Epidemiology of Child Tuberculosis (A Cross-Sectional Study at Pulmonary Health Center Semarang City, Indonesia)

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Abstract. Mycobacterium tuberculosis is an acid-resistant bacterium that caused tuberculosis. The children might suffer tuberculosis by direct transmission of adult smear positive. The analytic observational study with a cross sectional was conducted. Samples were pediatric patients from January 2015 until December 2016. The 344 subject as total sampling were included as samples. Data were obtained through interviews and direct observations then analyzed with Chi-Square method. The results of these study were the majority of subjects were 3 years old (51.7%), the majority were female (55.2%), already immunized BCG (82.6%), and had moderate nutritional status (40.7%). More than half subjects had no contact with adult smear positive (64.5%). Most of subject had house population density ≥ 8m² per person (99.4%), the level of humidity 40-70% (99.4%), the presence of ventilation 10% from floor area (75.6%), and all the composition of the floor made from tiles. In contrary, the lighting levels were not qualified <60 lux (99.5%). Most of the subject had family members who smoked inside (61.6%). The education level of the parents majority completed high school (41.9%), relatively had a good knowledge about tuberculosis (98%), and almost respondents were housewives (89.5%) with family income above the minimum wage Semarang (53.4%). The results of Chi-Square test showed that there was a relationship between the gender of the child (OR = 0.445; 95%CI = 0.241-0.821) and the presence of smokers (OR = 2.007; 95%CI = 1.074-3.751). It was suggested to educate the parents about smoker as the risk factor of child tuberculosis.

Keywords: tuberculosis, children, smoker

1. Introduction

Tuberculosis is an infectious disease of the respiratory system caused by Mycobacterium tuberculosis to the part of the lung parenchym. Tuberculosis is transmitted through the air (droplet nuclei) [1]. A person diagnosed as a suspect tuberculosis if found on his/her main clinical symptoms such as cough with phlegm for more than three weeks, coughing up blood, shortness of breath and chest pain [2]. Tuberculosis (TB) has existed for millennia and remains a major global health problem. In 2015, 6.1 million new TB cases were notified to national authorities and reported to WHO. Notified TB cases increased from 2013–2015, mostly due to a 34% increase in notifications in India. However, globally there was a 4.3 million gap between incident and notified cases, with India, Indonesia and Nigeria accounting for almost half of this gap [3].

Infection typically occurs when a child inhales Mycobacteria tuberculosis exhaled by an individual with pulmonary or laryngeal TB. Primary infection due to skin inoculation, ingestion into the gastrointestinal tract or congenital infection due to transplacental transmission occurs very rarely. After
inhalation, a primary reaction often occurs consisting of a small parenchymal lesion in the lung with regional lymphadenopathy, often perihilar or mediastinal. Bacilli may then spread throughout the lungs and pleura, which can result in intrathoracic TB [4].

Tuberculosis is arguably one of the major deadly diseases affecting children in developing countries, causing the death of approximately >80,000 children annually, and with over 500,000 new cases each year, reflecting ongoing transmission within communities. At least 1 million children become ill with TB each year. Children represent about 10-11% of all TB cases. Only 5 countries do not yet report to WHO the notification of cases among children [5,6]. There was an increase in the case notification rate of TB among children between 2011 and 2014 the Lagos State TB and Leprosy Control Programme (LSTBLCP) shown that the incidence of pediatric tuberculosis is higher than the number of notifications, particularly in young children [5,6]. Global Tuberculosis Report 2013 published by WHO states that among 530,000 cases of tuberculosis in the world, 74,000 cases are children tuberculosis cases [7] In 2015, 210,000 children died of TB, including 40,000 TB deaths among children who were HIV positive. Researchers estimate that 67 million children are infected with TB (latent TB) and are therefore at risk of developing disease in the future. Researchers estimate that 25,000 children develop multidrug-resistant TB every year [3]

According to Tuberculosis Recent Update of Indonesia January-December 2012 issue states that the proportion of children tuberculosis in Indonesia is 8.2%. While for the Central Java Province in 2012, the proportion of children tuberculosis is amounted to 11% and for Semarang in 2011 is amounted to 13% of all tuberculosis cases. The Center for Pulmonary Health Semarang is one of health services focuses on pulmonary health. BKPM Semarang also focuses on tuberculosis treatment. According to BKPM Profile in 2012 shows that there is an increasing number of children tuberculosis case in 2011-2013. This number indicates there is an increasing of cases found. The number of cases in 2011 amounted to 3.53%, then by 7% in 2012, and by 11.57% in 2013.

Childhood tuberculosis has been neglected by health programmers and academics, because the cases are few, non-infectious and the perception that effective TB control in adults will prevent TB in children. Childhood tuberculosis is underdiagnosed in many countries with high TB burden [8–10].

Factors that contribute to low case detection among children include inability of children to produce sputum. Even when sputum is produced by a child, cheap diagnostic tests, such as smear microscopy, can only accurately detect 30% of the cases. Other factors include low capability among healthcare staff to diagnose childhood TB, reliance on smear microscopy as the primary method of TB detection, ineffective family-centered contact tracing, paucity of printed workers aid/guidelines, dearth of adequate training on childhood TB screening and diagnosis, and lack of data-capturing tools [11].

Children are more susceptible to developing active TB compared with adults, and acquire the infection mostly from adults within their household, including their parents [12,13]. Lack of relevant data on age-related trends of TB in children. The understanding of the global epidemiology of childhood TB could have been better, and planning of effective control measures easier if relevant data were available [5].

2. Methods
2.1. Study site
The research was conducted at The Center for Pulmonary Health Semarang, Central Java Province, Indonesia.

2.2. Selection subject
For this study, cases of TB are defined in accordance with WHO recommendation. Initial screening criteria used to identify suspected TB cases included low grade fever and weight loss. Additional criteria were cough for more than 3 weeks for pulmonary TB, and localizing signs/symptoms including palpable lymph nodes, headache/vertigo, and backache. Children suspected of having pulmonary TB are encouraged to provide morning sputum for microscopy. Three morning sputum samples are examined for each child. Chest Xray and tuberculin skin test (TST) is carried out by the clinic staff (treating physician)
in those unable to produce sputum and those found to be sputum smear negative on microscopy. TST is performed using five tuberculin units (TU) of tuberculin purified protein derivative (PPD)-S with .5 mm induration as cut off.

2.3. Study design
The analytic observational study with a cross sectional was conducted. Samples were pediatric patients from January 2016 until August 2017. The 344 subject as total sampling were included as samples. Data were obtained through interviews and direct observations then analyzed with Chi-Square method.

2.4. Ethic statement
Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors. Ethical approval was obtained from the Committee of Public Health Research Ethics, Diponegoro University (126/EC/FKM/2015). Informed consent was acquired from parent or guardian.

3. Result and discussion
Table 1 shows the distribution incidence of Child Tuberculosis. From this table it can be seen that half of the subject suffered tuberculosis.

| Incidence of Child Tuberculosis | Total (f) | Percent (%) |
|-------------------------------|----------|-------------|
| Positive of Child TB          | 172      | 50          |
| Negative of Child TB          | 172      | 50          |

After a long period of neglected by health program planner in childhood tuberculosis due to lack of childhood TB cases, difficulty of diagnosis, non-infectious and the belief that effective TB control in adults will prevent TB in children [8,9,14], in this study, we found half of subject suffered from childhood tuberculosis (Table 1). TB in children is increasingly becoming an important cause of global child morbidity and mortality in developing countries. At least 1 million children fall ill with tuberculosis (TB) each year. Children represent about 11% of all TB cases [3,6]. All reflecting ongoing transmission within communities [15]. The estimated proportion of total childhood tuberculosis for each country ranged from 4% to 21% [6]. The burden of childhood TB infection and TB disease is an important indicator of the overall trend of disease and ongoing transmission within the community [15,16]. Estimating the TB burden in the children population, in any level, is important to encourage authorities to facilitate the next process such as new drugs and market appropriate pediatrics formulations [17].

Most of the children who are subject of this study are mostly 0-4 years old at (65.7%) and (55.2%) of them are female. A total of (82.6%) have been immunized with BCG classified as moderate nutritional status as much as (40.7%). It was similar with a result that stated uniform distribution of ages in the household model of exposure led to disease estimates that were 11% higher than the distribution based on adult age and sex notifications [6]. An assumption that the efficacy of BCG vaccination did not wane towards the equator resulted in disease estimates that were 27% lower for all methods of estimating infection [6].

Most children in this study also showed that (64.5%) had no contact history with positive BTA patients and do not have a history of contact with neighbors (79.7%). In contrary with other results that stated children are more susceptible to developing active TB compared with adults, and acquire the infection mostly from adults within their household, including their parents [12,18].

A study showed that 1.8% of children in household contacts of adult TB patients also had TB, higher proportion of TB in female children which showed vulnerability of the female child and considerable role of mother in disease transmission [19,20]. From our result we know that gender of the child were associated with the incidence of childhood tuberculosis (OR=0.445; 95%CI= 0.241-0.821), this in line
with the study conducted by Codlin et al in Pakistan, they found that TB is highly prevalent, translating, into thousands of excess female cases per year [21]. Higher frequency of disease in the females may reflect poor nutritional status of the girl child in making them more vulnerable to the disease [22]. In crowded houses, a greater degree of shared airspace increases exposure to \textit{M. tuberculosis}, which can even be increased by limited air movement in closed spaces—hence a greater risk of infection and tuberculosis disease [12,13]. There are many risk factors related to TB like living in the same house with close family members or friends who had active TB is significantly [8.69 confidence interval (CI): 3.00-25.18] associated with TB [23]. Large family size and small house predisposes 9 times a risk to develop LTBI (CI: 3.00-25.28) [24].

In terms of environmental factors (Table 2), (99.4%) of subject have qualified house environment regarding the population density, but the lighting levels are not qualified by (96.5%). Humidity level of house environment is already qualified by (99.4%) and already has qualified ventilation by (75.6%). The whole floor is already plastered or tiled. TB is also more prone to develop where ventilation and sunlight are inadequate because \textit{Mycobacterium} would not easily move away or killed [25,26]. Meanwhile, there are (61.6%) smokers who live with subject under the same roof. Most smokers smoke in the living room (32%). The education level of the parents by (41.9%) completed high school with relatively good knowledge about tuberculosis by (57%) As many as (89.5%) respondents are not working or can be said only as a housewife with family income per month by (63.4%) are above minimum wage. TB adult and childhood TB is prevalent in poor and marginalized population which associated with overcrowding and poor nutrition [12,27].

In this study some variables associated with the incidence of child tuberculosis are child age (\textit{p value} 0.023), sex (\textit{p value} 0.000), nutritional status (\textit{p value} 0.033), contact history with positive BTA patients (\textit{p value} 0.018), and presence of smokers (\textit{p value} 0.033). Age and sex variations in the prevalence of tuberculosis infection and disease have been reported worldwide, related to biologic mechanisms, socioeconomic and cultural factors may play a role in determining age and sex differences in rates of infection, progression to disease, and treatment outcome [28–30].

While immunization status, history of neighbor contact, population density, lighting level, humidity level, presence of ventilation, education level, knowledge level, and income level not significantly related with the incidence of child tuberculosis. For more details can be seen in Table 3. Vaccination provides a highly effective strategy to control vaccine-preventable diseases; however, the fact that only a few people develop tuberculosis after \textit{Mycobacterium tuberculosis} infection differentiates tuberculosis from classic vaccine-preventable diseases. The BCG vaccine offers some protection against disseminated forms of tuberculosis in young children (and against leprosy), but does not consistently protect against adult-type tuberculosis [31]. Disseminated BCG disease need careful consideration during genetically modified BCG vaccine development. Additionally, prominent T-cell epitopes are genetically highly conserved, similar to essential housekeeping genes, suggesting that \textit{M tuberculosis} subverts some T-cell-mediated immune response to benefit its own survival and spread. An accurate correlate or biomarker of protection has not yet been identified [32]. The important roles played by innate immune responses and localized (non-circulating) T-cell populations have only recently been described, and these might lead to new discoveries. The diverse range of pathological abnormalities related to the ontogeny of the immune response in children presents opportunities to characterise important immunological mechanisms. Immunohistological studies could also advance understanding of protective immune responses in children with latent \textit{M tuberculosis} infection and provide answers to many unresolved beliefs about latent tuberculosis infection [33,34].

Improvements in the mechanistic understanding of tuberculosis disease and protection are greatly needed, as is a reduction in major policy–practice gaps, since most children in tuberculosis endemic areas are unable to access effective tuberculosis care [35–38].
Table 2. Distribution of House Environment of the Respondents.

| Factors Related            | Total (f) | Percent (%) |
|----------------------------|-----------|-------------|
| Population Density         |           |             |
| 1. Unqualified             | 2         | 0.6         |
| 2. Qualified               | 342       | 99.4        |
| Lighting Level             |           |             |
| 1. Unqualified             | 332       | 96.5        |
| 2. Qualified               | 12        | 3.5         |
| Humidity Level             |           |             |
| 1. Unqualified             | 2         | 0.6         |
| 2. Qualified               | 342       | 99.4        |
| Presence of Ventilation    |           |             |
| 1. Unqualified             | 84        | 24.4        |
| 2. Qualified               | 260       | 75.6        |
| Composition of the Floor   |           |             |
| 1. Half or whole is soil   | 0         | 0           |
| 2. Whole plastered/tiled   | 344       | 100         |
| Presence of Smokers        |           |             |
| 1. Present                 | 212       | 61.6        |
| 2. None                    | 132       | 38.4        |
| Smoking area               |           |             |
| 1. No one smokes           | 164       | 47.7        |
| 2. Terrace                 | 18        | 5.2         |
| 3. Living room             | 110       | 32.0        |
| 4. Family room             | 52        | 15.1        |

Our study found that present of smoker in home were related to the incidence of tuberculosis (OR 0.498; 95% CI = 0.320-0.776). The present of smokers in home is an indisputable fact as risk factor of tuberculosis in many studies. Study also proved that family history of smoking related to incidence of TB (OR = 2.8, 95% CI: 2.3-18.2). Exposure of second-hand smoke increase for both the risk of TB infection and development of active TB disease, among children or adults. Smoking inside home will make their family also exposed. Smoking is also contributing factor for latent infections [odds ratio (OR) 3.20 (1.30-8.20)] [39]. A meta-analysis produced evidence that smoking is a risk factor for TB infection and TB disease [40,41]. TB infection and TB disease are biologically increased by smoking. Smoking causes histological changes in the lower respiratory tract, including peribronchial inflammation, fibrosis, vascular intimal thickening, and destruction of alveoli. This leads to alterations in the epithelial function, such as reduced ciliary activity, decreased clearance of inhaled substances, and abnormal vascular and epithelial permeability, alterations in macrophage number and response [42,43], and decrease in CD4 and CD8 cells that produce interferon gamma and TNF alpha [43].
Table 3. Factors related to the incidence of childhood tuberculosis

| Factor Related                               | Diagnosis of Child Tuberculosis | p value | POR  | CI (95%) |
|----------------------------------------------|---------------------------------|---------|------|----------|
| Child Age                                    |                                 |         |      |          |
| a. <3 years old                              | 94 56.6                         | 0.023a  | 1.674| 1.093-2.564|
| b. ≥3 years old                              | 78 43.8                         |         |      |          |
| Sex                                          |                                 | 0.000a  | 0.445| 0.288-0.686|
| a. Male                                      | 60 39.0                         | 0.118a  | 1.632| 0.926-2.876|
| b. Female                                    | 112 58.9                        | 0.033a  | 0.602| 0.386-0.939|
| Immunization status                          |                                 |         |      |          |
| a. No BCG                                    | 24 40.0                         | 0.018a  | 1.757| 1.123-2.748|
| b. BCG                                       | 148 52.1                        |         |      |          |
| Nutritional status                           |                                 | 0.118a  | 1.632| 0.926-2.876|
| a. Malnutrition                              | 52 41.9                         | 0.033a  | 0.602| 0.386-0.939|
| b. Moderate-good nutrition                  | 120 54.5                        |         |      |          |
| Contact History                              |                                 | 0.082a  | 1.662| 0.974-2.833|
| a. Present                                   | 72 59.0                         | 0.499b  | 0.947| 0.447-0.553|
| b. None                                      | 100 45.0                        |         |      |          |
| History of neighbor contact                  |                                 | 0.082a  | 1.662| 0.974-2.833|
| a. Present                                   | 42 60.0                         | 0.378a  | 0.488| 0.144-1.652|
| b. None                                      | 130 47.4                        |         |      |          |
| Population Density                           |                                 | 0.499b  | 0.947| 0.447-0.553|
| a. Unqualified                               | 0 0.0                           | 0.380a  | 0.777| 0.474-1.273|
| b. Qualified                                 | 172 50.3                        |         |      |          |
| Lighting Level                               |                                 | 0.003a  | 0.498| 0.320-0.776|
| a. Unqualified                               | 46 54.8                         |         |      |          |
| b. Qualified                                 | 126 48.5                        |         |      |          |
| Humidity Level                               |                                 | 0.013a  | 0.569| 0.371-0.873|
| a. Unqualified                               | 2 100.0                         |         |      |          |
| b. Qualified                                 | 170 49.7                        |         |      |          |
| Presence of Ventilation                      |                                 | 0.174a  | 1.445| 0.887-2.354|
| a. Unqualified                               | 46 54.8                         |         |      |          |
| b. Qualified                                 | 126 48.5                        |         |      |          |
| Education Level                              |                                 | 0.013a  | 0.569| 0.371-0.873|
| a. Completed kindergarten, etc.              | 50 56.8                         | 0.174a  | 1.445| 0.887-2.354|
| b. Completed high school, diploma/master     | 122 47.7                        |         |      |          |
| Knowledge Level                              |                                 | 0.446a  | 1.209| 0.789-1.854|
| a. Poor knowledge                            | 78 52.7                         |         |      |          |
| b. Good knowledge                            | 94 48.0                         |         |      |          |
| Income Level                                 |                                 | 0.057a  | 1.573| 1.011-2.448|
| a. Below minimum wage                        | 72 57.1                         |         |      |          |
| b. Above minimum wage                        | 100 45.9                        |         |      |          |

*a Continuity correction; b Fisher’s exact test*
Conclusion
The results of Chi-Square test showed that there was a relationship between the gender of the child (OR = 0.445; 95%CI = 0.241-0.821) and the presence of smokers (OR = 2.007; 95%CI = 1.074-3.751). It was suggested to educate the parents about smoker as the risk factor of child tuberculosis.

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