	88 / 165 (53.3%)	NA	88 / 750 (11.7%)
Nguyen et al. (2009)	Laos	200 6	SS (+) PTB	72	Adult & childre n	Share the same meal or the same bed, or live in the same room	From the onset of the disease to the beginnin g of the directly observed therapy (DOT).	317	TST Sputum smear	⩾10mm 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	200 2 – 200 4	SS (+) PTB	317	Adult & childre n	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	200 3 – 200 5	SS (+) PTB	161	Adult & childre n (≤5 y.o.)	Household / same room	NA	195	TST	⩾10mm (⩾5mm if HIV +)	88 / 195 (45.1%)	CXR & sputum smear	44 / 195 (22.6%)

Singh et al. (2005)	India	2005	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	2006 – 2007	SS (+) PTB	54	NA	NA	NA	250	TST	⩾10mm	115 (46%)	NA	NA
									IGRA (QFT)		135 (54%)		
Lewinsohn et al. (2008)	Uganda	1995 – 1999 & 2002 – 2006	SS (+) & SS (−) but CXR (+)	NA	Adult & children	NA	NA	1267	TST	⩾5mm	943 / 1267 (74.4%)	NA	NA
									IGRA (ELISA)		880 / 1267 (69.5%)		
Bakir et al. (2008)	Turkey	2002 – 2004	SS (+) PTB	443	Children (≤16 y.o.)	Household	NA	908	TST		550 (60.6%)	CXR & sputum smear & culture or gastric lavage	12 / 722 (1.7%)
									IGRA (ELISPOT)		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 than5 years old;[14, 15,] iv) children with

malnutrition;[15] v) spouses;[8] vi) absence of BCG scar[15] 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
≥ 5 years old	3.1%	(especially if index case is their mothers)		higher risk among ≤ 12 yo; OR: 3.3)
≤ 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); (OR2.68)		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 contacts[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.[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 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.[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 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.[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.

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