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Assessment of children in contact with sputum positive adult patients with respect to TB disease and latency

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Abstract:

Introduction: Tuberculosis (TB) contacts are people who have close contact with patients with infectious TB. TB contacts should be investigated systematically and actively for TB infection and disease. Such interventions are called 'tuberculosis contact investigations'. They contribute to early identification of active TB, thus decreasing its severity and reducing transmission of Mycobacterium tuberculosis to others, and identification of latent TB infection (LTBI), to allow preventive measures. The present study was undertaken to study epidemiological,socio-economic ,clinical factors in contact children of sputum positive cases. During study ,investigations were also carried out to differentiate stages of tubercular infection ,latency and disease.

Aims & Objectives: 1. To identify children in contact with adult index case and to assess contact investigation according to WHO guidelines. 2. Evaluate socioeconomic and Clinical parameters 3. Investigate as per guidelines and perform IGRA. 4. To find proportion of infection, disease and latency in contact children.

Materials and Methods Study Design: It was a prospective observational study, conducted in MGM Medical College and Hospital which is a tertiary care referral unit in Navi Mumbai, Raigad District of Maharashtra.

Study Period: The study was performed over a period from April 2015 to October 2016.

Sample Size: (80) SS = Z 2 x P x (1-P) 2 Z: value (1.96 for 95% CI) P: % of picking choice C: confidence interval.

Sampling Technique: *Selection of index cases*: An index case was defined as a newly pulmonary tuberculosis case in DOTS OPD (confirmed by 3 consecutive sputum smears positive for acid-fast bacilli and/or positive culture).Selection of contacts: Children contacts were defined as a family members or living with the index case in the same house before the starting of tuberculosis treatment of index case. They were recruited into study, and consent was obtained from the parent/ representatives to undertake the study.

Methodology: This was a prospective observational study consisting of 80 contact children, of smear positive PTB. The parents were interviewed using a standard questionnaire to obtain demographic and socio-economic information of the household and the health condition of the children. After the interview, children were examined by a clinician as well as nutritional assessment was done according to WHO protocol and necessary laboratory tests (x-ray, induced sputum and gastric lavage) were done to rule out active TB. All children were given a TST and 3 ml of blood was obtained for laboratory tests for IGRA.

Conclusion: Active tuberculosis (TB) and TB Infection is common among household contacts of index cases in India, especially among young children. Although all children with household exposure have a high risk of contracting the infection and disease, specific risk factors include severity of disease in cases and the intensity of exposure of the child.

Present study found that IGRAs is a good diagnostic tool for the diagnosis of latent tuberculosis infection as well as active disease.

Keywords: Active tuberculosis, Latent tuberculosis, IGRA, TST, Mantaux test

Introduction:

Tuberculosis (TB) contacts are people who have close contact with patients with infectious TB. TB contacts should be investigated systematically and actively for TB infection and disease. Such interventions are called 'tuberculosis contact investigations'. They contribute to early identification of active TB, thus decreasing its severity and reducing transmission of Mycobacterium tuberculosis to others, and identification of latent TB infection (LTBI), to allow preventive measures.

Contacts are commonly investigated in high-income countries with low TB burdens and in settings in which a TB elimination policy is implemented, in order to identify persons with early active TB or who have recently been infected. People identified as infected are then treated for LTBI with isoniazid for at least 6 months (usually 9 months) or with shorter combination regimens including isoniazid and rifampicin.

TB contact investigations are rarely and inconsistently carried out in resource-limited settings. In most low and middle-income countries, it is included in the national policy to control and prevent TB. However, in the vast majority of countries, it is either not undertaken or is implemented on the basis of no or poor standards, because of the absence of clear definitions of index cases, contacts and procedures. Furthermore, the health personnel who should be involved are usually not clearly identified.

Information on the contribution of routine contact investigations to early TB case detection is scarce in these countries or is non-standardized, thus precluding an assessment of its impact on reducing transmission.

Many studies in countries with a high TB incidence have shown that the prevalence may reach 5% or more among contacts, particularly among household members. Other data suggest that contact investigations could be particularly useful for identifying childhood TB.

WHO estimates show that worldwide highly infectious smear-positive pulmonary TB develops in over 4 million people annually. If we assume that each of these patients has at least three close contacts, such as in their household, and that the prevalence of active TB among the close contacts is 2.5%, the number of early TB cases that could be identified among close contacts is at least 300 000 per year.

Early identification means a better chance of cure and especially a reduction in further transmission. Furthermore, contact investigation allows identification of people who are latently infected and at high risk for active TB, who can be treated preventively.[1,2,3]

The present study was undertaken to study epidemiological, socio-economic ,clinical factors in contact children of sputum positive cases. During study, investigations also carried out to differentiate stages of tubercular infection, latency and disease.

Aims & Objectives:

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Inclusion Criteria*:* Contact children from 6 months to 15 yr.

Exclusion Criteria: Children with immunodeficiency.

Methodology: This was a prospective observational study consisting of 80 contact children, of smear positive PTB. The parents were interviewed using a standard questionnaire to obtain demographic and socio-economic information of the household and the health condition of the children. After the interview, children were examined by a clinician as well as nutritional assessment was done according to WHO Protocol and necessary laboratory tests (x-ray, induced sputum and gastric lavage) were done to rule out active TB. All children were given a TST and 3 ml of blood was obtained for laboratory tests for IGRA.

Tuberculin Skin Test: All the children received 2 TU of PPD RT 23 with Tween 80 injected on the volar aspect of arm using the Mantoux method on the day of the initial visit. TST readings were obtained using the palpation method where horizontal diameter of the induration to the long axis of the arm was measured (WHO, 2006b) at 48-72 hours by trained laboratory technicians and results were classified according to the degree of indurations as negative (<5 mm), intermediate (5 to 9 mm) and positive (e" 10 mm).

IGRAs: The test was performed by drawing 1 ml of blood into one of each of the three manufacturer-precoated, heparinised tubes. Within 16 hours of blood collection, the tubes were incubated for another 16 to 24 hours at 37 °C. The plasma was harvested after centrifugation (tubes contain a gel plug that separates the plasma from the cells when centrifuged) and used to assess the concentration of IFN-α by ELISA test.

ELISA assay(3) - Immunocheck TB Platinum(IGRA) Make-Immunocheck

- 50 µl of working conjugate added to each well, then 50 µl of plasma or standard was added.

- The covered plate was shaked for 1 minute, and then incubated for 120 minutes at room temperature.

- The plate was washed 6 times with washing buffer and 100 µl substrate was added & incubated for 30 minutes at room temperature.

- 50µl stop solution was added and absorbance was read at 450 nm (620 ref) - IFN-α values (IU/ml) for TB-specific antigens were corrected for background by subtracting the value obtained for the respective negative control.

As recommended by the manufacturer, the cut-off value for a positive test was IFN-α e" 0.35 IU/ml.

Treatment: All active cases were treated with AKT according to RNTCP guidelines, rest children less than 6 years old with latent infection received INH chemoprophylaxis.

Results:

Most of the contacts were in between 5 to 10 years of age (57.5%). Rest 35% were <5 years and 7.5% were more than 10 years. Distribution of gender was done and out of total 80 contacts, 53.8% were males while 46.3% were females.

We had 43 index cases and 80 contact children related to them .The distribution of cases based on sputum grade out of 43 index cases 30.2% had +1 sputum positivity while 46.5% and 23.3% had +2 and +3 sputum positivity.

We assessed the relationship of index and contact cases. In most of the cases index case was either father (48.8%) or mother (18.8%).

We found in our study that BCG scar was absent in 18.8% contacts and was present in 81.3 %.The nutritional evaluation was based on WHO classification of malnutrition.57.5% were normal, 37.5% had chronic malnutrition and 2.5% had Acute and Acute on chronic malnutrition each.

Socio economic status was assessed by modified Kuppuswami scale. Most of the contacts were from lower (57.5%), middle (36.3%) and Upper (11.6%) socio-economic status respectively.

Out of 80 contact cases household size of </=4, 5-6 and > 6 was seen in 43.8%, 31.3% and 25% contacts respectively. Most of the children were asymptomatic; cough was present in (5.3%), weight loss (5%) and fever was seen in 2.5% cases. All the contacts underwent X ray examination of chest; however it is not advised according to RNTCP. Abnormal chest x-ray was seen 8.8% contacts.

Out of 80 contacts Mantoux test was positive in 13 (16.3%) contacts**.** Out of 80 contacts who were only MT (n=13) or had an abnormal x-ray (n=7) and both x-ray and MT positive (n=6) . Sputum or gastric lavage for AFB was done however we did not find sputum positive in any of the contacts suggesting they are non-infective.

Distribution of cases based on Interferon-gamma release assay (IGRAs) results was done and out of 80 contacts IGRA was positive in 34(42.5%) contacts.

The prevalence of active TB in contacts was in 7 (8.8%) contacts in our study

while latent TB was seen in 27 (33.8%) contacts. All the contacts of active TB were started on AKT as per RNTCP guidelines, while Isoniazid chemoprophylaxis was given in 41 (51.3%).

A significant association was seen between incidences of Tb in contacts with the grade of sputum positivity of cases ($p<0.05$). The incidence of TB in sputum grade 1 and 2 and 3 was 7.7%, 2.6% and 25%.

In the present study there was no association seen between presence of BCG scar and incidence of TB in contacts (p-0.311), socio-economic status and incidence of TB in contacts (p-0.281) household size and incidence of TB in contacts (p-0.794). In our study there was no association seen between number of rooms and incidence of TB in contacts (p-0.141).

A significant association was seen between incidences of Tb in contacts with malnutrition ($p<0.01$). The incidence of TB was 14.7% in children with malnutrition as compared to 4.3% in those with normal nutritional status.

In our study IGRA was positive in all the cases of active (n=7) and latent tuberculosis (n=27). Out of 80 contact children Abnormal chest x-ray findings was seen in all active TB cases (n=7). Out of 80 contacts Mantoux positivity (> 10 mm) was seen in 85.7% cases with active TB while it was positive in 25.9% cases with latent TB. A significant association was seen between IGRA and MT results ($p<0.05$). All the IGRA negative cases were negative on MT too while 38.2% cases with positive IGRA results were MT positive. The sensitivity and specificity of IGRA compared to MT in our study was 100% and 68.6% respectively.

MT was positive in 85.7% cases with active TB (6/7) and 25.9% cases with latent TB (7/27) while IGRA was positive in all cases of active/ latent disease.

Discussion :

The present study was thus conducted to find the incidence of Tuberculosis Infection and active disease in children in contact with adult index case.

Incidence of TB Infection & Disease

The prevalence of active TB in contacts was 8.8% in present study while latent TB was seen in 33.8% contacts.

Studies conducted in the 1960s and 1970s showed that household contacts of individual with TB had higher risk of infection than individuals in the general population[4,5]. This was confirmed in several recent studies conducted among children in New York City[6], Botswana[7], and Brazil[8] in which contact with an individual with TB came out as the strongest risk factor for TB infection.

Guwatudde D et al.[9], Among the 1,206 household contacts, 76 secondary cases (6%) of tuberculosis were identified. The risk for secondary tuberculosis was greater among young children than adults (10% vs. 1.9%). In another study by Gessner et al. [10], Infection developed in 25% of the children and progressed to active disease in 9.6%. In another study by Songpol Tornee et al[11] prevalence of tuberculosis infection among household contacts to be 47.80%. In another study by Hiral H Shah et[12] 90(30%) out of 300 children were positive for the latent infection. In a similar study by Seddon et al.[13], 4.7% children were classified as infected and 14.7% had TB disease. In a study by Kinikar et al.[14], in 15 (30%) of the 50 pediatric index cases, the household contained known TB contacts, 14 (86%) of whom were adults. Singh et al. 36, in their study observed the prevalence of tuberculosis infection and disease as 33.8% in children with household contacts of sputum positive cases.

Risk Factors:

In present study a significant association was seen between incidences of Tb in contacts with malnutrition ($p<0.01$). The incidence of TB was 14.7% in children with malnutrition as 58 compared to 4.3% in those with normal nutritional status. However no association was seen between SES, household size and no. of rooms with incidence of TB in contacts ($p>0.05$).

Seventy-eight percent of children have received a BCG vaccination according to NFHS-3 55. In our study we found that BCG scar was present in 81.3 percent contacts while BCG was not given in 18.8 percent.

It is now universally accepted that the risk of acquiring TB is directly proportional to the number of bacilli to which a subject is exposed[15]. In the first place, it depends on the characteristics of the source case: contagiousness is generally limited to subjects with lung disease, and is greater among the patients with bacilleferous forms (i.e. those with positive microscopic test results), in whom the estimated transmission rate is about 35% as against the 17% observed among those with non-bacilleferous forms[16]. Similarly, it is important to evaluate the time spent in an enclosed space with the source case.

The effect of the combination of these two variables has been clearly shown in studies of the contacts arising during air flights[17]. Living together gives rise to the greatest exposure to TB: this has been documented in studies such as that of Singh et al. who evaluated the prevalence of TB in children living with adults with active TB and found a significant difference between those living with adults with microscopic positive or negative expectorate (respectively 68.4 and 31.6%)[18].

A recent meta-analysis[19] has shown that contact with expectorate positive TB patients is a factor indicating a similar risk of infection in both high income (odds ratio [OR] 3.3; 95% confidence interval [CI] 2.2–4.8) and low income countries (OR 3.3; 95% CI 2,2– 5.1). The risk of acquiring tuberculous infection is particularly high in children who live with expectorate-positive adults (relative risk [RR] 6.78; 95% CI 3.51–13.10) or adults with cavitating lesions revealed by chest X-ray (RR 2.45; 95% CI 1.60–3.76), or in those who have close contacts with drug users (RR 1.81; 95% CI 1.03–3.19)(20,21). Children whose families include women with TB are exposed to an even higher risk

Table 1: epidemiological and socioeconomic factors (N=80)

Criteria of study	Percentage	Association With TB
Age <5 years 5 to 10 years >10 years	35 57.5 7.5	Not Significant
Sex males females	53.8 46.2	Not Significant
Sputum positivity +1 +2 +3	 30.2 46.5 23.3	Significant (p,0.05) 7.71 12.6 25
Relation with child Father Mother Other	 48.8 18.8 30.4	 Not Significant
BCG scar Absent Present	18.8 81.2	Not Significant
Nutrition Normal Chronic Acute Acute on chronic	57.5 37.5 2.5 2.5	Significant
Socio economic status Lower Middle Upper	57.5 36.3 11.7	Not Significant
Household size </=4 5-6 > 6	43.8 31.2 25	Not Significant

(RR 1.34; 95% CI 1.34–3.14), probably because their contacts are more frequent than in the case of male relatives.

One case-control study carried out in Thailand found that the risk of developing the disease was high in children having any kind of contact with TB patients (very close: OR 85.67; 95% CI 33–647.79; p < 0.001; close: OR 31.11; 95%CI 4.18–255.94; p = 0.001; not close: OR 32.70; 95% CI 4.18–255.94; p < 0.001).(22) In present study too, we observed a significant association between incidences of TB in contacts with the grade of sputum positivity of cases (p<0.05). The incidence of TB in sputum grade 1 and 2 and 3 was 7.7%, 2.6% and 25%.

Living arrangements and housing conditions play an important role: a case-control study carried out in Bangladesh (23)found that co-dwellers were protected against transmission if there were < 2 people per bedroom (OR 0.29; 95% CI 1.79–6.03; p < 0.0001), if the kitchen was separated from the bedroom (OR 0.35; 95% CI 0.2–0.62; p = 0,001), and if the home was adequately ventilated (OR 0.25; 95% CI 0.13–0.49; p < 0.0001). The risk of transmission is also affected by overcrowding and

the economic conditions of the family (OR 1.35; 95% CI 1.06–1.72; p < 0.017). 4 as well as by an inadequate supply of food (OR 1.52; 95% CI 1.15–2.02; p < 0.003) .(24)

Diagnosis:

In present study Interferon-gamma release assay (IGRAs) was positive in 34 (42.5%) cases, out of which X-ray was abnormal in 7 cases (8.8%) showing presence of active disease. All the IGRA negative cases were also negative on TST too while only 13 out of 34 (38.2%) cases with positive IGRA results were also TST positive. Thus TST was positive in 85.7% cases with active TB (6/7) and 25.9% cases with latent TB (27/47).

A large number of studies have evaluated the efficacy of IGRAs in diagnosing LTBI (25-29). An IGRA is recommended by WHO, for subjects who have been vaccinated with BCG in order to confirm /exclude the presence of TB in subjects with a positive TST 21.

It is therefore recommended that these tests should not be used in individuals suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status. This recommendation also applies to paediatric TB based on the generalisation of data from adults."[30]

Management:

The overall prevalence of active TB in contacts was 8.8% in present study while latent TB was seen in 33.8% contacts. All the cases of active TB were started on AKT as per RNTCP guidelines, while isoniazid chemoprophylaxis was given for LTBI cases .The rationale underlying the treatment of LTBI is based on the possibilityof eliminating dormant bacilli, thus reducing their activation and the development of active disease.

A Cochrane review has shown that treating LTBI with isoniazid reduces the risk of pulmonary and extra-pulmonary TB and the related deaths, but there does not seem to be any significant difference in the efficacy of 6- and 9-month treatment.[31]

Table:2 clinical and investigation related factors

	Percentage	Association
Symptom asymptomatic cough weight loss fever	 87.2 5.35 2.5	Not Significant
X ray examination Abnormal Normal	 8.89 1.2	Not Significant
Mantoux test Positive Negative Mantoux test Positive and Xray positive	16.3 83.7 8.7	 Significant
Sputum or gastric lavage for AFB Positive Negative	 NIL	 Not Significant
IGRA Positive Negative	42.5 57.5	Significant
Active TB Latent TB	8.7 33.8	Significant

Conclusion:

Active tuberculosis (TB) and TB Infection is common among household contacts of index cases in India, especially among young children. We assessed 43 contacts an d 80 children in contact with them. A significant association was seen between incidences of Tb in contacts with malnutrition ($p<0.01$). The incidence of TB was 14.7% in children with malnutrition as compared to 4.3% in those with normal nutritional status.

In our study IGRA was positive in all the cases of active (n=7) and latent tuberculosis (n=27). Out of 80 contact children .Abnormal chest x-ray findings was seen in all active TB cases (n=7). Out of 80 contacts Mantoux positivity (> 10 mm) was seen in 85.7% cases with active TB while it was positive in 25.9% cases with latent TB. A significant association was seen between IGRA and MT results ($p<0.05$). All the IGRA negative cases were negative on MT too while 38.2% cases with positive IGRA results were MT positive. The sensitivity and specificity of IGRA compared to MT in our study was 100% and 68.6% respectively.

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Declarations:

Contribution of authors - Rakesh Thamke- concept, strategy; Vijay kamale - supervision and revision of manuscript, guidance, Ragi Rajan - data collection,statistical analysis, initial manuscript,

Conflict of interest - Nil

Funding source and its role in the study - No

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