MAJOR ARTICLE

# A Prospective Evaluation of the Symptom-Based Screening Approach to the Management of Children Who Are Contacts of Tuberculosis Cases

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**(See the Editorial Commentary by Jeena on pages 19–20.)**

***Background.*** Child tuberculosis contact screening and management can enhance case finding and prevent tuberculosis disease. It is universally recommended but rarely implemented in tuberculosis-endemic settings. The World Health Organization (WHO)–recommended symptom-based screening approach could improve implementation but has not been prospectively evaluated.

***Methods.*** We conducted a cohort study of children who were close contacts of pulmonary tuberculosis patients in Indonesia from August 2010 to December 2012. We performed clinical assessment, tuberculin skin test, and chest radiography in all eligible children irrespective of symptoms at baseline. Mycobacterial culture and Xpert MTB/RIF assay were performed on sputum from children with persistent symptoms of suspected tuberculosis. Children were managed according to WHO guidelines and were prospectively followed for 12 months.

***Results.*** A total of 269 child contacts of 140 index cases were evaluated. At baseline, 21 (8%) children had tuberculosis diagnosed clinically; an additional 102 (38%) had evidence of infection without disease. Of children with any tuberculosis-related symptoms at baseline, 21% had tuberculosis diagnosed compared with none of the asymptomatic children ($P < .001$). After 12 months of follow-up, none of the 99 eligible young child contacts (<5 years) who received isoniazid preventive therapy (IPT) had developed disease compared with 4 of 149 (2.6%) asymptomatic older children who did not receive IPT.

***Conclusions.*** Symptom-based screening is an effective and simple approach to child tuberculosis contact management that can be implemented at the primary healthcare level.

***Keywords.*** tuberculosis; child; contact screening; preventive therapy.

Tuberculosis is a global public health challenge, with estimates that approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* [1]. Although progress has been made in global tuberculosis control over the last decade, the burden of disease remains high in many communities and transmission of *M. tuberculosis* is common [2, 3]. It has been recognized that infants and young children infected with *M. tuberculosis* following exposure are at a high risk of developing tuberculosis, including severe, disseminated forms of tuberculosis associated with a high morbidity and mortality, and that preventive therapy is effective in greatly reducing this risk [4–7]. Although screening of children who are close contacts of tuberculosis cases has been recommended almost universally for decades, it has rarely been implemented in endemic settings [8, 9].

The prevalence of disease and infection due to *M. tuberculosis* among contacts is high [10–12]. Contact screening has 2 important potential roles for tuberculosis control. The first is as active case finding aiming to increase case detection of tuberculosis in the community,

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and potentially providing earlier detection and treatment than passive case finding. The second role is to identify at-risk groups among close contacts that require preventive therapy such as young children (<5 years) without active tuberculosis. Despite the obvious potential, for a variety of reasons implementation in tuberculosis-endemic settings is almost negligible [13].

Until recently, a major barrier has been that contact screening and management guidelines required a number of investigations (ie, tuberculin skin test [TST] and chest radiograph [CXR]) that either were not available, were costly when available, were difficult to access in many endemic settings, or required multiple visits and travel to a secondary or tertiary healthcare facility [13]. In recognition of the wide policy–practice gap and the challenges in resource-limited settings, World Health Organization (WHO) guidelines in 2006 proposed a symptom-based screening approach that did not require further investigation for most child contacts and would allow provision of preventive therapy at a primary or community care level [14]. However, this approach has not been prospectively evaluated in children. We therefore aimed to prospectively evaluate the performance of the symptom-based screening approach to child contact screening and management.

## METHODS

### Study Site and Population

A prospective cohort study was conducted in Yogyakarta, Indonesia, from August 2010 to December 2012. Index cases were adults with a diagnosis of pulmonary tuberculosis treated in Yogyakarta district between 1 January 2010 and 31 December 2011. Children aged ≤15 years who were in close contact with an index case were recruited to the study following informed consent. "Close contact" was defined as living in the same house with the index case within the last 3 months, or having had frequent contact with the index case for a minimum of 8 hours per day, within the last 3 months if not living in the same house. Child contacts were excluded if they were currently receiving antituberculosis therapy or preventive therapy, or if they lived >20 km from the study hospital.

### Symptom Screening and Investigations

At initial baseline screening, all eligible children, irrespective of symptoms, underwent clinical evaluation including nutritional assessment, TST, and CXR. For each child contact, we specifically inquired about any symptoms related to tuberculosis: cough, fever, poor appetite, weight loss or failure to thrive, hemoptysis, fatigue, and night sweats. The presence and duration of any of the symptoms at the time of baseline assessment or within the previous 3 months were noted, as well as persistence and response (or not) to appropriate treatment. The symptom was characterized as "well defined" if it met the criteria as described in Table 1. Weight to the nearest 0.1 kg and height/length to the nearest 0.5 cm were measured and used to define nutritional status (Table 1). Those with symptoms were managed appropriately (eg, antibiotic or bronchodilator or nutritional support) and then reevaluated for either symptom resolution or persistence. Those with persistent symptoms despite appropriate treatment had sputum collected as outpatients. Human immunodeficiency virus (HIV) testing was not performed in this study.

A trained study nurse performed TST: intradermal injection of 0.1 mL of 2 tuberculin units of tuberculin purified protein derivative RT 23 in the volar aspect of the forearm. The transverse diameter of any induration was measured at 72 hours and was considered positive if it was ≥10 mm regardless of the BCG vaccination status. CXR included anteroposterior and lateral views, and was interpreted by a radiologist and a pediatrician who were blinded to the clinical information. Two separate samples of sputum were collected from all children with persistent symptoms by the induced sputum technique as previously described [15]. The second sputum specimen was obtained on the same day a minimum of 4 hours after the first specimen was obtained. All sputum specimens were examined for acid-fast

**Table 1. Definitions Used in the Study**

- Well-defined symptoms include:
  - Persistent cough: an unremitting cough that is not improving and has been present for >21 days
  - Fever: body temperature of >38°C for 14 days, after common causes such as malaria or pneumonia have been excluded
  - Weight loss or failure to thrive: in addition to asking about weight loss or failure to thrive, it is necessary to have evidence from the child's growth chart
- Tuberculosis disease: if the child met the criteria for certain, probable, or possible tuberculosis
  - Certain tuberculosis: culture confirmation for *Mycobacterium tuberculosis*
  - Probable tuberculosis: had at least 1 of the well-defined symptoms; AND CXR was consistent with intrathoracic tuberculosis OR there was supportive evidence of extrapulmonary tuberculosis; AND there was a positive clinical response to antituberculosis treatment
  - Possible tuberculosis: had at least 1 of the well-defined symptoms; AND either of the following: a positive clinical response to antituberculosis treatment OR CXR was consistent with intrathoracic tuberculosis
- Latent tuberculosis infection: a positive TST in the absence of tuberculosis disease
- Tuberculosis exposed only: a negative TST in the absence of tuberculosis disease
- Nutritional assessment on basis of WFH:
  - Normal: 0–4 years, *z* score of the WFH ≥ −2 of the WHO median; ≥5 years, percentage of expected WFH ≥90%
  - Moderate undernutrition: 0–4 years, WFH *z* score −3 to < −2 of the WHO median; ≥5 years, percentage of expected WFH 70%–90%
  - Severe malnutrition: 0–4 years, WFH *z* score < −3; ≥5 years, percentage of expected WFH <70%

Abbreviations: CXR, chest radiograph; TST, tuberculin skin test; WFH, weight-for-height; WHO, World Health Organization.

bacilli (AFB) and cultured for mycobacteria on Lowenstein-Jensen media, and sputum pellets were stored at −20°C for analysis by Xpert MTB/RIF assay (Cepheid, Sunnyvale, California) when this became available during the study.

### Patient Management and Follow-up

Following initial baseline screening and investigations, the children were classified as having either tuberculosis disease, latent tuberculosis (LTBI), or tuberculosis exposure only. The study definitions are listed in Table 1. Children with a diagnosis of tuberculosis were treated with antituberculosis therapy for 6 months (Daily Rifampicin, Isoniazid and Pyrazinamide in the first 2 months and daily Rifampicin and Isoniazid for 4 months) as per national guidelines. Children aged <5 years with LTBI or tuberculosis exposure only were commenced on isoniazid preventive therapy (IPT) as per guidelines (isoniazid 10 mg/kg daily for 6 months). Children who were aged ≥5 years with LTBI or tuberculosis exposure only did not receive IPT and were observed. All children were reevaluated at 2, 6, and 12 months following baseline assessment, including for presence of symptoms and weight. Sputum smear and culture were performed at follow-up for any child who had developed well-defined symptoms of tuberculosis.

### Evaluation

The primary study aim was to evaluate a symptom-based approach to contact screening. We compared the proportion of children diagnosed with tuberculosis at baseline (on basis of clinical and radiological findings) between the symptomatic and asymptomatic children. Furthermore, we determined the proportion of children who developed tuberculosis disease at follow-up among those who were not diagnosed with tuberculosis at baseline. Of this group, the numbers of children who developed tuberculosis disease during follow-up could be determined for those receiving IPT (<5 years) and for the older children who did not receive IPT (as per guidelines).

### Statistical Analysis

The data were summarized as a proportion or a mean or median, where appropriate. We described baseline demographic and clinical characteristics for index cases and child contacts using simple frequencies and median/mean. Comparison of proportions of outcomes between groups was tested using $\chi^2$ test or Fisher exact test if the expected value for 1 or more cells is <5. A $P$ value <.05 was considered as statistically significant. CIs were calculated for the prevalence of an outcome. All data analysis was conducted using Stata software, version 12 (StataCorp, College Station, Texas).

## RESULTS

There were 1247 cases of pulmonary tuberculosis treated in Yogyakarta district during the study period. The numbers of cases treated in each site and the number of children recruited are shown in Figure 1. Information relating to child contacts was less available for cases treated at the central health facilities such as hospital or lung clinic, compared to primary healthcare settings. Overall, 269 child contacts of 141 index cases were included in the study, among a total of 413 identified child contacts. Reasons for ineligibility were as follows: parents did not consent for their child to be included in the study for a variety of reasons (108 children); the child was already receiving treatment for tuberculosis or had already been investigated in the private healthcare setting (21 children); or the child lived >20 km from Dr Sardjito Hospital (15 children).

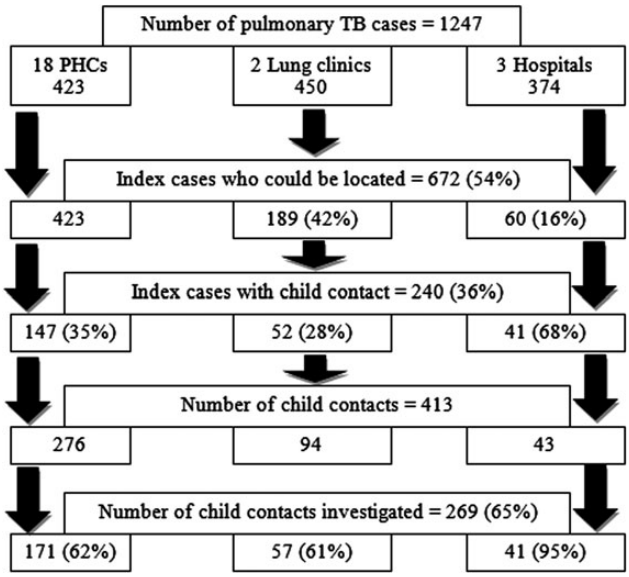


**Figure 1.** Flow of study recruitment. Abbreviations: PHC, primary health clinic (*Puskesmas*); TB, tuberculosis.

Characteristics of the eligible index cases and of the child contacts are presented in Tables 2 and 3, respectively. The majority (75%) of the index cases were sputum AFB smear positive. Forty percent of the child contacts were <5 years of age. Most children were a household contact of a sputum smear-positive case. The index case was a parent in 53% of the cases.

### Findings at Baseline Assessment

The majority (64%) of the child contacts were asymptomatic at the time of screening and none of these had parenchymal changes consistent with tuberculosis on CXR. Ninety-eight (36%) children had at least 1 symptom, whereas 26 (9.7%) children had at least 1 well-defined symptom. The most common reported symptoms were weight loss (22% of all contacts), cough (13%), and fever (3%). TST was positive in 119 (44%) children. Seventy-eight percent of children had a normal CXR; the commonest CXR abnormality was hilar lymphadenopathy, reported

**Table 2. Characteristics of the Index Cases (n = 141)**

| Characteristic | No. (%) |
|---|---|
| Age, y, median (IQR) | 38 (30–50) |
| Sex, female | 53 (37.6) |
| 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 tuberculosis | 1 (0.7) |
| Ever smoker | 40 (28.4) |

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; MDR, multidrug resistant.

**Table 3. Characteristics of the Child Contacts (n = 269)**

| Characteristic | No. (%) |
|---|---|
| Sex, female | 131 (49) |
| Age, y, median (IQR) | 6 (3.2–10.7) |
| <2 y | 40 (15) |
| 2–4 y | 68 (25) |
| ≥5 y | 161 (60) |
| Nutritional status, weight for height | |
| Normal | 186 (69) |
| Moderate undernutrition | 83 (31) |
| Severe malnutrition | 0 (0) |
| BCG vaccination | |
| Yes | 267 (99) |
| No | 1 (0.4) |
| Unknown | 1 (0.4) |
| BCG scar | 217 (81) |
| Relationship to the index case | |
| Child | 143 (53) |
| Grandchild | 50 (19) |
| Siblings | 6 (2) |
| Cousin/nephew | 43 (16) |
| Others | 27 (10) |
| Sputum smear of index case | |
| Negative | 53 (20) |
| Positive 1 | 83 (31) |
| Positive 2 | 43 (16) |
| Positive 3 | 90 (33) |
| Household contact | 239 (89) |
| Sleeping in the same room | 111 (41) |
| No. of household members, median (IQR) | 6 (4–8) |
| Indoor air pollution[a] | 161 (60) |

Abbreviations: BCG, bacillus calmette guerin; IQR, interquartile range.

[a] Indoor air pollution: reported indoor exposure at home to tobacco smoke, burning kerosene, or wood.

in 28 (11%) of all children and in 11 (6%) of asymptomatic children. Pleural effusion and miliary pattern on CXR were each identified in 1 symptomatic child. The child with the miliary pattern also had headache, fever, vomiting, neck stiffness, and abnormal cerebrospinal fluid findings consistent with a diagnosis of tuberculosis meningitis.

About half of the children (54.3%; 95% confidence interval [CI], 48.1%–60.3%) were classified as having tuberculosis exposure only, 37.9% (95% CI, 32.1%–44.0%) as having LTBI, and 21 (7.8%; 95% CI, 4.9%–11.7%) as having tuberculosis. All tuberculosis cases diagnosed at baseline had at least 1 "well-defined" symptom. Solid culture and Xpert MTB/RIF assay for *M. tuberculosis* were negative for all children. Therefore, all those treated for tuberculosis were on the basis of clinical and radiological abnormalities following discussion by 2 experienced pediatricians (R. T. and S. M. G.). On the basis of these findings and response to antituberculosis treatment, 10 of the 21 (48%) were classified as "possible" tuberculosis and 11 (52%) as "probable" tuberculosis (Table 1). The probable tuberculosis cases included 1 with tuberculosis meningitis, 1 with pleural tuberculosis, and 9 with pulmonary tuberculosis.

Figure 2 presents the findings and classification of cases from the time of screening until the end of follow-up. Of the 98 children with any symptom, 21% (95% CI, 14%–31%) were diagnosed with tuberculosis at baseline evaluation, compared with 0% (95% CI, 0%–2.1%) of the 171 asymptomatic children ($P < .001$). Of the 26 children with well-defined, persistent symptoms, 81% (95% CI, 55%–89%) were diagnosed with tuberculosis at baseline compared with 0% (95% CI, 0%–1.5%) of 243 asymptomatic children ($P < .001$).

### Final Outcome at 1-Year Follow-up

Eighteen of the 269 (6.7%) eligible children were lost to follow-up before completion of 12 months of follow-up (Figure 2). None of these children had tuberculosis diagnosed at baseline. Six of 248 (2.4%) children with LTBI or tuberculosis exposure only at baseline developed tuberculosis-related symptoms during follow-up. The evaluation and outcome for these children are listed in Table 4. All of these children had a normal CXR finding at baseline and all presented with weight loss. Four were diagnosed with tuberculosis (Figure 2), accounting for 1.6% of children without tuberculosis disease at baseline. Of the 171 children initially screened as asymptomatic, 2 developed tuberculosis (1.2%: 95% CI, .3%–3%) during follow-up. Of the 77 children with symptoms at baseline (72 with any symptom and 5 with at least 1 well-defined symptom) who were considered not to have tuberculosis, 75 (97%: 95% CI, 91%–99%) had symptom resolution without antituberculosis therapy and remained well over the subsequent 12 months.

Figure 3 shows the final outcome for all study children by age. All 21 children who were diagnosed with tuberculosis at baseline

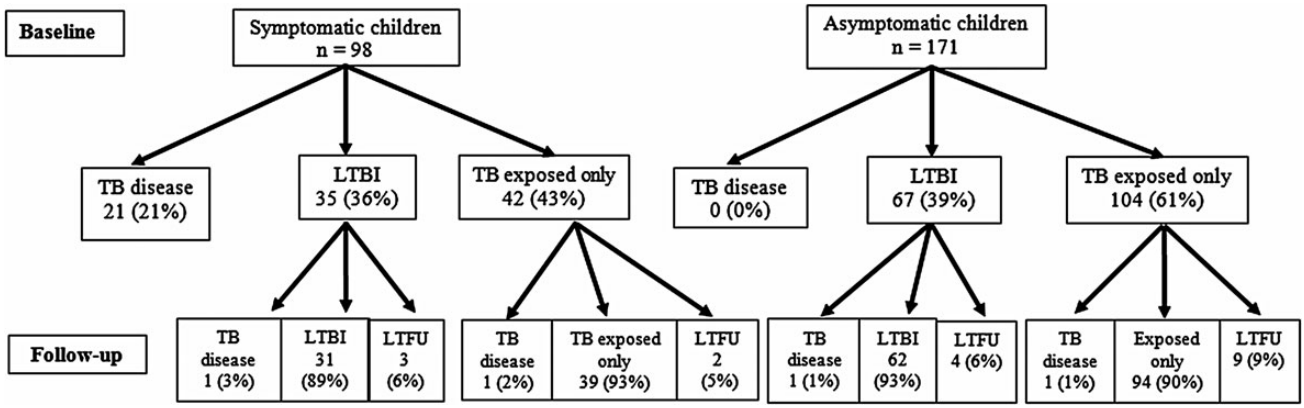


**Figure 2.** Outcome of investigations at baseline and follow-up in relation to symptom-based screening at baseline. Abbreviations: LTBI, latent tuberculosis; LTFU, lost to follow-up; TB, tuberculosis.

showed a good response to antituberculosis therapy, with symptom resolution and weight gain. All 99 children who were aged <5 years without tuberculosis diagnosis at baseline were offered IPT for 6 months. The majority completed at least 4 months of IPT (50% completed the full 6 months), and none (0%: 95% CI, 0%–4%) developed tuberculosis within 12 months of follow-up. This compared to 4 of 149 (2.7%; 95% CI, .1%–5%) children aged ≥5 years who did not have tuberculosis diagnosed at baseline and did not receive IPT due to their age.

## DISCUSSION

In regard to screening of child contacts of tuberculosis patients, WHO recommends that only symptomatic children require referral to a level of care where appropriate assessment for suspected tuberculosis can be undertaken. This assessment may include TST, CXR, and sputum examination [14]. WHO recommends that child tuberculosis contacts aged ≤5 years (or HIV-infected children of any age) without any symptoms suggestive of tuberculosis should be started on preventive therapy. If any child, whether receiving IPT or not, subsequently develops symptoms suggestive of tuberculosis, then appropriate referral and further investigation should be performed. With this approach, child contact screening and management can be implemented at a primary care level where the index case is being managed. Our study provides original evidence that a symptom-based approach is a simple and safe screening method that can be implemented at the primary care level.

A major strength of our study is that contacts were followed for 1 year to determine outcomes from this approach to contact screening and management, and there were low numbers lost to follow-up. Natural history data suggest that the majority of children exposed to and infected with *M. tuberculosis* who develop tuberculosis disease will do so within 1 year of infection [6]. A previous study in South Africa also aimed to evaluate the symptom-based screening approach [16]. However, this cross-sectional analysis focused on evaluation of symptoms to predict the presence of tuberculosis, and no follow-up was undertaken; therefore, the important outcomes such as the proportion of asymptomatic children who developed disease could not be determined.

The major limitation in interpretation of our study's findings is the inherent problem of using symptoms for both screening

**Table 4. Characteristics and Outcomes of Children Who Became Symptomatic During the Follow-up Period**

| | Baseline | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| Age, y | Symptom | TST, mm | CXR | Treatment | Symptom | TST, mm | Sputum Culture | Treatment |
| 1 | None | 0 | Normal | IPT | Weight loss at month 6 | 0 | Negative | Observe |
| 14 | None | 20 | Normal | None | Weight loss at month 12 | ND | Negative | ATT |
| 6 | None | 5 | Normal | None | Weight loss at month 3 | 16 | Negative | ATT |
| 7 | None | 0 | Normal | None | Weight loss at month 12 | 0 | Negative | Observe |
| 11 | Weight loss | 11 | Normal | None | Weight loss at month 4 | ND | Negative | ATT |
| 9 | Weight loss | 0 | Normal | None | Weight loss at month 6 | 9 | Negative | ATT |

Abbreviations: ATT, antituberculosis treatment; CXR, chest radiography; IPT, isoniazid preventive therapy; ND, not done; TST, tuberculin skin test.

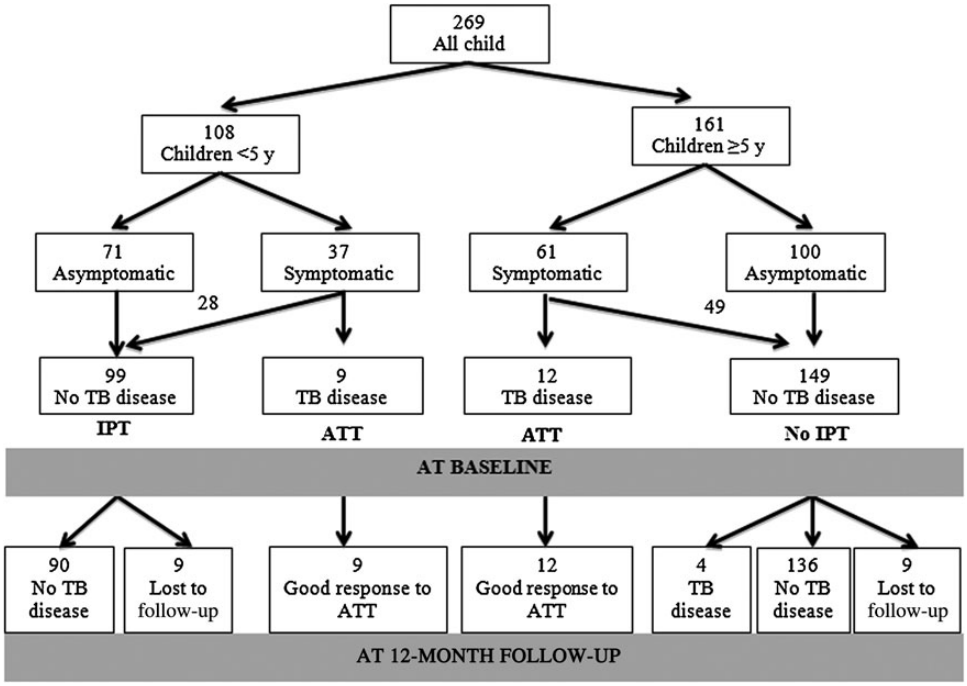


**Figure 3.** Outcome of child contacts at 12 months in relation to age, symptoms, and use of isoniazid preventive therapy. Abbreviations: ATT, antituberculosis treatment; IPT, isoniazid preventive therapy; TB, tuberculosis.

and evaluation of disease as this creates uncertainty in clinical diagnosis. We acknowledge that no cases in our study were microbiologically confirmed. There are also potential problems of recall bias and subjectivity in the reporting of symptoms. Nevertheless, all cases underwent careful clinical and radiological assessment, including checking information from the interview with objective data such as the growth chart for reported weight loss. Moderate undernutrition is reportedly common in Indonesian children, with a reported prevalence of 37% in 2012 [17], which is similar to our study population. Only recorded weight loss or failure to gain weight were considered "well-defined" symptoms in this study. Symptomatic contacts were reviewed to document response to other appropriate treatment such as antibiotics or nutritional support to determine symptom persistence. Regular follow-up allowed us to monitor treatment responses to antituberculosis therapy for those diagnosed with tuberculosis as well as evaluation of outcome for symptomatic children without tuberculosis at baseline.

There are a number of important issues raised by the use of a symptom-based approach for child contacts. The first is that there will be children with abnormal CXR findings such as hilar lymphadenopathy among those evaluated as asymptomatic at baseline. In a South African study of children diagnosed with intrathoracic tuberculosis, 9% reported no symptoms, and all had evidence of primary complex disease on CXR [18]. In our study, 6% of children asymptomatic at baseline had hilar lymphadenopathy on CXR. None were diagnosed with tuberculosis and none developed symptoms of tuberculosis at follow-up. Natural history cohort studies have found that hilar lymphadenopathy on CXR does not necessarily indicate disease [6].

The second is that this approach will mean that some young children not infected with *M. tuberculosis* will be treated with IPT. A negative TST does not exclude infection, especially recent infection, but nonetheless as many as 50% of the contacts may not be infected at time of screening [11]. This represents a classic public health conundrum where overall population potential benefit needs to be considered against individual potential risk. The main potential isoniazid-related toxicity for children is hepatotoxicity, and although there are occasional reports of severe adverse events [19], this risk in children receiving isoniazid in dosages up to 15 mg/kg daily is almost negligible [20, 21].

Preventive therapy is widely recommended to be provided to nondiseased young child contacts. The benefit of IPT has been reported elsewhere [5, 22–24], but despite the benefits, studies consistently report poor uptake and/or usage of IPT among child contacts in endemic areas [25–28]. Our study was not designed to determine efficacy of IPT, and numbers treated with IPT were small. Nonetheless, effectiveness is suggested by the fact that none of the young, high-risk cohort that received IPT developed tuberculosis and only older, lower-risk children not receiving IPT developed tuberculosis at follow-up. It is important to recognize that the risk of reinfection over the follow-up period from

completion of IPT is very low in our setting. It was also noted that full adherence to 6 months of IPT was achieved in only half of the eligible contacts. The effectiveness of IPT used for a shorter duration in young children is unknown, as the evidence for the recommended regimen of at least 6 months' duration was from studies that mainly included adults [24]. It is possible that a duration of <6 months might be effective in young children because they have a lower bacillary load and prevalence of comorbidities compared with adults, but this is not known.

All 4 children who were diagnosed with tuberculosis during follow-up showed weight faltering. Although monitoring of weight is an accepted measure of treatment response for children receiving treatment for tuberculosis, its role in the follow-up of children receiving IPT or asymptomatic children receiving no treatment remains to be determined. Weight faltering was noted to be common in young children with bacteriologically confirmed tuberculosis who were identified through active case finding in a vaccine trial [29].

In conclusion, the symptom-based approach to screening and managing child contacts recommended by WHO is an effective strategy that can be implemented at a primary care level. A lack of available TST and CXR should not be a barrier to child contact screening and management.

## Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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