FACTORS ASSOCIATED WITH ACCEPTANCE OF STOOL-XPERT® MTB/RIF ULTRA FOR EARLY TUBERCULOSIS SCREENING AMONG CHILDREN IN PADANG, INDONESIA USING A HEALTH BELIEF MODEL

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ARTICLE HISTORY
Received: 19 April 2024 **Revised:** 3 May 2024 **Published:** 17 May 2024

ABSTRACT

The World Health Organization recommends stool-Xpert examination for tuberculosis (TB) diagnosis in children because they cannot produce sputum for TB examination. However, the acceptance rate is still low. This study aimed to evaluate factors associated with the acceptance of stool-Xpert for TB screening based on the health belief model. A cross-sectional study was done in six community health centers and two hospitals in Padang Municipality, Indonesia between September 2023 to January 2024. The study recruited 51 and 46 pediatric patients from the community health centers and the hospitals, respectively. Sixty-seven stool specimens were collected and tested for tuberculosis infection. Parents were interviewed. Perceived susceptibility included socio-demographic status and perceived TB signs and symptoms. Perceived severity included suspected TB from screening results. Perceived benefit included history of BCG vaccination. In-depth interview was done to identified perceived barriers and cue to action. Fisher's exact test and Chi-square test were used for data analysis. The study reported 69% of acceptance rate. Higher family' household income, history of BCG vaccination, and evidence of suggestive TB could increase acceptance of stool-Xpert. Cue to action are TB signs and symptoms and advices from health worker. Perceived barriers included low susceptibility to TB and inconvenience.

Keywords: Acceptance, Tuberculosis, Screening, Stool-Xpert, Children

CITATION INFORMATION: Pelawi, C. A., Chotipanvithayakul, R., Yani, F. F., & Chongsuvivatwong, V. (2024). Factors Associated with Acceptance of Stool-Xpert® Mtb/Rif Ultra for Early Tuberculosis Screening among Children in Padang, Indonesia Using a Health Belief Model. *Procedia of Multidisciplinary Research, 2*(5), 24.

INTRODUCTION

Worldwide, Indonesia sits as the second rank country with the highest number of TB incidents. In 2022, the Global Tuberculosis Report (World Health Organization, 2023) estimated there was 1.060.000 TB cases in Indonesia, with only 724.309 cases reported. Children (aged <15 years) accounted for approximately 15.3% of cases, higher than findings in 2021 (9.7%) and second-highest group (after 45-54 years group; 16.5%) (Kemenkes, 2023).

In Indonesia, child TB detection program is available in all levels of health services, starting from the community health center as primary level health service. However, child TB control and prevention of the National Tuberculosis Program (NTP) in Indonesia face poor performance of early screening and diagnostic equipment in community health center which leads to high morbidity and high mortality of TB among children (UNICEF Indonesia, 2022). Partly, it is still underutilized for child TB program since children unable to expectorate sputum used as the main specimen for TB testing. Sputum induction and gastric aspiration can be done to obtain specimen from children; however, both are invasive which become stressful for children and parents, moreover it cannot be done in low-resources setting. Other available screening methods such as symptoms screening and TST, cannot differentiate TB infection and disease which leads to high number of false positive and risk of putting children under unnecessary treatment. Thus, suspected children need to be referred to higher-level healthcare, go through further clinical assessment, and do invasive method of sample collection procedure such as sputum induction and gastric aspiration (Gous et al., 2015). This referral system is time-consuming and costly, which leads to delayed early TB diagnosis and increasing risk of developing active or severe TB in children (Cattamanchi et al., 2015).

Therefore, in 2020, WHO started to recommends stool-Xpert testing as initial TB diagnostic among children with signs and symptoms of TB to fill the gap of child TB program (World Health Organization, 2020). Studies have shown the possibility of using stool-Xpert in primary level of health service with non-invasive, simple, and cheap procedure to make it able to routinely run in lower-level laboratory with Xpert machine and none additional equipment (Chipinduro et al., 2017; de Haas et al., 2021; Marcy et al., 2016). The study aimed to examine factors associated with acceptance of stool-Xpert based on the health belief model.

LITERATURE REVIEWS

Childhood tuberculosis

Tuberculosis (TB) is an old disease which affected humans for thousands years (Hershkovitz et al., 2015). A global modelling estimated that about a quarter of the world's population had been infected with *Mycobacterium tuberculosis* or *M. tuberculosis* (Houben & Dodd, 2016). The bacteria infection spreads within the air through routine inhalation and exhalation, coughing or sneezing (Adigun & Singh, 2023; Dinkele et al., 2021; Patterson et al., 2021). *M. tuberculosis* mostly infects the lungs (pulmonary TB), but also can infects other sites in the body (extrapulmonary TB). TB is high prevalent in densely population area with poor application of clean and healthy living behavior (Noviyani et al., 2021).

Childhood tuberculosis, also known as pediatric tuberculosis, is TB cases among children and young adolescent aged under 15 years (World Health Organization, 2022). The greatest number of childhood TB cases are found in children under-5 and young adolescents >10 years. Even nearly 50% young children under-5 are likely to have significantly higher TB mortality rates than older children. It is because they face a higher risk of getting severe-forms of TB with higher rate of mortality and morbidity such as TB meningitis and miliary TB (Chiang et al., 2014; Daniel et al., 2019).

Screening methods for childhood tuberculosis

Several procedures are standardized to screen TB among general and high-risk populations (not including people living with HIV). Currently, WHO suggested to use symptoms screening,

chest X-ray (CXR), and rapid molecular test. CXR is the most recommended screening procedure, followed by rapid molecular test, screening for any TB symptom, and screening for any cough or cough lasting 2 weeks or longer (World Health Organization, 2022).

CXR provide a high sensitivity and specificity with 84% and 91%. However, CXR alone may overdiagnosis the TB diseases since it is sensitive to any lung abnormalities. The CXR findings among younger and older children also will be differed due to the disease presentation. Moreover, in younger children, the image may be subtle and the diagnosis may be hard to decide (Vonasek et al., 2021).

Symptoms screening is a standard required in children with close contact to bacteriologically TB confirmed. Since 2011, WHO recommended cough, fever, and weight loss as symptoms screened for TB disease. The sensitivity and specificity of this technique are estimated to be 89% and 69%. Symptom screening is highly acceptable since it can be repeated without invasive approach when necessary. However, this technique alone will overdiagnosis about 30% of children and leads to unnecessary TB treatment, it is way higher than false-positive cases in adults (Triasih et al., 2015; World Health Organization, 2022).

Besides those procedures above, there are tuberculin skin tests and interferon-g release assays (IGRA) to support TB detection in children. The disadvantage of TST and IGRA are that the tests cannot differentiate TB infection from TB disease, cannot predict the developing risk of TB disease in TB infected children, and the probability of false-negative or false-positive results after non-tuberculosis mycobacteria infection (Jones et al., 2020; World Health Organization, 2021).

Stool-Xpert for childhood tuberculosis

Closing the diagnostic gap, in 2020, WHO recommends stool-Xpert as primary diagnostic test for TB in children with presumptive TB (World Health Organization, 2020). *MTBC* will recoverable in stool samples since swallowed sputum will also pass through the intestines. In particular, stool is easy to obtain from infants and young children who are unable to produce sputum (LaCourse et al., 2018; Walters et al., 2017).

The evidence showed that induce or expectorated sputum and gastric aspirates provide the highest detection yield. However, stool specimens can rapidly give similar diagnostic accuracy and advantage by being non-invasive. This make stool-Xpert may have high acceptability among caregivers in the lower levels of healthcare system with GeneXpert MTB/RIF machine available (World Health Organization, 2022).

The health belief model

The acceptance of stool-Xpert can be explained with the health belief model (HBM) which developed from psychological and behavioral theory. The HBM was applied to understand the factors of participating in stool-Xpert and suggests that belief in a personal threat along with belief in the effectiveness of stool-Xpert will predict the likelihood of the acceptance.

We proposed the health belief model of stool-Xpert acceptance as shown in Figure 1. Socio-economic and demographic data were factors indirectly affecting stool-Xpert acceptance. Perceived susceptibility, the perception of vulnerability to TB, included household contact. Perceived severity included medical consequences due to severe signs and symptoms and result of TB screening such as tuberculin skin test (TST) and chest X-ray. Perceived benefits included history of BCG and access to pediatrician. Perceived barriers included condition where children have no signs and symptoms, inconvenience stool collection and delivery method, and time-consuming process (Gebremariam et al., 2021; Li et al., 2015; Nackers et al., 2012). A cue is necessary for attracting engagement in health behaviors. Cues to action can be health promotion and education with counseling, print material, or social media to incite the compliance of all TB screening, diagnosis, and treatment process (Tola et al., 2017).

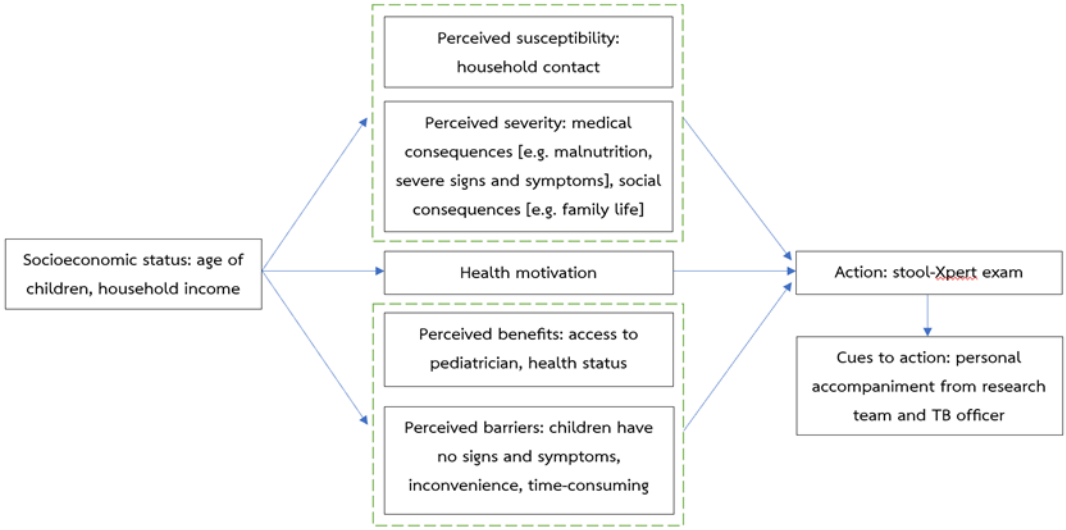

Figure 1 The proposed health belief model for stool-Xpert screening for childhood tuberculosis

RESEARCH METHODOLOGY

Study design and setting of the study

This study used a screening cross-sectional study conducted eight health services in Padang Municipality, Indonesia, between September 2023 to January 2024. These health facilities consisted one provincial referral hospital, one regional hospital, and six community health centers.

Study population: children under 15 years of age

a) For children in community health center, the children investigated from index cases with bacteriologically confirmed pulmonary TB and had household contact with children at least 3 months before their TB treatment started.

b) For children administered to hospital, the children admitted to hospital with different level of signs and symptoms of TB, several of them may have clear history of TB contact or even unknown.

Stool collection

We requested stool specimen from all children for research purposes and additional TB screening. Stool collection took place at home except for inpatients from hospital. We instructed the parents and children (if possible) to empty the bladder to avoid mixing urine with the stool sample. Put some clean plastic sheeting on the spot where the stool will be dropped to ensure the collection of a clean sample from contamination with soil, detergent, disinfectant, or other bacteria from the toilet. In children who use diaper, either collect the stool directly from the diaper as soon as the defecation process or taking stool from the upside of the diaper (assuming the stool is not contaminated with urine). The stool specimen can be filled to the container with spoon provided. Only a small amount of stool required (8 gram or thumbnail size). The container will be placed in sealable plastic bag. The stool specimen will be sent back to health services or picked up by health worker as soon as possible or stored in house in cool place or place with indirect sunlight. Freezing the specimen is prohibited.

Stool processing and analysis

Sample processing and testing was performed with Xpert MTB/RIF Ultra machine. The stool processing will adopted the simple one-step (SOS) method (World Health Organization, 2020). The stool specimen will be transferred into liquid sample reagent bottle (liquid SR bottle; which already available in Xpert MTB/Ultra machine packages). The bottle will be shaken vigorously for 30 seconds and then incubated for 10 minutes in room temperature; this step is repeated once. This process will form solid particles, assumed that this allows bacteria of TB float to the

top of liquid SR. As much as 2 ml of this liquid solution will be transferred from the bottle to Xpert MTB/RIF Ultra cartridge. The cartridge is then inserted to the Xpert machine. The Xpert machine will run molecular test automatically for 2 hours. The existence of TB bacteria will show up in monitor connected to the machine.

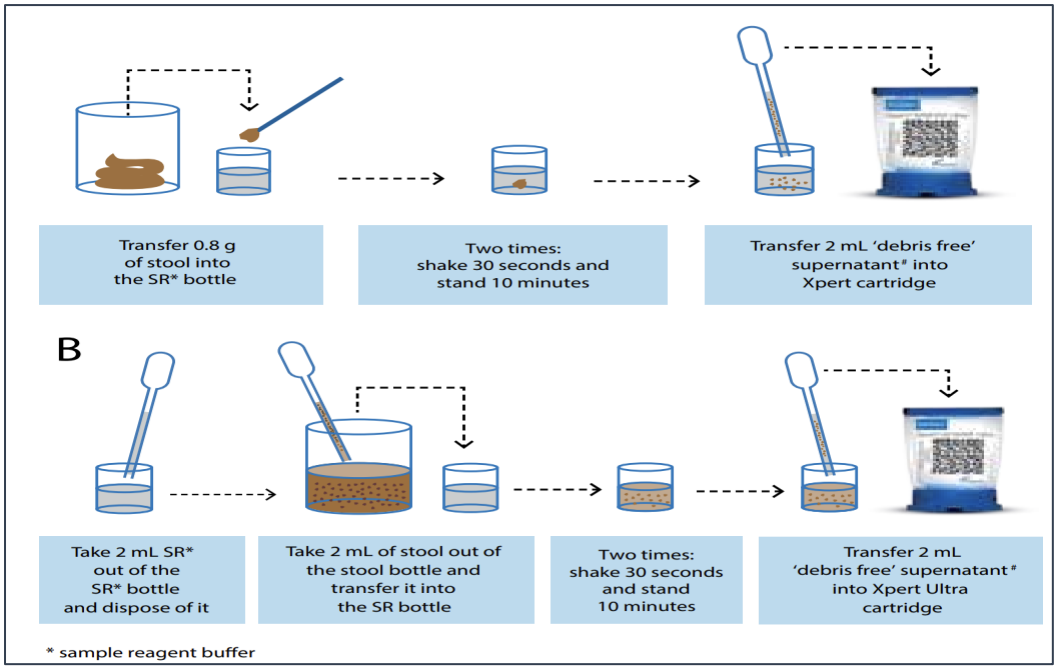

Figure 2 The stool procedures Source: (World Health Organization, 2020)

Data management and analysis

Data were recorded with paper-based case report form and coded into Excel at the end of each examination. The data recorded will be checked for completeness, accuracy, and consistency before participants leave the health services by rotating check of all research team involved in data collection. We used chi-square and Fisher's exact test to find the association among each factor and acceptance of stool-Xpert. All analysis were performed with R version 4.2.3 and the epicalc package.

Ethics

This research was approved by the Health Research Ethics Committee of the M. Djamil General Hospital, Padang, Indonesia (LB.02.02/5.7/444/2023) and Faculty of Medicine, Prince of Songkla University, Thailand (REC.66-295-18-1).

RESEARCH RESULTS

We recruited a total of 97 pediatric patients; however, we could obtain only 67 stool specimens resulting in 69% acceptance rate of stool-Xpert investigation. Table 1 compares family's socio-demographic information between children whose parents did not accept and accept stool-Xpert investigation. There are no differences in demographic factors. However, household income showed statistically significant association. Family with high income group had 2.1 times higher acceptance rate than low to middle income group.

Table 1 Association between socio-demographic factors and acceptance of stool-Xpert (N=97)

Socio-demographic factors	Stool-Xpert acceptance		P value
	No (n=30) n (%)	Yes (n=67) n (%)	
Age group (years old)			0.544
0-4	9 (30.0)	27 (40.3)	
5-12	14 (46.7)	24 (35.8)	
13-15	7 (23.3)	16 (23.9)	
Sex			0.532
Male	12 (40.0)	33 (49.3)	
Female	18 (60.0)	34 (50.7)	
Ethnicity			0.473
Minangkabau	23 (76.7)	57 (85.1)	
Other minorities	7 (23.3)	10 (14.9)	
Current education			0.877
Too young for education	13 (43.3)	32 (47.8)	
Kindergarten-primary school	10 (33.3)	19 (28.4)	
High school	7 (23.3)	16 (23.9)	
Average household income (IDR*/ month)			0.021
Low-to-middle	25 (83.3)	38 (56.7)	
High	5 (16.7)	29)43.3)	

Note: Indonesian Rupiah (1 USD = IDR 15,594)

Table 2 compared association between TB susceptibility and acceptance of stool-Xpert examination. Only parents of children who ever got BCG vaccinated had statistically higher acceptance to participate in stool-Xpert. Overcrowded house and specific behavior in household such as having air conditioner (AC) and someone smoking at home may determine the stool-Xpert acceptance, but the association is not statistically significant.

Table 2 Association between TB susceptibility at household level and acceptance of stool-Xpert (N=97)

TB susceptibility	Stool-Xpert acceptance		P value
	No (n=30) n (%)	Yes (n=67) n (%)	
Initial TB investigation provider			0.447
Hospital	12 (40.0)	34 (50.7)	
Community health center	18 (60.0)	33 (40.3)	
Source of TB contact			0.447
Household	18 (60.0)	33 (49.3)	
Unknown	12 (40.0)	34 (50.7)	
History of BCG vaccination	20 (66.7)	59 (88.1)	0.026
Number of household member (persons)			0.243
< 4	27 (90.0)	52 (77.6)	
5-8	3 (10.0)	15 (22.4)	
Sharing bedroom with TB patients	6 (20.0)	16 (23.9)	0.873
Having air conditioner in the room	5 (16.7)	21 (31.3)	0.208
Someone smoking at home	24 (80.0)	45 (67.2)	0.295

Table 3 examined health care services factors and acceptance of stool-Xpert. Positive TB signs and symptoms assessed by healthcare providers and suggestive of TB by chest x-ray had higher acceptance rate. In contrast, positive result of sputum-Xpert group had lower acceptance rate for further stool-Xpert examination.

Table 3 Association between healthcare services factors and acceptance of stool-Xpert

Healthcare service factors	Stool-Xpert acceptance		P value
	No (n=30) n (%)	Yes (n=67) n (%)	
Signs and symptoms positive	14 (46.7)	47 (70.1)	0.047
Tuberculin skin test positive	9 (60.0)	25 (49.0)	0.650
Chest X-ray positive	8 (47.1)	33 (76.7)	0.055
Sputum-Xpert positive	3 (75.0)	3 (13.0)	0.025

Last but not least, Table 4 shows having no signs and symptoms perceived by parents was the most common reasons for parents to withdrawn from stool-Xpert examination. Other reasons were constipation, disagreement between parents, inconvenience to collect the stool specimen such as having bad odor or difficult to refer the specimen to health centers. The only reason for health providers not to do stool-Xpert test was long waiting time to receive fresh specimen from parents. Moreover, two patients died of TB before the appointment date of stool collection.

Table 4 Reasons for not performing stool-Xpert test (n=28)

Reason of withdrawal of stool-Xpert test	n (%)
Parents perspective	
No signs and symptoms perceived by parents	11 (36.7)
Children had constipation	6 (20.0)
Disagreement between parents	5 (16.7)
Inconvenience of the procedure and delivery	5 (16.7)
Health provider perspective	
Long waiting time of the stool specimen from patients	1 (3.3)

DISCUSSION & CONCLUSION

The acceptance rate of stool-Xpert was 69%. Higher family' household income, history of BCG vaccination, and evidence of suggestive TB from assessment of signs and symptoms and chest x-ray had higher acceptance of stool-Xpert. Lower acceptance rate was found among parents perceived no TB signs and symptoms among their children, difficulties in stool-Xpert procedure, and positive result of sputum-Xpert.

This is the first study to use health belief model on acceptance of stool-Xpert examination. We could identify household income and TB signs and symptoms as significant perceived susceptibility. Perceived severity included suspected TB result from chest X-ray and perceived benefit was history of BCG.

The result of this study proves that average monthly household income is positively related to the increasing acceptance to stool-Xpert. Thus, the result gives a hint that higher income pursued self-efficacy or readiness in getting further TB examination and treatment for the family. This result was in line with study in Ethiopia where financial support and commitment from the family will increase the adherence of TB treatment (Gebremariam et al., 2021). The evidence of signs and symptoms, which supported by the result of chest X-ray, also has a statistically significant influence on stool-Xpert acceptance among parents with TB presumptive children with and without TB household contact. The same study revealed that

perceived susceptibility and perceived severity, knowing the TB risk such as household contact and signs and symptoms have positive impact to the acceptance of stool-Xpert (Li et al., 2015). No TB signs and symptoms perceived by parents, disagreement between parents, and inconvenience to collect and deliver stool specimen were identified as perceived barriers. Cue to action can be advices from health providers to do stool-Xpert after negative result of sputum-Xpert or not done sputum-Xpert since most children could not expectorate sputum specimen with certain quality for TB examination, while children have TB signs and symptoms. Knowing there are five different reasons of stool-Xpert refusal in Table 4, every family have different method to approach (Parwati et al., 2021). To support the decision making to participate in stool-Xpert, health worker [e.g. pediatrician and TB officer] will explaining the benefits of the stool-Xpert and volunteers will provide personal accompaniment during all TB testing and treatment process.

Based on this study, on one hand we could increase perceived susceptibility and severity, and perceived benefits. On the other hand, we could reduce perceived barriers. Thus, health providers can increase stool-Xpert acceptance following these recommendations:

a) Give knowledge to both parents that childhood tuberculosis had nonspecific signs and symptoms, or mimic to other respiratory disease (Zingman et al., n.d.). Thus, without signs and symptoms does not warrant TB free. Ensure that parents and primary caretakers receive the same information to reduce risk of disagreement.

b) Explain the results of all TB investigations including assessment of signs and symptoms, tuberculin test, sputum exam, chest x-ray, sputum-Xpert to reveal susceptibility and severity of TB

c) Explain how stool-Xpert would be beneficial to a child with a risk of tuberculosis

d) Provide stool softener before collecting the specimen to reduce risk of constipation

e) Ask a health volunteer to collect specimen from parents

Research and innovation to simplify stool specimen collection procedure should be further conducted.

This study recruited all pediatric patients from both community health centers and the hospitals in that area suggesting high internal validity. We had adequate sample size to test our main hypothesis. Using health belief model can suggest study implication. Our study was limited by a preliminary analysis using univariate analysis. Thus, we plan to do multivariate analysis and structure equation modelling in the future.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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