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**Risk of infection and disease with *Mycobacterium tuberculosis* among children identified through prospective community-based contact screening in Indonesia**

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**ABSTRACT**

**Objective:** To identify characteristics of the child contact, index case or environment that are associated with infection or tuberculosis in child contacts in an urban community in Indonesia.

**Method.** Children that were close contacts of an index case with pulmonary tuberculosis were screened for infection and disease in Yogyakarta, Indonesia from August 2010 to December 2012. Data of the index case and child were collected prospectively, and all child contacts had clinical assessment, tuberculin skin test (TST) and chest X-ray performed. Those with clinically suspected tuberculosis also had sputum examined by Xpert MTB/RIF and culture. Child contacts were managed according to national guidelines, followed for 12 months and had a final classification of either tuberculosis "disease", latent tuberculous infection (LTBI) or "exposed only".

**Results**. 269 children of 141 index cases were investigated. Final classification was tuberculosis in 25 (9%) and LTBI in 121 (45%). The risk of infection was significantly greater if the source case was female (AOR 1.7; 95% CI: 1.0–2.8), had sputum smear-positive tuberculosis

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(AOR 3.0; 95% CI 1.5–6.0), or slept in the same room (AOR 1.7, 95% CI 1.0–2.9). A positive TST was independently associated with a diagnosis of tuberculosis (AOR 7.3; 95% CI 2.4–22). **Conclusion**. This study highlights the high risk and the risk factors associated with tuberculosis and LTBI among child contacts in Indonesia.

**Keywords:** risk, infection, disease, tuberculosis, child, contact

## INTRODUCTION

Tuberculosis is an important cause of morbidity and mortality in children.[1,2] Children are infected with *Mycobacterium tuberculosis* by aerosol transmission from an infectious case, usually an adult or adolescent with tuberculosis. It has long been recognised that close contacts of an infectious case of tuberculosis are at high risk of infection with *M. tuberculosis*.[3-6] The risk of infection for a child that is exposed to a case of tuberculosis relates to a number of factors such as the infectiousness of the source case, the intensity and duration of the exposure, and the environmental conditions. If infected, the risk of disease is more related to inherent characteristics of the child contact that relate to the maturity or competence of the immune system to contain the infection, for example age or the presence of co-morbidities such as HIV infection or malnutrition.[7-9]

The recognition that risk of disease and severe, disseminated disease after infection is particularly high for infants and young children (< 5 years) provides the rationale for WHO's policy of routine screening and management of children that are close contacts of a case of sputum smear-positive tuberculosis.[10] While this policy is almost universally adopted, it is rarely implemented in tuberculosis endemic countries.[11,12] We have recently conducted a prospective cohort study that evaluated the WHO symptom-based screening algorithm for the management of child contacts of tuberculosis cases in a primary care setting in Indonesia.[13] From this cohort, we report characteristics of the children, index cases and environmental conditions in relation to infection or disease among the child contacts.

## METHODS

A prospective cohort study was undertaken of children that were contacts of a tuberculosis index case in Yogyakarta, Indonesia, from August 2010 to December 2012. Ethical approval for the study was obtained from the Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia and the Human Research Ethics Committee, the University of Melbourne, Melbourne Australia.

The details of the study and of the cohort have been reported previously.[13] Index cases were adults with a diagnosis of pulmonary tuberculosis, sputum smear positive or sputum smear negative. Children aged 15 years or less in close contact with an index case were recruited to the study following informed consent from parent or guardian. “Close contact” was defined as living in the same house with the index case within the last three months, or having had frequent contact with the index case for a minimum of eight hours per day, within the last three months if not living in the same house. Child contacts were excluded if they were currently receiving anti-tuberculosis therapy or preventive therapy, had a previous tuberculin skin test (TST) or if they lived more than 20 kilometres from the study hospital.

Demographic, clinical and environmental data of both child contact and index case were collected on standardised data collection forms. All child contacts underwent clinical evaluation including nutritional assessment, TST and chest radiography. For each child contact, we specifically enquired about symptoms related to tuberculosis. All children were evaluated and managed at initial screening, and then followed for 12 months. They were managed according to current guidelines: those with tuberculosis received standard anti-tuberculosis regimen for 6 months; those without tuberculosis at initial evaluation were followed up for 12 months and offered isoniazid preventive therapy for 6 months if less than 5 years of age.

The TST was considered positive if the transverse diameter of induration was 10 mm or more, regardless of the BCG vaccination status.[14] Chest radiography included antero-posterior and lateral views, and radiographs were interpreted independently by a radiologist and a paediatrician who were blinded to the clinical information. Those with persistent symptoms had sputum collected by the induced sputum techniquefor solid culture (Lowenstein-Jensen media) and analysis by Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). Following investigations, the children were classified as having either tuberculosis (i.e. disease), latent tuberculous infection (LTBI) or exposed to *M.tuberculosis* only. The study definitions used are listed in the Box.  Only children that developed symptoms during follow-up underwent repeat investigations including CXR, TST (if previously TST negative at baseline) and sputum examination.

The sample size was a convenience sample of all child contacts that could be identified and recruited within the time period of the study that included the need to follow all children for 12 months.[13] Data analysis was conducted using STATA version 12 (Stata Corp., Texas USA). Comparisons of median used Mann-Whitney rank sum test for non-parametric data. Univariate associations of variables with infection with *M. tuberculosis* or tuberculosis were calculated using logistic regression and are presented as odds ratios (OR) and 95% confidence intervals (95%CI). The variables that were statistically significant (to the level of $p< 0.05$) associated with the outcome in the univariate analysis or that have been shown in previous studies to have association with the risk for infection or disease were included in multiple logistic regression analysis, and expressed as adjusted odds ratio (AOR).

**RESULTS**

A total of 269 eligible children of 141 index cases were recruited to the study. Of them, 25 (9%) had a diagnosis of "probable" tuberculosis(see Box): one with tuberculous meningitis, one with pleural tuberculosis and the remainder with pulmonary tuberculosis, as previously reported.[13] Of these 25 with tuberculosis, 21 (84%) also had a positive TST also At initial screening, there were 21 child contacts diagnosed with tuberculosis and 17 of these were also TST positive. An additional 4 children were diagnosed later during 12 month follow-up, one each at 3, 4, 6 and 12 months. The TST had been positive at initial evaluation in two of these and later became positive in the other two. All four cases were 5-14 years of age, and so not receiving isoniazid preventive therapy. None of the children treated for tuberculosis were lost-to-follow-up and all had a good outcome with symptom resolution and treatment complete.

An additional 100 (37% of 269) children were categorised as having LTBI (i.e. were TST positive but without active disease) at baseline and remained well during follow-up, with seven (7%) of these lost-to-follow-up at 12 months. The remaining 144 (54%) children were considered as exposed to tuberculosis only (i.e. were TST negative without active disease). However, TST was not repeated during follow-up in these children unless they became symptomatic and 11 (7.6%) of them were lost-to-follow-up at 12 months.

The characteristics of the child contacts are presented in Table 1, including by final diagnosis. One-third of the child contacts were undernourished, defined as weight-for-height Z score -2 to -3 for those less than 5 years or weight-for-height percentage of 70-90%

for the 5-14 year age group. No child contact had severe malnutrition. The characteristics of the index cases are listed in Table 2.The index case had sputum smear positive disease in 80% and was related to the child and resident in the same household in the majority. A parent was the index case in around one half of the children, with grandparents being the next most common. The index case was an older sibling in 6 (2%) children, a cousin, aunt or uncle in 43 (16%) and not related in the other 27 (10%).

Table 3 compares characteristics between those with evidence of infection as defined by a positive TST with or without active disease, and those defined as exposed to tuberculosis only. The risk of infection was higher if the index case was sputum smear-positive or was female, or if the child was sleeping in the same room as the index case. Symptomatic children were significantly more likely to have a positive TST. These risks remained significant on multivariate analysis. The proportion with a positive TST was highest (63%) in those that were contacts of an index case with smear-positivity of 3+ and lowest (26%) in those that were contacts of a sputum smear negative tuberculosis case. There was a significant trend between prevalence of infection or disease in child contacts and smear positivity of the index case (Chi-squared for trend, 20.29: $p<0.001$).

Table 4 lists and compares characteristics associated with a diagnosis of tuberculosis. The only characteristics associated with disease on univariate and multivariate analysis were the child contact being undernourished or having a positive TST. Nutritional status was part of the clinical evaluation for disease but a positive TST was not. The risk of disease was not associated with young age, sleeping proximity or smear positivity of the index case.

**DISCUSSION**

We report a high prevalence of infection and disease among children that were close contacts of tuberculosis cases in an urban community setting in Indonesia. The smear positivity of sputum on diagnosis of the index case, the index case being female and sleeping proximity were all associated with an increased prevalence of infection. These findings are consistent with those from previous studies in the south-east Asia region.[15-19]A recent study from another urban setting in Indonesia documented a significantly increased risk of infection in child contacts whose parent was the index case.[16] We did not find this in our study but a number of studies have reported the association with a female index case such as mother or grandmother.[19-22] Mothers and grandmothers in most societies have more prolonged and closer contact with young children than fathers or other male relatives, and the findings are potentially useful for targeting the highest risk groups for screening.

A limited number of previous studies have evaluated characteristics associated with the risk of having tuberculosis disease among household child contacts.[22-26] All but one of these were cross-sectional studies that did not follow-up the child contacts, such as the 12 months of follow-up in our study. A retrospective study of 282 child contacts in Alaska found that those with tuberculosis were younger than those without disease.[24] Further, previous studies from South Africa and Uganda reported a high prevalence of disease in child contacts of less than 5 years of age, of 34% and 16% respectively.[23,26] It is recognised that the risk of developing tuberculosis after infection with *M.tuberculosis* is much higher in infants and young children compared to school-aged children.[7] We did not find an association of disease with young age. However, in this study the actual risk of developing disease within 1 year of screening in contacts that were less than 5 years of age is likely to have been reduced due to the use of isoniazid preventive therapy in this at-risk group.[13] All children diagnosed with tuberculosis during follow-up were older children not receiving isoniazid preventive therapy.

A positive TST was associated with a diagnosis of tuberculosis, and the majority of the children diagnosed with tuberculosis had a positive TST. This would be expected, especially because the prevalence of risk factors for a false-negative TST such as HIV infection or severe malnutrition is very low in this population. However, including the TST as part of contact screening is recognised as a barrier to implementation.[27] This is because tuberculin solution is rarely available in tuberculosis endemic settings, and certainly not at the primary care level where contact screening is initiated. WHO provides an approach to child contact screening for settings wheretuberculin solution is not available.[10,13]

There are a number of study limitations that relate to diagnostic categorisation. First, none of the child contacts diagnosed with tuberculosis were microbiologically confirmed. Second, being categorised as having “LTBI” was reliant on a positive TST result which is not fully sensitive or specific. Finally, none of those categorised as “TB exposed only” at baseline and that remained well during follow-up had a repeat TST. Therefore, those with recent infection that may have converted during follow-up were not identified.

While the prevalence of infection or disease was significantly higher in children that were contacts of sputum smear-positive tuberculosis cases, infection or disease was identified in one quarter of contacts of cases with sputum smear-negative disease. Therefore, the risk for contacts of smear-negative tuberculosis is not negligible. WHO recommendations that are primarily for tuberculosis endemic settings in low and middle income countries recommend routine screening of contacts of sputum smear-positive cases.[10] However, in low tuberculosis endemic settings that are often better resourced, screening is extended to contacts of all tuberculosis cases. Unfortunately, it is only in the latter settings where routine contact screening is actually implemented.[27]

Our study provides original data from Indonesia that adds to a large and consistent body of evidence that shows that infection and disease due to *M.tuberculosis* is common among children that are close contacts of tuberculosis cases.[28,29] No particular characteristics were identified that could better target contact screening than current recommendations.

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**Box 1.** Definitions used for this study in children with known contact with a person with sputum smear-positive tuberculosis

- Tuberculosis: if the child met the criteria for certain or probable tuberculosis:
    - Certain tuberculosis: culture confirmation for *M.tuberculosis*
    - Probable tuberculosis: at least one well-defined symptom; AND
      chest radiograph abnormality* consistent with intrathoracic tuberculosis OR supportive evidence of extra-pulmonary tuberculosis; AND
      positive clinical response to anti-tuberculosis treatment
- Latent tuberculous infection: a positive TST in the absence of active tuberculosis
- Exposed to tuberculosis only: a negative TST in the absence of active tuberculosis

* agreed by two independent readers

**Table 1.** Characteristics of the child contacts

| Characteristics | Total child contacts<br>N = 269 | TB disease*<br>n = 25 | LTBI**<br>n = 100 | TB exposed only<br>n = 144 |
|---|---|---|---|---|
| **Child contacts** | | | | |
| Sex, female | 131 (49%) | 12 (48%) | 51 (51%) | 68 (47%) |
| Age, year (median; IQR) | 6 (3-10) | 8(3-11) | 7 (3-11) | 6 (3-10) |
| <2 years | 40 (15%) | 4 (16%) | 11 (11%) | 25 (17%) |
| 2–4 years | 68 (25%) | 5 (20%) | 24 (24%) | 39 (27%) |
| ≥5 years | 161 (60%) | 16 (64%) | 65 (65%) | 80 (56%) |
| Undernourished # | 83 (31%) | 13 (52%) | 29 (29%) | 41 (29%) |
| BCG scar presence | 217 (81%) | 21 (84%) | 85 (85%) | 111 (77%) |
| **Environmental** | | | | |
| Household contact | 239 (89%) | 22 (88%) | 90 (90%) | 127 (88%) |
| Sleep in the same room | 111 (41%) | 15 (60%) | 47 (47%) | 56 (39%) |
| Number of household members (median, IQR) | 6 (4-8) | 6 (4-8) | 6 (5-10) | 5.0 (4-8) |
| Indoor air pollution | 161 (60%) | 18 (72%) | 60 (60%) | 83 (38%) |
| **Source case** | | | | |
| Parent | 143 (53%) | 17 (68%) | 51 (51%) | 75 (52%) |
| Grandparent | 50 (19%) | 2 (8%) | 23 (23%) | 25 (17%) |
| Sex, female | 118 (44%) | 8 (32%) | 56 (56%) | 54 (38%) |
| Sputum smear-positive | 214 (80%) | 20 (80%) | 90 (90%) | 106 (74%) |

* Note that 21 with TB disease were also TST positive. The prevalence of characteristics in this sub-group of 21 was similar to those listed (data not shown)
** LTBI: latent tuberculosis infection, defined as a positive TST but no active disease
# undernourished: defined as weight-for-height Z score -2 to -3 for < 5 years, and weight-for-height percentage of 70-90% for 5-14 years

**Table 2.** Characteristics of the source case

| Characteristics | n = 141 |
|---|---|
| Age, years (median; IQR) | 38 (30; 50) |
| Sex, female | 53 (37.6%) |
| Relationship to child contacts | |
| Mother | 31 (22%) |
| Father | 55 (39%) |
| Grandmother | 11 (7.8%) |
| Grandfather | 13 (9.2%) |
| Others | 31 (22%) |
| Sputum smear | |
| Negative | 35 (24.9%) |
| Positive 1+ | 45 (31.9%) |

| | |
|---|---|
| Positive 2+ | 24 (17%) |
| Positive 3+ | 37 (26.2%) |
| HIV infected | 2 (1.4%) |
| MDR TB | 1 (0.7%) |
| Smoking | 40 (28.4%) |

**Table 3.** Factors associated with evidence of infection with *M. tuberculosis*

| **Characteristics** | **TST positive*<br>n = 121** | **TST negative<br>n = 144** | **OR**<br>(95% CI)** | **AOR**<br>(95% CI)** |
|---|---|---|---|---|
| **Child contacts** | | | | |
| Sex, female | 16 (50%) | 68 (42%) | 1.1<br>(0.7–1.8) | |
| Age, years median(IQR) | 7 (3-11) | 6 (2-9) | | |
| < 5 years | 42 (35%) | 64 (44%) | 0.7<br>(0.4–1.1) | 0.7<br>(0.4 – 1.2) |
| Undernourished # | 40 (33%) | 41 (28%) | 1.2<br>(0.7–2.1) | |
| Symptomatic | 53 (44%) | 41 (28%) | 2.0<br>(1.2 – 3.3) | 2.1<br>(1.2 – 3.6) |
| BCG scar presence | 103 (85%) | 111 (77%) | 1.7<br>(0.9–3.2) | |
| **Environmental** | | | | |
| Household contact | 110 (91%) | 127 (88%) | 1.3<br>(0.6 – 3.0) | |
| Sleep in the same room | 61 (50%) | 56 (39%) | 1.6<br>(1.0 – 2.6) | 1.7<br>(1.0 – 2.7) |
| Number of household members median (IQR) | 6 (4-8) | 5 (4-8) | | |
| Household members > 6 | 70 (48.6%) | 62 (51.2) | 1.1<br>(0.7 – 1.8) | 0.8<br>(0.5 – 1.4) |
| Indoor air pollution | 74 (61%) | 83 (38%) | 1.2<br>(0.7 – 1.9) | 1.4<br>(0.8 -2.5) |
| **Source case** | | | | |
| Parent | 66 (55%) | 75 (52%) | 1.1<br>0.7 – 1.8) | |
| Sex, female | 62 (51%) | 54 (38%) | 1.8<br>(1.1 – 2.7) | 1.9<br>(1.1 – 3.2) |
| Mother | 22 (18%) | 28 (19%) | 0.9<br>(0.5 – 1.7) | |
| Sputum smear-positive | 107 (88%) | 106 (74%) | 2.7<br>(1.4 – 5.4) | 3.0<br>(1.5 – 6.1) |

* 21 children with disease were included in this “TST positive” group
** OR: Odds Ratio; AOR: Adjusted Odds Ratio
# undernourished: defined as weight-for-height Z score -2 to -3 for < 5 years, and weight-for-height percentage of 70-90% for 5-14 years

**Table 4.** Characteristics associated with tuberculosis disease

| Characteristics | Tuberculosis n = 25 | Not tuberculosis n = 244 | OR* (95% CI) | AOR* (95% CI) |
|---|---|---|---|---|
| **Child contacts** | | | | |
| Sex, female | 12 (48%) | 119 (49%) | 1.0 (0.4 – 2.2) | |
| Age, year (median; IQR) | 8 (2-10) | 6(3-10) | | |
| <5 years | 9 (36%) | 99 (41%) | 0.8 (0.4 – 1.9) | |
| Undernourished # | 13 (52%) | 70 (29%) | 2.7 (1.2 – 6.2) | 2.6 (1.1 – 6.2) |
| BCG scar present | 21 (84%) | 196 (80%) | 1.3 (0.4 – 3.9) | |
| Positive TST | 21 (84%) | 100 (41%) | 7.6 (2.5 – 22.7) | 7.3 (2.4 – 22.1) |
| **Environmental** | | | | |
| Household contact | 22 (88%) | 217 (89%) | 0.9 (0.3 – 3.3) | |
| Sleep in the same room | 15 (60%) | 103 (42%) | 2.1 (0.9 – 4.8) | 1.4 (0.5 – 3.8) |
| Number of households (median, IQR) | 6 (4-8) | 5 (4-9) | | |
| Household members > 6 | 9 (36%) | 126 (52%) | 1.8 (0.7 – 4.5) | |
| Indoor air pollution | 18 (72%) | 143 (59%) | 0.5 (0.2 – 1.2) | |
| **Source case** | | | | |
| Parent | 17 (68%) | 126 (52%) | 2.0 (0.8 – 4.8) | 1.6 (0.6 – 4.6) |
| Sex, female | 8 (32%) | 110 (45%) | 0.6 (0.2 – 1.4) | |
| Mother | 6 (24%) | 45 (18%) | 1.25 (0.4 – 3.6) | |
| Sputum smear-positive | 20 (80%) | 196 (80%) | 1.0 (0.4 – 2.7) | |

* OR: Odds Ratio; AOR: Adjusted Odds Ratio
# undernourished: defined as weight-for-height Z score -2 to -3 for < 5 years, and weight-for-height percentage of 70-90% for 5-14 years