Prevalence of Latent Tuberculosis in Contacts of Pulmonary Tuberculosis patients: A Systematic Review

Manvi Singh MD[1], Nishant Jaiswal PhD [1], Shreya Singh MD[2], Pranita Pradhan MLIS [1], Amit Agarwal PhD[1], Anil Chauhan PhD[1],Harnoor Sra MBBS[1], Suresh Varukolu M.Pharm[1,]Meenakshi Sharma PhD[3], Meenu Singh MD[1]

1-Advanced Center for Evidence Based Child Health, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

2- Department of Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

3-Department of Community Medicine and SPH, Chandigarh

Running Head- Prevalence of Latent Tuberculosis in Contacts

Word count of the summary-189

Word count of the text-1305

Number of references-17

Tables-1

Figures-3

Keywords: Latent Tuberculosis, Prevalenve, India, Systematic Review

Corresponding Author- Dr. Manvi Singh

19 Advanced Center for Evidence Based Child Health, Department of Pediatrics, Postgraduate
20 Institute of Medical Education and Research, Chandigarh 160012, India.

21 Email-drmanvisingh89@gmail.com

22 Phone-9779249953

23

24

25

26

27

28

29

30

31

32

33

34

35

36

Abstract

Introduction: Tuberculosis is still a leading cause of morbidity and mortality in the world, especially the low and middle income countries. While a lot is being done on the programmatic level, the burden of the disease is still underestimated owing to problems in diagnostics and infrastructure.

Objective: The objective of this study was to estimate the prevalence of Latent Tuberculosis infections in the pediatric household contacts of patients of pulmonary tuberculosis in India.

Methods: We searched electronic databases PubMed, EMBASE and Ovid for relevant articles. Search of grey literature and unpublished data was also done.The protocol of the study was registered in the PROSPERO. The quality of included studies was assessed using the Hoy et, al. checklist. The data extraction from relevant studies and subsequent data synthesis and analysis was done. The calculation of the pooled prevalence of LTBI, and the construction of galbraith plot for heterogeneity was done using STATA software.

Result: The searches yielded 600 studies out of which 19 were included in the review. The pooled prevalence of LTBI among household contacts was 39.27[26.05-52.49]. On subgroup analysis, the prevalence of LTBI from studies with only pediatric contacts included was 26.73[17.70-35.76].There was significant heterogeneity amongst the various studies with overall I^2=99.7%. A Galbraith Plot was constructed which also shows significant heterogeneity among the different studies. All studies had a low risk of bias with a score of 3 or less, except one, which had a moderate risk of bias with a total score of 4.

Conclusion: In India, almost 40% of the household contacts of patients with Pulmonary Tuberculosis harbor latent infection which can progress to disease during their lifetime.

Main Text

Tuberculosis is a disease which is endemic in India and many countries. In 2020, tuberculosis will still likely kill more people than any other infectious disease caused by a single pathogen.(1) In 2017, the number of under 5 children estimated to be eligible for tuberculosis prophylactic therapy globally was 1.27 million. This estimate corresponded to only a 23% of global preventive treatment coverage in children, which is significant under-utilization of Tuberculosis preventive treatment.(2)The figures for the Indian subcontinent as of 2018 indicate that only 26 % of the under 5 population received IPT. (3) One of the targets to implement End TB strategy by 2025 is to provide TB Preventive treatment to≥ 90% of those who warrant it. The current figures are dismal in that respect, and we need to scale up the active case finding and contact screening in order to facilitate meeting this target. The provision of prophylactic anti-tubercular drugs to the close contacts of TB patients will help eliminate the pool of infection likely to progress to disease. However, indiscriminate use may lead to over treatment and development of resistance as has been observed with monotherapy. It is therefore vital to estimate the prevalence of latent tuberculosis in close contacts of active TB patients as it will help inform policy makers of the the magnitude of the problem. Tuberculosis is still a leading cause of morbidity and mortality in the world, especially the low and middle income countries. The CDC recommends treatment of all cases of latent tuberculosis with Isoniazid, Rifapentine or Rifampin (Rifampicin) based regimens.(4) Guidelines in India do not suggest such a regimen. While a lot is being done

on the programmatic level, the burden of the disease is still underestimated owing to problems in diagnostics and infrastructure. The objective of this study was to estimate the prevalence of Latent Tuberculosis infections in the pediatric household contacts of patients of pulmonary tuberculosis in India.

Methods

We searched three electronic databases for articles reporting prevalence of LTBI in contacts of patients of pulmonary Tuberculosis. We searched PubMed, EMBASE and Ovid for relevant articles. Search of grey literature and unpublished data was also done. The search was updated till July 2020. Ethical approval was not required for this study as no human subjects were involved. The protocol of the study was registered in the PROSPERO international prospective register of systematic reviews with registration number CRD42020206459.

The study inclusion criteria were: (1) Cross-sectional or cohort studies (2) The population was household contacts of pulmonary tuberculosis patients in India (3) The exposure was Smear positive or negative Pulmonary tuberculosis patients (4) The outcomes of interest were Latent tuberculosis infection diagnosed by a positive Tuberculin Sensitivity test or Interferon gamma release assay(IGRA) and the absence of clinical disease among contacts and active tuberculosis disease among contacts. We excluded abstracts, editorials, case studies and case series.

Search strategy: The search strategy for all databases included search terms and synonyms of Latent Tuberculosis, contacts, children, prevalence and India. Search (((((((((tuberculosis) OR mycobacterium tuberculosis)OR pulmonary tuberculosis) OR latent tuberculosis infection)OR latent tuberculosis) OR LTBI)) AND ((((((contact tracing) OR contact investigation) OR contact screening) OR household contact) OR close contact) OR family contact)) AND ((((((Pediatrics)

OR child) OR infant) OR preschool child) OR adolescent) OR children)) AND India. There was no specified time period and only English language studies were included.

Initial review of Studies

The abstracts and title screening was done by MS and PP. The relevant studies were included and the data extraction was done by MaS, PP,AC,NJ,AA,SS, HS,MeS and SV on a predesigned data extraction sheet. The data extracted included the following information: study site, design, description of index cases, description of household contacts, definition of household contacts, investigations performed, tuberculin skin test (TST) results, CXR, sputum smear microscopy of AFB, and culture of Mycobacterium tuberculosis, outcomes among child contacts (healthy, TB infection, or TB disease), and the criteria used to determine the outcomes. The data extraction for each study was done independently by 2 authors and any disagreements were resolved by contacting MaS. The extracted data was entered into an excel sheet and a narrative synthesis was done. The calculation of the pooled prevalence of LTBI, and the construction of galbraith plot for heterogeneity was done using STATA software. The quality of included studies was assessed using the Hoy et, al. checklist.(5) The checklist consists of 9 questions to check the internal validity of the study and address selection bias, non-response bias and measurement bias. A score is given from one to nine, 0-3 is low, 4-6 is moderate and 6-9 is high risk of bias. Causes for heterogeneity were explored and have been discussed.

Results

The search yielded 746 studies, out of which 600 studies were left after removal of duplicates. Title and abstract screening was done by two authors MS and PP independently. The full texts of 28 studies was retrieved. Data extraction was done according to a pre defined proforma by two

authors independently for each study. Out of these, 9 studies were excluded and 19 were included in the data synthesis. The PRISMA flow chart is provided in figure 1. The included studies and the calculated prevalence of active TB and LTBI are tabulated in table 1.(6–24) The prevalence of LTBI among household contacts was 39.27%[26.05-52.49]. On subgroup analysis, the prevalence of LTBI from studies with only pediatric contacts included was 26.73%[17.70-35.76].(Figure 2)There was significant heterogeneity amongst the various studies with overall I^2=99.7%. The pooled prevalence of active tuberculosis in the contacts was 7.74% [5.23-9.60], with the pediatric studies reporting a pooled prevalence of 8.92% [4.42-13.42]. There was a significant heterogeneity with I^2=96.7%. (Figure 3) A Galbraith Plot was constructed which shows significant heterogeneity among the different studies. (Figure 4)The quality assessment of the studies was done using the Hoy et.al checklist. All studies had a low risk of bias with a score of 3 or less, except one by Kirtilaxmi et.al, which had a moderate risk of bias with a total score of 4.

Discussion

There have been systematic reviews in the past that have reported the prevalence of Tuberculosis in Low and Middle Income countries. This is the first systematic review for prevalence of LTBI infections in the Indian subcontinent. In a WHO commissioned systematic review published in 2015, ninety-five studies from low- and middle-income countries were included. The prevalence of active TB in all contacts was 3.1% (95% CI 2.2-4.4%), and latent TB infection was 51.5% (95% CI 47.1-55.8%). (25) The heterogeneity between studies was very high, with I^2 more than 98% for the pooled estimates. In an earlier review published in 2008, also from LMICs, Latent tuberculosis infection was found in 51.4% (95% CI 50.6-52.2) of the contacts investigated. In this review too, the heterogeneity was above 99.4% (26) In India, almost 40% of the household

contacts of patients with Pulmonary Tuberculosis harbor latent infection which can progress to disease during their lifetime. These estimates are lower than those from previous reviews. Current guidelines in India recommend 6 months of INH prophylaxis to contacts who are under 5 years of age, immunosupressed or are HIV positive. Guidelines from high income countries with areas of low disease burden recommend treatment of all contacts of Pulmonary TB patients who are TST/IGRA positive. Are we missing an opportunity of controlling the epidemic of TB by forgoing treatment of those above 5 years? What are the risks versus benefits of treatment of all contacts of PTB patients. We attempt to explore these questions.

This is the first systematic review for prevalence of LTBI infections in the Indian subcontinent. This pool of latent infection serves as a reservoir for reemergence of the disease at a later period when the host immunity is compromised. Hence it is vital to target this group of people in the TB elimination effort to facilitate eradication of Tuberculosis. Latent tuberculosis in pediatric population is especially important to treat, as malignant forms of TB are known to occur in children.

There was significant heterogeneity in the results, with possible causes of clinical heterogeneity being smear status of the index case, the nutritional status of the contacts, the immune status of the contacts, which is influenced be age and HIV status. Methodological heterogeniety due to the variable strengths of the tuberculin reagents, variations in the methods used for LTBI diagnosis(TST/IGRA/both), variation in the cutoffs used to define TST positivity, variable definations of household contacts used also contributed to the overall statistical heterogeneity with an I^2value of 99.7% . The current guidelines of the National Tuberculosis program in India

state that 10 mm induration is the ideal cutoff when TST is administered using the 2TU reagent. (27) In the studies included in this review, the strength of the reagent as well as the manufacturer of the reagent were variable. The strength of the reagent varied from 1TU to 5TU. The measurement of induration considered positive also varied from 5 to 10 mm.

The level of proximity with the household contact may also have a bearing on the development of LTBI. Different studies used somewhat varying definitions of the term household contacts. Singla et.al. defined household contacts as "individuals who had shared the same kitchen and sleeping area as the index case for at least 3 months before the diagnosis of the index case."(14) Andrews et. al. defined close contacts as "those living, cooking and feeding in the same house as the index case for the period of three months immediately preceding the start of treatment."(12)

In a mathematical modeling risk-benefit analysis study by Yeun et. al., it was proposed that for an estimated LTBI prevalence of 50%, a treat all approach versus a treat TST+ only approach could prevent 6.8 incident TB cases per 1000 contacts with an additional 1.3 severe adverse events per 1000 contacts in the age group of less than 17 years, and with the 6 H regimen currently employed in India. (28) With increasing age, the number of incident cases prevented decreased whereas the number of adverse events increased. Future directions of research are to consider effects of expansion of IPT to uptil 18 years of age, and the comparison of various regimens of IPT in the Indian population.

As with all secondary research, this review has its strengths and limitations. Its strengths are an extensive literature search and the rigorous methodology adopted. Its limitations are a lack of generalisability of the results as only studies from India were included. Also, the subgroup analysis pooled studies with pediatric contacts, but did not pool the prevalence calculated from

the pediatric contacts in the mixed adult and pediatric studies. This was not done due to the different pre-specified age ranges in each study, and sometimes, the lack of age related data. In general, pediatric age group was considered to be children less than 15 years of age.

In conclusion, the prevalence of active tuberculosis among contacts of pulmonary tuberculosis patients ranges from 0-30.36 % with a pooled prevalence of 7.42%, whereas the prevalence of Latent Tuberculosis Infection ranges from 5.52% to 78.76%, with a pooled prevalence of 39.27%. These figures highlight the need for contact screening among newly diagnosed cases of pulmonary tuberculosis in order to initiate prophylactic therapy or Anti-tubercular therapy in the to prevent progression to disease and its complications.

References

1. Schluger NW. Prevention of Multidrug-resistant Tuberculosis in Close Contacts: Back to the Future? Am J Respir Crit Care Med [Internet]. 2020 Jul 27 [cited 2020 Aug 6]; Available from: https://www.atsjournals.org/doi/abs/10.1164/rccm.202006-2488ED

2. Hamada Y, Glaziou P, Sismanidis C, Getahun H. Prevention of tuberculosis in household members: estimates of children eligible for treatment. Bull World Health Organ. 2019 Aug 1;97(8):534-547D.

3. Country Profiles for 30 High Burden TB countries. World Health Organ. TB19_Report_country_profiles_15October2019.pdf [Internet]. [cited 2020 Oct 9]. Available from:https://www.who.int/tb/publications/global_report/tb19_Report_country_profiles_15October2019.pdf?ua=1

4. Sterling TR. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep [Internet]. 2020 [cited 2020 Sep 30];69. Available from: https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm

5. Hoy D, Brooks P, Woolfe A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement [Internet]. Vol. 65, Journal of clinical epidemiology. J Clin Epidemiol; 2012 [cited 2020 Aug 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/22742910/

6. Pothukuchi M, Nagaraja SB, Kelamane S, Satyanarayana S, Shashidhar, Babu S, et al. Tuberculosis Contact Screening and Isoniazid Preventive Therapy in a South Indian District: Operational Issues for Programmatic Consideration. Marais BJ, editor. PLoS ONE. 2011 Jul 22;6(7):e22500.

7. Tuberculosis Research Centre, Indian Council of Medical Research (ICMR), Chennai, India. Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2011 Jun;15(6):782–8.

8. Singh J, Sankar MM, Kumar S, Gopinath K, Singh N, Mani K, et al. Incidence and Prevalence of Tuberculosis among Household Contacts of Pulmonary Tuberculosis Patients in a Peri-Urban Population of South Delhi, India. Wilkinson RJ, editor. PLoS ONE. 2013 Jul 26;8(7):e69730.

9. Dayal R, Agarwal D, Bhatia R, Bipin C, Yadav NK, Kumar S, et al. Tuberculosis Burden among Household Pediatric Contacts of Adult Tuberculosis Patients. Indian J Pediatr. 2018 Oct;85(10):867–71.

10. Mazahir R, Beig FK, Ahmed Z, Alam S. Burden of tuberculosis among household children of adult multi drug resistant patients and their response to first line anti tubercular drugs. Egypt Pediatr Assoc Gaz. 2017 Nov;65(4):122–6.

11. Mishra S, Singh SK, Mohan U, Sahu R, Verma AK, Srivastava K. Risk Factors Associated with Tuberculosis Infection Among Household Children Contacts of Sputum Smear Positive Tuberculosis Cases. 2017;29(02):6.

12. Andrews RH, Devadatta S, Fox W, Radhakrishna S, Ramakrishnan CV, Velu S. Prevalence of Tuberculosis among Close Family Contacts of Tuberculous Patients in South India, and Influence of Segregation of the Patient on the Early Attack Rate. :48.

13. Singh M. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child. 2005 Jun 1;90(6):624–8.

14. Singla N, Singla R, Jain G, Habib L, Behera D. Tuberculosis among household contacts of multidrug-resistant tuberculosis patients in Delhi, India. Int J Tuberc Lung Dis. 2011 Oct 1;15(10):1326–30.

15. Rekha B, Jagarajamma K, Chandrasekaran V, Wares F, Sivanandham R, Swaminathan S. Improving screening and chemoprophylaxis among child contacts in India's RNTCP: a pilot study. Int J Tuberc Lung Dis. 2013 Feb 1;17(2):163–8.

16. Chauhan S, Gahalaut P, Rathi AK. Tuberculin Skin Test, Chest Radiography and Contact Screening in Children ≤5 Y: Relevance in Revised National Tuberculosis Control Programme (RNTCP). Indian J Pediatr. 2013 Apr;80(4):276–80.

17. Benachinmardi KK, Sangeetha S, Rao M, Prema R. Validation and Clinical Application of Interferon-Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection in Children. Int J Appl Basic Med Res. 2019 Dec;9(4):241–5.

18. Gupta A, Swindells S, Kim S, Hughes MD, Naini L, Wu X, et al. Feasibility of Identifying Household Contacts of Rifampin-and Multidrug-resistant Tuberculosis Cases at High Risk of Progression to Tuberculosis Disease. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 16;70(3):425–35.

19. Dolla CK, Padmapriyadarsini C, Thiruvengadam K, Lokhande R, Kinikar A, Paradkar M, et al. Age-specific prevalence of TB infection among household contacts of pulmonary TB: Is it time for TB preventive therapy? Trans R Soc Trop Med Hyg. 2019 11;113(10):632–40.

20. Narasimhan P, MacIntyre CR, Mathai D, Wood J. High rates of latent TB infection in contacts and the wider community in South India. Trans R Soc Trop Med Hyg. 2017 Feb;111(2):55–61.

21. Bekken GK, Ritz C, Selvam S, Jesuraj N, Hesseling AC, Doherty TM, et al. Identification of subclinical tuberculosis in household contacts using exposure scores and contact investigations. BMC Infect Dis. 2020 Jan 31;20(1):96.

22. Passey, Rashmi, Sethi GR, Mantan, Mukta, Khanna ,Ashwani. Latent Tuberculosis Infection in Children- A High Risk but Neglected Group in India [Dissertation]. [Delhi]: Delhi University; 2014.

23. Chandrasekaran P, Mave V, Thiruvengadam K, Gupte N, Shivakumar SVBY, Hanna LE, et al. Tuberculin skin test and QuantiFERON-Gold In Tube assay for diagnosis of latent TB infection among household contacts of pulmonary TB patients in high TB burden setting. PloS One. 2018;13(8):e0199360.

24. Paradkar M, Padmapriyadarsini C, Jain D, Shivakumar SVBY, Thiruvengadam K, Gupte AN, et al. Tuberculosis preventive treatment should be considered for all household contacts of pulmonary tuberculosis patients in India. PloS One. 2020;15(7):e0236743.

25. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2013 Jan;41(1):140–56.

26. 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 Jun;8(6):359–68.

27. Revised National Tuberculosis Control Program and Indian Academy of Pediatrics.RNTCP Updated Pediatric TB Guidelines 2019, Guidance document. Central TB Division, Ministry of Health and Family Welfare, Govt of India. Draft as on 04th February 2019

28. Yuen CM, Seddon JA, Keshavjee S, Dodd PJ. Risk-benefit analysis of tuberculosis infection testing for household contact management in high-burden countries: a mathematical modelling study. Lancet Glob Health. 2020 Apr 27;8(5):e672–80.

Table 1: The Prevalence of Active and Latent Tuberculosis in household contacts of patients of Pulmonary Tuberculosis

Study ID	Age of contacts	No. of Index cases	Contacts Screened	Active TB Prevalence(%)	LTBI Prevalence(%)
Potukuchi 2011	Pediatric	848	116	0	NA
Radhakrishnan 2011	Adult and Pediatric	2086	6416	Excluded	57.6
Singh 2013	Adult and Pediatric	432	1389	5.9	76.6
Dayal 2018	Pediatric	120	271	1.1	20.3
Mazahir 2017	Pediatric	21	80	11.25	23.75
Mishra 2017	Adult and Pediatric	97	200	0	48
Andrew 1960	Adult and Pediatric	148	647	7.1	44.7
Singh 2005	Pediatric	200	281	3.2	30.6
Singla 2011	Adult and Pediatric	92	135	5.3	68.8
Rekha 2011	Pediatric	308	53	0	NA
Chauhan 2013	Pediatric	80	200	14	39
Kirtilaxmi 2020	Pediatric	36	77	NA	40.25
Gupta 2020	Pediatric	284	1001	0.9	10.9
Dolla 2019	Adult and Pediatric	441	1050	2.8	69
Narsimhan	Adult	114	359	30.3	53.7

2017	and Pediatric				
Bekken 2020	Adult and Pediatric	176	525	1.3	5.5
Passey 2014	Pediatric	47	100	0	29
Chandrasekaran 2020	Adult and Pediatric	Not given	869	4.7	74.3
Paradkar 2020	Adult and Pediatric	464	997	3.9	30.2

297

298 Figure Legends

299 Figure 1: PRISMA flow diagram of the systematic review.

300 Figure 2: Forest Plot showing pooled prevalence and subgroup analysis of Latent Tuberculosis in
301 household contacts of pulmonary tuberculosis cases in India.

302 Figure 3: Forest Plot showing pooled prevalence and subgroup analysis of Active Tuberculosis
303 in household contacts of pulmonary tuberculosis cases in India.

304 Figure 4: Galbraith Plot showing significant heterogeneity among studies on prevalence of
305 Latent Tuberculosis Infection.

306