Stool-Xpert® MTB/RIF Ultra for Tuberculosis Screening and Diagnosis in Children at Primary and Higher-level Healthcare Centers in Padang Municipality, Indonesia

Chairunnisa Athena Pelawi

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Epidemiology (International Program)
Prince of Songkla University
2024

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ABSTRACT

Background

In 2023, Indonesia notified 137,969 childhood TB cases or 16% of total 821,200 TB cases in Indonesia. The NTP found 79,566 children aged <5 years and 58,403 children aged 5-14 years with TB disease. It means there were 50 per 10,000 children aged <5 years and 21 per 10,000 children aged 5-14 years living with TB disease. However, these numbers indicate under-TB detection since there were 335,691 cases estimated to be unreported during 2022 in Indonesia.

In Indonesia, childhood TB detection program is available in all levels of health services, starting from the community health center as primary level health service. However, childhood 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.

Partly, it is still underutilized for childhood 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. This referral system is time-consuming and costly, which leads to delayed TB diagnosis and increasing risk of developing active or severe TB in children.

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 childhood TB program. Furthermore, 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. The study aimed to estimate the properties and feasibility of stool-Xpert MTB/RIF Ultra for childhood TB screening in primary healthcare and childhood TB diagnosis in higher-level healthcare centers.

Methods

The study was divided into community screening program with cross-sectional study design and key informant interviews conducted eight health services in Padang Municipality, Indonesia, between September 2023 to April 2024. These health facilities consisted one provincial referral hospital, one regional hospital, and six primary healthcare. The stool-Xpert MTB/RIF Ultra screening was done among two groups of children aged ≤15 years: children in primary healthcare who investigated from index cases with bacteriologically confirmed pulmonary TB and had household contact with children at least 3 months before the start of current TB treatment, and children referred to hospital with different level of signs and symptoms of TB, several of them may have clear history of TB contact or even unknown.

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. Descriptive analyses were used for participant characteristics. We used chi-square and Fisher's exact test to analyzed information related to socio-demographic characteristics, risk of TB identification, investigation of index TB cases, result of clinical assessment, tuberculosis screening and diagnosis, and final diagnosis. Prevalence, sensitivity,

specificity, PPV, and NPV with 95% CI will be applied as statistical measurements for performance of stool-Xpert exam. Concordance and discordance were showed to explained the agreement among stool-Xpert with other screening and diagnostic tests. All analysis were performed with R version 4.2.3 with 'epicalc', 'dplyr', 'epiR', and 'epitools' packages.

The key informant interviews were done among health workers and primary caretakers from Puskesmas as primary healthcare and hospitals as higher-level healthcare. The recordings from the interviews were transcribe verbatim and translated into English. A quality check was done on all transcripts before the coding and analysis. Thematic analysis was conducted with ATLAST.ti 24. The codebook was developed and applied to a specimen of transcript; cross-checked codes; resolved discrepancies; and refined the codes. This process was repeated until the codebook adequately captured the interview content. The final codebook was applied to all transcripts. Trends and patterns were discussed by and some of the themes were refined. Following the process, all 40 interviews started to reveal similar information therefore saturation was reached.

Results

There were 125 children who were met the eligible criteria and their primary caretakers approached to collect stool specimen. All of primary caretakers from 125 child patients showed interest but 2 child patients from hospital passed away before stool collection procedure done due to critical illness, 31 child patients not adhere due to several reasons and 6 child patients lost to follow-up. Therefore, a total of 86 child patients including 42 children with TB household contact from Puskesmas and 44 children with presumptive TB from hospitals enrolled in the study.

In total, 54 children (43.2% of 125) were diagnosed with TB, of whom, 8 (15%) had bacteriologically TB whether with sputum-AFB, sputum-Xpert, or culture with any specimen. A valid stool-Xpert test was obtained for 86/125 children with 15% (95% CI: 5.7-29.8) of sensitivity and 100% (95% CI: 92.2-100.0) specificity against to final diagnosis made by pediatrician with PPV and NPV were 100% (95% CI: 54.1-100.0) and 57.5% (95% CI: 54.3-60.1). The sensitivity was increased to 18.2% (95%

CI: 6.9-35.5) among children with presumptive TB and various severity of disease with PPV and NPV were 100% (95% CI: 54.1-100.0) and 51.8% (95% CI: 47.8-55.8).

Stool-Xpert results showed low agreement with final TB diagnosis made by pediatrician while it showed high agreement with another laboratory exam such as sputum-Xpert and sputum-AFB. It also highly agreed with the result of culture with several specimen such as sputum, blood, and LCS. Unfortunately, stool-Xpert also showed low agreement with other TB screening method of signs and symptoms screening, TST, and CXR.

In the other hand, most of the informants from key interviews agreed that stool-Xpert have chance to be implement. This chance came after the benefits of stool is out such as applicable for younger children or asymptomatic children who cannot produce sputum and no need referral process. Others still unsure about the referral specimen mechanism from Puskesmas to hospitals.

Stool collection found to be more acceptable for primary caretakers since it was non-invasive than TST that commonly used for early screening. However, implementation of stool-Xpert is still debatable since there is no standardized guideline provided from the Ministry of Health, specimen cannot be assessed at Puskesmas to limited biocontainment equipment. It was also notified by the primary caretakers.

Therefore, several recommendations come from primary caretakers and health workers if stool-Xpert will be implemented further in Puskesmas and hospital: need to be done alongside with other screening and diagnosis method, comprehensive training for all health workers related with TB , clear instructions or guideline, health promotion related with TB and stool-Xpert, availability of the tools or equipment, expansion on health workers number, and children aged under-5 years.

Conclusion

The performance of stool-Xpert MTB/RIF Ultra for TB screening was not comparable with other screening methods or standard care. However, the result of stool-Xpert specimen showed an agreement with sputum-Xpert for TB diagnosis. In general, the main barriers of further implementation of stool-Xpert in Padang Municipality is limited resources available in each healthcare. Nonetheless, primary caretakers and health workers who done stool collection and stool exam believe that

stool specimen can be used as an alternative for respiratory specimen and was shown to be non-invasive test for children who cannot produce sputum.

Keywords: Tuberculosis, screening, diagnosis, stool-Xpert, children, household contact, presumptive tuberculosis

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LIST OF ABBREVIATIONS

AC	: Air conditioner
AFB	: Acid-fast bacillus
AP	: Anteroposterior
ART	: Antiretroviral therapy
BCG	: Bacille Calmette-Guerin
BMI	: Body mass index
CI	: Contact investigation (in TB household contact algorithm)
CI	: Confidence interval (in statistical analysis)
CFR	: Case fatality rate
CRF	: Case report form
CXR	: Chest X-ray
DALY	: Disability-adjusted life years
DS-TB	: Drug sensitive tuberculosis
EPTB	: Extrapulmonary tuberculosis
FDC	: Fixed-dose combination
FN	: False-negative
GA	: Gastric aspiration
HIV	: Human immunodeficiency virus
IGRA	: Interferon gamma release assay
LCS	: Liquor cerebrospialis
LJ	: Lowenstein-Jensen
LR+	: Likelihood ratio positive
LR-	: Likelihood ratio negative
LTBI	: Latent tuberculosis infection
MDR-TB	: Multidrug-resistance tuberculosis
MGIT	: Mycobacteria Growth Indicator Tube
mWRDs	: molecular WHO-recommended rapid diagnostic
MTB	: *Mycobacterium tuberculosis, M. tuberculosis*
nasoGA	: nasogastric aspiration
NPV	: Negative predictive value

NTP	: National Tuberculosis Program
OSF	: Optimized Sucrose Floatation
PPV	: Positive predictive value
PTB	: Pulmonary TB
Puskesmas	: *Pusat Kesehatan Masyarakat* (primary healthcare)
RR-TB	: Rifampicin-resistance tuberculosis
Sn	: Sensitivity
Sp	: Specificity
SOS	: Simple One-step
SPK	: Stool Processing Kit
SR	: Sample reagent
TB	: Tuberculosis
TPT	: Tuberculosis preventive treatment
TST	: Tuberculin skin test
Xpert MTB/RIF	: Automated rapid molecular assay test for *Mycobacterium tuberculosis* complex detection
Xpert MTB/RIF Ultra	: Automated rapid molecular assay test for *Mycobacterium tuberculosis* complex and rifampicin resistance detection which had faster time to results, is more sensitive among patients living with HIV and people with pauci-bacillary disease
WHO	: World Health Organization

CHAPTER 1
INTRODUCTION

1. Background

1.1 Childhood tuberculosis (TB)

Tuberculosis (TB) is a contagious and airborne disease caused by *Mycobacterium tuberculosis*.[1] People who exposed to *M. tuberculosis* have a chance to be infected, and develop active TB disease with several signs and symptoms such as cough, fever, weight loss, and malaise. Meanwhile, in children, TB often have nonspecific and broad clinical symptoms which similar to another childhood diseases. Children with asymptomatic TB or latent TB infection (LTBI) with several factors such as age and comorbidities increase the risk of infection progression to active TB disease.

Children aged <5 years is most often infected after close-contact to bacteriologically TB confirmed patient under the same household. Meanwhile, in school-age children and young adolescent (5-14 years), possible TB transmission outside household also can occur.[2–5]

Recently, TB is a top-ten the leading cause of death from infectious diseases for children. A mathematical modelling estimated 96% of childhood TB deaths occur in children who are not receiving TB preventive treatment (TPT).[6,7] In fact, a systematic review in 2017 also found that the case fatality rate (CFR) of children who consumed TPT can be as low as 0.9% (95 CI 0.5-1.6) compared to 21.9% (95% CI 18-26.4) of children who are not consumed TPT.[8]

1.2 Current practice of childhood tuberculosis control and prevention program

World Health Organization (WHO) targeted 3.5 million children with drug-sensitive (DS) TB and 115,000 children with multidrug-resistant (MDR) or rifampicin-resistant (RR) TB will be treated in 2018 to 2022. Global Tuberculosis Report 2023 stated 2.5 million children with DS TB and 21,600 children with MDR/RR-TB treated from 2018 to 2022, only 71% and 19% of the target achieved.

While in all ages group, 84% (34 million of 40 million) and 55% (825,000 of 1.5 million) of the target achieved.[9]

Same situation goes to household contact investigation and TB preventive treatment (TPT) program between 2018 to 2022. From 4 million household contacts aged <5 years targeted to be treated with TPT, only 2.2 million (55%) achieved. Underperformed TPT program also happened among household contacts aged ≥5 years, from 20 million targeted, only 2.0 million (10%) have been treated with TPT. While in all ages group, 52% from 30 million people targeted was achieved.[9]

Indonesia is one of high burden countries which implement TB decentralization program. It means TB care are decentralize from the primary healthcare or known as *Pusat Kesehatan Masyarakat* (Puskesmas) in district level. The National TB Program (NTP) in this level is working on TB services, training and mentoring for healthcare workers and volunteers, improved screening for comorbidities and high-risk population, and introduction and optimization TB testing under the supervision of Health Office of each region.[10]

In Indonesia, childhood TB detection program is supported by contact investigation (CI) program in Puskesmas. Based on Indonesian Childhood TB Management Guideline 2016, children and young adolescent aged 0-14 years is the priority group of CI program.[11] However, there are several challenges and lack faced by the childhood TB control and prevention program of the NTP in Indonesia.

1.3 Challenges and lack of childhood tuberculosis control and prevention program

In 2023, Indonesia notified 137,969 childhood TB cases or 16% of total 821,200 TB cases in Indonesia.[12] The NTP found 79,566 children aged <5 years and 58,403 children aged 5-14 years with TB disease. It means there were 50 per 10,000 children aged <5 years and 21 per 10,000 children aged 5-14 years living with TB disease. However, these numbers indicate under-TB detection since there were 335,691 cases estimated to be unreported during 2022 in Indonesia.

Within 2023, 77% of the estimated TB cases of general population in Indonesia were notified while in Sumatera Barat Province, only 61% TB of the estimated cases found. It is 29% lower than the NTP target for TB detection rate in each province made Sumatera Barat Province ranked 25 from 38 provinces in TB case

finding program. There is a huge possibility that childhood TB detection program also affected by this situation. TB in children presents a greater likelihood of being underdiagnosed and undertreated as high as 69% among those aged 0-4 years and 40% among those aged 5-14 years, in contrast to the 35% detection gap observed in other age groups.[13]

Several factors can affect the childhood TB detection program. One of these factors is the poor performance of existing diagnostic tools in Puskesmas. In childhood TB, children usually have pauci-bacillary disease. This cause children have TB negative smear result and positive *M. tuberculosis* culture results from respiratory specimens, which contributes to the low microbiological confirmation of TB.[14,15]

In order to increase the TB detection rate, WHO recommends chest X-ray (CXR), molecular WHO-recommended rapid diagnostic (mWRDs) with Xpert MTB/RIF assay or Xpert MTB/RIF Ultra, screening for any symptom, and screening for any cough or cough lasting for 2 weeks or longer as screening methods in TB.[16] Children suspected or exposed to TB will be treated based on combination of history of TB contact, clinical examination including assessing the possible comorbidities such as HIV-infection, and radiological features with CXR.

The problem is these methods become impractical since TB officer in Puskesmas are not allowed to establish clinical TB diagnosis. There are no authorized and trained health workers such as pediatrician and radiologist to establish final diagnosis of childhood TB based on CXR result in Puskesmas. Besides that, CXR equipment also not provided in lower-level healthcare such as Puskesmas in Indonesia.[17]

The NTP of Indonesia also provided Xpert MTB/RIF machine to provide semi-quantitative result for TB diagnosis in several Puskesmas and hospital. However, since 2023, the NTP and the Health Office of Sumatera Barat Province progressively switching Xpert MTB/RIF program to Xpert MTB/RIF Ultra which reported to have higher sensitivity and specificity in TB diagnosis.

Xpert MTB/RIF Ultra is commonly used to do rapid molecular diagnosis with sputum specimen for TB diagnosis among high-risk population. However, Xpert MTB/RIF Ultra for childhood TB program is still underutilized due the difficulties of obtaining sputum and other respiratory samples in children, especially in young

children aged <5 years. In this case, health workers need to use advance yet invasive approach such as nasogastric aspiration and sputum induction to collect sample for child, which also are not available in Puskesmas.[18]

In the other side, symptoms screening is the standard requirement yet highly feasible method for childhood TB detection with high-risk of TB infection. This method is less invasive and can be repeated as often as necessary during the diagnosis and treatment process.[16] The downfall of symptoms screening is low specificity its provided leads to high number of false-positive and unnecessary treatment for children.[19]

In such limited resources setting, children need to be referred to the hospital or higher-level healthcare which time-consuming and resulting substantial financial costs.[20] Furthermore, TB detection in children was delayed and risk of developing active or severe TB is keep increasing during the untreated phase.

1.4 Potential solutions to improve childhood tuberculosis control and prevention program

In 2020, to close the gap in detection rate, WHO started to recommends stool-Xpert testing as initial TB diagnostic among children with signs and symptoms of pulmonary TB.[21,22] Studies report sensitivity of stool-Xpert MTB/RIF Ultra for childhood TB diagnosis is between 45.5 to 88.9% with specificity ranging from 83.7 to 94.7%.

Several studies have shown the possibility of using stool-Xpert MTB/RIF or Ultra in primary healthcare 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.[23–25] Considering the procedure and resources available, stool-Xpert has the potential to significantly impact of the number of non-invasive bacteriological confirmation of TB disease among children with household contacts in CI program of Puskesmas.

If Puskesmas prioritizing Xpert MTB/RIF Ultra with stool sample as screening method for children with household contacts as high-risk population, this method will reduce referral and reassessment of suspected childhood TB to hospital or higher-level of healthcare. Thus, the TB investigation procedure will be time-saving

and low-cost for both healthcare system and families which may increase the number of detection rate among children in primary healthcare and the NTP.

However, further evidence on the properties and feasibility of stool-Xpert MTB/RIF Ultra as screening method for children with household contacts as routine in CI of Puskesmas is needed. Therefore, we will include stool-Xpert MTB/RIF Ultra as one of screening method besides the reference standard in CI workflow of Puskesmas. We aimed to estimate the properties of stool-Xpert MTB/RIF Ultra as screening method among children with household contacts. Besides that, we also recruit children with presumptive TB in hospital to estimate the properties of stool-Xpert MTB/RIF Ultra as diagnostic method, and determine the feasibility of its implementation in Puskesmas as primary healthcare and higher-level healthcare.

2. Literature Review

2.1 Childhood tuberculosis

Tuberculosis (TB) is an old disease which affected humans for thousands years.[34] The bacteria infection spreads within the air through routine inhalation and exhalation, coughing or sneezing.[1,36,37] *Mycobacterium 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 (*Perilaku Hidup Bersih dan Sehat,* PHBS).[29]

A global modelling estimated that about a quarter of the world's population had been infected with *M. tuberculosis.*[30] The World Health Organization (WHO) has estimated that approximately 7.5 million children aged 0-14 years are annually infected with *M. tuberculosis*, with 1-1.2 million children advancing to active TB disease. Of those affected, more than half are under the age of 5. This lead childhood TB cases identical to 12% of TB burden worldwide.[13]

The greatest number of childhood TB cases are found in children aged <5 and young adolescents >10 years. While nearly 50% young children <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.[31,32] This lead childhood TB cases identical to 12% of TB burden worldwide.[13,33]

Nevertheless, TB in children presents a greater likelihood of being underdiagnosed and undertreated as high as 69% among those aged <5 years and 40% among those aged 5-14 years, in contrast to the 35% detection gap observed in other age groups.[13] Numerous factors can influence the effectiveness of childhood TB detection initiatives. Among these factors is children affected by TB typically have nonspecific signs and symptoms, and mimic to other disease such as pneumonia and meningitis.[34,35]

Several children have absence of cough or symptoms related to extrapulmonary TB (EPTB), caused them to cannot produce sputum to undergo microbiological confirmation unless they went to higher healthcare and do sputum induction which is invasive.[18,36,37] Although microbiological confirmation is considered optimal for pulmonary TB (PTB), the availability of TB microbiological exam facilities is often limited. As a result, most childhood TB diagnosis rely on clinical assessments, utilizing practical yet imperfect algorithms that consider the history of TB contact, and clinical examination such as HIV-infection and presenting signs and symptoms of child patients.[38]

2.2 Childhood tuberculosis management recommendation

In general, the childhood TB diagnosis is held based on concept below:[11]

a. Childhood TB patient bacteriologically confirmed, when children diagnosed with positive TB disease and confirmed under bacteriologically examination.
b. Childhood TB patient clinically diagnosed, when children not detected as positive TB disease under the bacteriologically examination. Therefore, the diagnosis as TB patient comes from doctor decision based on clinical assessment and TB patient is suggested to initiate the TB treatment.
c. Children with TB infection, when children have positive TST result or have history of close contact to infectious TB patient.
d. Children with suggestive TB CXR result

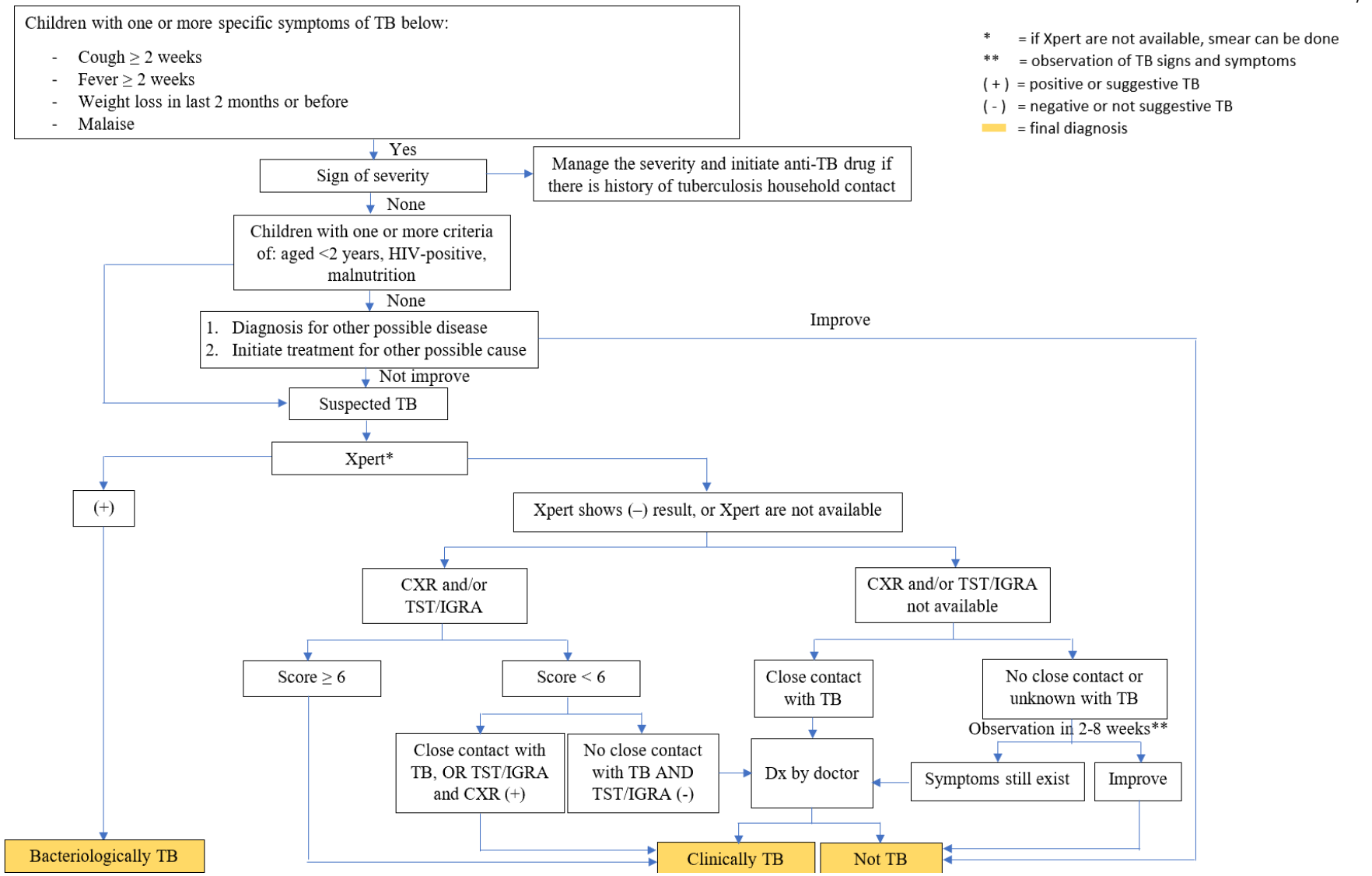

Figure 1. The national algorithm of childhood tuberculosis management of Indonesia[11]

Following the National Guideline of Childhood TB Management in Indonesia, there are several considerations in establish a final diagnosis of childhood TB as written below:[11]

1. If the microbiology examination (molecular or smear microscopy examination are accepted depends on the resources available in the healthcare) shows positive result, children will be diagnosed with TB and suggested to initiate anti-tuberculosis drug.
2. If the microbiology examination (molecular or smear microscopy) shows negative or respiratory specimen cannot be collected due to limited resources, health worker needs to do TST and CXR.

   I. If there is no facility or access to TST and CXR

   a. If asymptomatic children <5 years have history of close contact with infectious TB patient, children can be suggested to take TPT treatment.
   b. If asymptomatic children ≥5 years with history of close contact with infectious TB patient, health worker need to do further clinical observation in 2-8 weeks. If in the follow-up period children have sign and symptoms of TB, health worker will refer children to higher-level healthcare.
   c. If children have signs and symptoms of TB, health worker will refer children to higher-level healthcare.

   II. If TST or CXR equipment are provided, do scoring system

Scoring system is a childhood TB diagnosis method by combining history of close contact with infectious TB, existing sign and symptoms of TB, TST result, and CXR result to assess if children is likely or unlikely to have TB disease. The interpretation of scoring system is followed below:[11]

   a. If total score ≥6, children will be diagnosed with TB and suggested to take anti-TB drug.
   b. If total score <6 with positive TST result or there is history of close contact with infectious TB patients, children will be diagnosed with TB and suggested to take anti-TB drug.

c. If total score <6 with negative TST result or there is no close contact history, children will be observed for 2-8 weeks. If the symptoms are still existed, children must be referred to higher-level healthcare or hospital.

The childhood TB diagnosis workflow in Indonesia is prioritizing bacteriologically examination such as microscopy and molecular test to establish childhood TB diagnosis. Even though scoring system are still used in most of healthcare in Indonesia, scoring system is known to providing overdiagnosis TB, and are not suitable to differentiate TB infection and TB disease.[39]

However, if children are clinically diagnosed or have household contact but not bacteriologically confirmed, children must go under a regular observation for 2-months. If in the second month children does not show any clinical improvement, children need to be referred for further examination to prevent the risk of false-positive, underlying disease existing, drug susceptibility, or other problem with TB drug obedience.[11]

2.3 Childhood tuberculosis screening method

Several procedures are standardized to screen TB among general and high-risk populations. 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.[16]

CXR provide a high sensitivity and specificity with 84% and 91%.[19] 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.[40]

Rapid molecular test is not currently suggested for screening TB disease in children and young adolescent due to several considerations. In high-risk populations with non-HIV infection, the sensitivity and specificity of rapid molecular test for screening are estimated to be 69% and 99%. Despite the high specificity, the implication of this properties may be different for clinical interpretation for screening and diagnosis. People with positive result must be followed up by further clinical evaluation.[41]

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.[16,42]

Besides three 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.[43–45]

Based on WHO recommendation and national guidelines, the standard protocol of TB screening among household contact in Indonesia, including among children exposed, is following the steps below:[11,46–48]

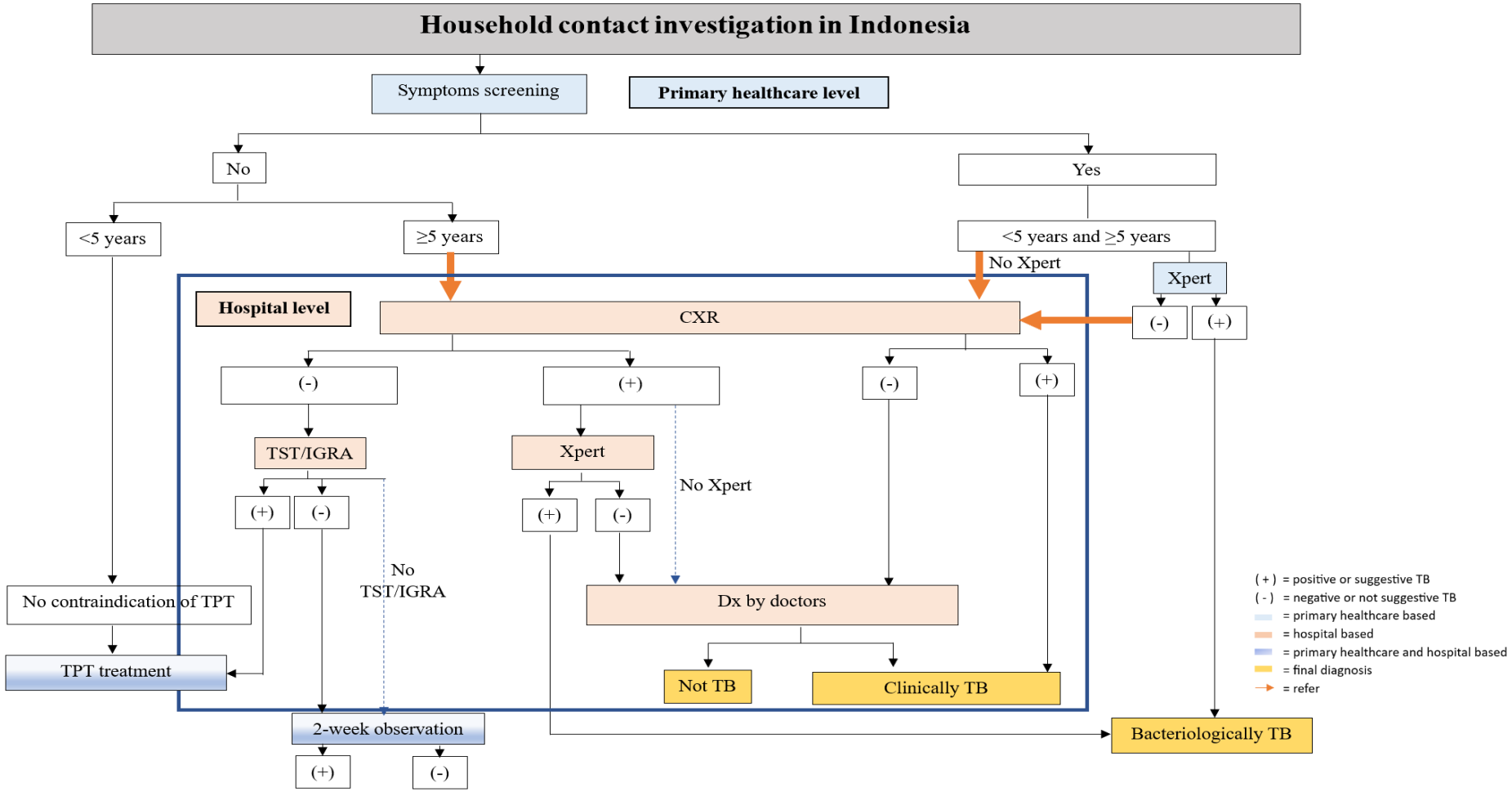

Figure 2. The national algorithm of screening among tuberculosis household contact

In children with TB household contact, there is an urgency to assess children for TB infection and criteria of initiating TPT. The algorithm above showed that each person with TB household contact should be screened for TB symptoms and/or undergo CXR, followed by appropriate diagnostic evaluation.

Asymptomatic children with household contact, and children with household contact and severe signs and symptoms should undergo CXR if available. However, in most settings of Indonesia, CXR are not available in Puskesmas or other lower healthcare level. Puskesmas will refer children into hospital and do further assessment under pediatrician supervision.

In Puskesmas with TST available, using TST to confirm TB infection in children is accepted. While in Puskesmas, rapid molecular test with sputum-Xpert available, children with household contact are among prioritized groups to be screened with Xpert. However, the result of CXR and sputum-Xpert result are not a specific requirement for initiating TPT for children <5 years. Children can be initiate the TPT if TB disease is ruled out based on negative symptom screening.[46]

2.4 Stool-Xpert for childhood tuberculosis

Childhood tuberculosis faced a struggle in low case detection rate since children have pauci-bacillary TB and do not excrete enough bacilli to be detected by available bacteriological tests; screening and diagnostic test available are lack of sensitivity; difficulties in collecting suitable sputum sample; and misdiagnosis due to overlap or no specific symptoms and signs of TB in children.[46]

Closing the diagnostic gap, in 2020, WHO recommends stool-Xpert as primary diagnostic test for TB in children with presumptive TB.[22] *M. tuberculosis* will recoverable in stool samples since swallowed sputum will also pass through the intestines.[49–51] In particular, stool is easy to obtain from infants and young children who are unable to produce sputum.[49,50]

Table 1. Comparison of diagnosis accuracy with Xpert MTB/RIF and Xpert MTB/RIF Ultra[45]

Specimen type (population)	Sensitivity (Sn)	Specificity (Sp)	Certainty of evidence
Xpert MTB/RIF			
Sputum	0.65	0.99	Moderate
Gastric aspirate	0.73	0.98	Very low (sn) to low (sp)
NPA	0.46	1.00	Moderate (sn) to high (sp)
Stool	0.61	0.98	Low (sn) to moderate (sp)
Stool (HIV-positive)	0.70	0.98	Low (sn) to high (sp)
Xpert MTB/RIF Ultra			
Sputum	0.73	0.97	Low (sn) to high (sp)
Gastric aspirate	0.64	0.95	Moderate
NPA	0.46	0.98	Very low (sn) to low (sp)
Stool	0.53	0.98	Moderate

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-level of healthcare system with Xpert MTB/RIF or Ultra machine available.[47]

Previous studies with stool-Xpert MTB/RIF in children indicated sensitivity of 53-78% among children with bacteriologically confirmed TB, while very poor sensitivity (9-11%) among clinically diagnosed TB.[23,25,50,52,53] While the sensitivity of stool-Xpert MTB/RIF Ultra for childhood TB diagnosis is between 45.5

to 88.9%. Variation of amount of stool sample used, processing methods, reference standards and populations may be affected the sensitivity.

Table 2. Comparison of sensitivity and specificity of Xpert MTB/RIF and Xpert MTB/RIF Ultra with stool specimen for childhood TB diagnosis

Study, year/country	Age (years), range, median [IQR]	Population	B+	B-	Reference standard	Stool-Xpert performance	
						Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Ainan et al. (2021)/ Tanzania[52]	NR, 2.17 [1.16-5.19]	Children with presumptive TB in 6 health facilities in Dar es Salaam N= 225/258	8 (3.6)	42 (18.7)	Xpert and/or solid culture on sputum or gastric aspiration	62.5 (25-92)	100 (98-100)
de Haas et al. (2021)/ Ethiopia[25]	NA	Children presenting with presumptive TB in selected health facilities, for whom routine nasoGA was requested upon clinical examination	9 (7.3)	-	Xpert and/or LJ culture and/or MGIT culture on nasoGA	78	-

LaCourse et al. (2018)/ Kenya[50]	0-12, 2 [1.1-4.8]	N= 123/147 HIV-positive children eligible for ART, hospitalized for acute illness in 4 hospitals	11 (7.5)	-	MGIT culture/ Xpert on sputum or GA	70 (35-93)	100 (97-100)
	0-12, 2 [1.1-4.8]	N= 147/165 HIV-positive children eligible for ART, hospitalized for acute illness in 4 hospitals	-	85 (52)	Clinical	9 (4-19)	100 (95-100)
Chipinduro et al. (2017)/ Zimbabwe[23]	5-16, 10.6 [8-13]	N= 165/165 Presumptive TB in 8 PHCs: TB symptoms or history of close contact	19 (8.7)	-	LJ culture/Xpert on induced sputum	68 (43-87)	98 (95-99)

		with TB patient					
	5-16, 10.6 [8-13]	N= 218/218 Presumptive TB in 8 PHCs: TB symptoms or history of close contact with TB patient	-	32	Clinical	53 (35-71)	NR
Marcy et al. (2016)/ Burkina Faso, Cambodia, Cameroon, Viet Nam[53]	0-13, 7.2 (4.1-7.2)	N= 32/218 HIV-positive children presenting with presumptive pulmonary TB in 8 tertiary or child hospitals	27 (10)	-	MGIT/LJ culture on GA, induced sputum, NGA, string sample	67 (46-83)	100 (98-100)
	0-13, 7.2 (4.1-7.2)	N= 272/272 HIV-positive children presenting	-	245 (90)	Clinical	11 (8-16)	96 (81-100)

	with presumptive pulmonary TB in 8 tertiary or child hospitals N= 272/272	

B+, bacteriologically confirmed TB. B-, clinically TB without bacteriological confirmation.

Nowadays, there are several methods in processing stool-Xpert developed such as Simple One-step (SOS), optimized sucrose floatation (OSF) and Stool Processing Kit (SPK) for Xpert MTB/RIF assay and Xpert MTB/RIF Ultra testing as written below.[21,54,55]

Table 3. Overview of the main technical aspects of the 3-centrifuge-free stool processing solutions

	SOS	OSF	SPK
Development stage	Completed	Design validation	Design transfer (prototype)
Additional supplies	Stool transfer supplies	Stool transfer supplies, scale, sample preparation tubes, 56% sucrose solution (Seather's solution)	Kit (including filter device, stool transfer supplies, SPB/buffer)
Steps	Estimate stool volume visually Mix with SR Let sediment Transfer supernatant into MTB/RIF machine	Weight stool Mix with 56% sucrose solution Let sediment Transfer supernatant, mix with SR Transfer into MTB/RIF machine cartridge	Measure stool Mix with SBP and SR Filter in MTB/RIF machine cartrigde
Preparation time (median, range)	23' (20-30')	56' (45-87)	38' (33'-55')

Preliminary data suggests that the SOS method is the easiest and cost-effective to implement in laboratories with limited resources.[24,47,49] Although the use of stool-Xpert MTB/RIF Ultra shows high sensitivity and specificity with high feasibility after a simple and non-invasive methods developed, stool-Xpert MTB/RIF Ultra is not become a routine childhood TB test neither for screening and diagnostic in most settings.

2.5 Contact investigation for childhood tuberculosis

2.5.1 Risk of tuberculosis disease after household contacts

In epidemiology, number of childhood TB cases is a representative of recent TB transmission among their community. It is because most of childhood TB cases get infected after close contact to infectious adult or adolescent as index case. It makes childhood TB become a sentinel event and serious public health issue.[56]

Close contact is person who frequently have contact with the index case. The index case is the TB case that expected as the source of TB infection among their contacts. A person or group who live together under the same household and share a common source of food is called as household contact. A meta-analysis found that children who were household contacts had four times higher chances of having infection to non-household contact children.[57]

Infants (children ≤ 12 months) with TB infection after TB household contacts will have 20-50% probability to develop TB disease rapidly within 1-year. While children aged <5 years will have 19% probability in 2-years after the infection. However, in older children, the probability of TB disease progression will be decreasing at 9% after 2-years of infection, respectively.[3,7]

Table 4. Prevalence of children developing TB disease after household contact

Study, year/country	Study design	Index age	Household contact age	Prev	Method
Triasih et al. (2015)/ Indonesia[58]	Cross sectional	≥18	<5	9%	TST, CXR
Bonnet et al. (2017)/ Uganda[59]	Cross sectional	≥18	<5	15.70%	TST, GX, culture
Egere et al. (2017)/ Gambia[60]	Cross sectional	-	<5	1.60%	TST, microscopy, GX
Azit et al. (2019)/ Malaysia[61]	Cross-sectional	-	<15	1.50%	TST, CXR, culture

Laghari et al. (2019)/ Pakistan[62]	Cross sectional	All ages	<15	13.40%	TST, microscopy, CXR
Schwoebel et al. (2020)/ Benin, Burkina Faso, Cameroon and Central African Republic[63]	Cross sectional	≥18	<15	2.80%	TST, CXR

Previous cross section studies show the prevalence of TB disease among children with household contacts are varying from 1.5 to 15.7% in several study settings.[58–63] The variation of estimated number of TB disease may explained by different TB screening and diagnosis methods, and inclusion and exclusion criteria of those studies. Most of the studies also showed high prevalence in TB infection or LTBI among children with household contacts from 15.8 to 45%.[58,60,64]

Nevertheless, based on reports indicating under-performed of CI and under-reporting childhood TB cases[9], the actual prevalence may be higher. In fact, Triasih et al. (2011) suggested 3.3 to 5.5% prevalence of TB disease and 24.4 to 69.2% prevalence of TB infection among children aged <15 years with household contacts in South East Asia.[65]

2.5.2 Contact investigation principle

Contact investigation (CI) is one of top-ten priority indicators in the End TB Strategy. In 2025, World Health Organization is targeting ≥ 90% people with close contacts to bacteriologically confirmed TB will be investigated to reduce TB deaths.[66] CI aims to detect risk of TB infection and disease among contacts and high-risk groups, as well as the urgency of TB treatment initiation.

In Indonesia, children aged 0-14 years is the priority group of CI in Puskesmas. It is because children who shared the same specific household with index TB case who is initially identified with new or recurrent TB, for frequent periods during the 3 months before the index case start current treatment have higher risk of getting TB disease.[11] This risk will be increased in children under-5 with limited outdoor

activities and their mother or the caregiver is the index TB cases.[58] A previous study suggested that there is about 690,000 children living with TB household contacts in Indonesia.

Those information above show the importance of early diagnosis and and treatment of contacts with active TB, to interfere transmission and reduce TB morbidity and mortality in children. Based on WHO recommendation, active case finding (ACF) and CI will be used to identify, find, and assess active or LTBI among children with household contacts.[9,46] Therefore, CI will be the key of increasing the early diagnosis and detection rate of childhood TB.

In Indonesia, CI is done by the TB officer and health volunteers in Puskesmas, and local community organization under the supervision of Health Office from each district. It involves systematic screening by using symptoms screening, TST, and microbiological evaluation. In some cases, Puskesmas with limited resources and not be able to establish TB diagnosis, also referred suspected TB to hospital or higher healthcare level for further clinical assessment such as CXR.[11]

2.5.3 Contact investigation procedure

The CI procedure will be started from the healthcare facility where the index TB case get diagnosed and treated.[11,48]

1. Health worker ask and record the information from the index TB case
   Possibility of household contact or close contact
   Name, sex, and age of contacts
   Occupation of the index case
2. If the index case has contact with children, the index case or caregiver will be asked to bring the children to Puskesmas nearby. If contact do not come for TB screening in Puskesmas, the TB officer or health volunteers in Puskesmas are responsible to do active investigation or home visit.
3. Health worker complete the clinical examination to decide the status TB disease or LTBI
   1) If children have no TB symptoms, then:
      - Age ≤5 years, without looking at the HIV status or TB diagnosis result, initiating TB preventive therapy (TPT)

- Age >5 years and HIV (+), initiating TPT
- Age >5 years and HIV (-), further examination

2) If children have TB symptoms such as:
   - Cough more than 2 weeks and there is no indication of getting better with antibiotics or asthma disease medical treatment;
   - Fever (≥ 38C) in 2 weeks without clear reason;
   - Weight loss constantly in the last 2 months which cannot be improve even with adequate nutrition consumption;
   - Extreme tiredness and fatigue; then

Children must be examined with sputum microscopy examination, TST, and CXR.

4. Health worker establish the final diagnosis and start the treatment process
   1) If the examination shows indication of TB, children will take anti-TB drug or fixed-dosed
   2) If the examination shows no indication of TB and referral process cannot be done, health worker will observe other disease possibilities in 1-2 months. If after the evaluation symptoms are getting better, children will be suggested to take TPT. Meanwhile, if symptoms still exist, children will be suggested to take anti-TB drug or fixed-dosed.

2.6 Feasibility of stool-Xpert MTB/RIF Ultra for contact investigation program in primary healthcare

Feasibility in healthcare system is used to describe the appropriateness of a health intervention for further implementation.[67] Previous studies assessed the feasibility of stool-Xpert MTB/RIF intervention in lower healthcare level with cost analysis, and the experiences and perceptions of caregivers and health workers during the stool-Xpert MTB/RIF procedure.

Table 5. Feasibility of stool-Xpert MTB/RIF Ultra in primary healthcare

Study, year/ country	Study design	Participant and setting	Results	Appraisal
Mafirakureva et al. (2022)/ Ethiopia and Indonesia[24]	Systematic review, with model parameters	Children aged <15 years presenting with presumptive TB at primary healthcare or hospital in Ethiopia and Indonesia.	1. The intervention increased the sensitivity of TB diagnosis 19-25%, leading to 14-20% mortality relative reduction. 2. Number of children initiating anti-TB treatment is 18-25%, and 85% initiated in primary healthcare. 3. Costs increased under the intervention compared with base case using smear microscopy in ratio US$132 and US$94 per DALY in Ethiopia and Indonesia. 4. A cost-effectiveness threshold of 0.5xgross domestic product per capita, with 87% and 96% cost-effectiveness.	1. This research using projected probability of the intervention being cost-effectiveness. 2. The settings are very diverse and likely to have global relevance to countries with high TB burden. 3. Patient costs were not included, meaning any patient benefits from reduced referrals were not captured.

Olivier Marcy et al., (2023)/ Cambodia, Cameroon, Cote d'Ivoire, Mozambique, Sierra Leone, Uganda[68]	Cluster-randomized trial	Children aged <5 with severe pneumonia	1. For feasibility and yield: of 1169 children in the same group, 942 (80.6%) had stool collected, 922 (78.9%) had stool-Xpert MTB/RIF Ultra exam, 16 (1.4) tested positive, 11 (0.9%) with invalid or errors results. 2. Meanwhile, there were 26 (2.2%) children with bacteriologically confirmed TB and 62 (5.3%) clinically diagnosed with TB. The yield of using stool testing is 16/88 (18.2%)	1. The research implemented decentralization strategies at the district hospital level and primary healthcare level. 2. Study included parents and nurses of the primary healthcare to assess the feasibility of stool testing, compare to others method. 3. Stool sample was safe and highly feasible for TB diagnose in children with presumptive TB and severe pneumonia in subdistrict level.

Previous studies suggested that the use of stool-Xpert is potentially useful and feasible in lower-level healthcare. However, further studies are needed to assess individuals (TB officer, clinicians and caregivers) perspectives to identify the adherence and sustainability of using stool in childhood TB surveillance and screening in the specific settings.[69,70] The idea of feasibility of stool-Xpert MTB/RIF Ultra from individuals perspectives can be described with,

1. Adherence, which explained how children and primary caretakers responds to the recommendation, participate, and get a valid result of stool-Xpert from healthcare provider or health worker
2. Implementation, which concerned how the intervention can be fully implemented under kind of resources needed and available, factors of ease and difficulty, quality of implementation, and the success or failure of the program.[70,71]

3. Rationale

3.1 Statement of the problems

Children with household contacts to TB infectious adult or adolescent are having a high-risk for developing TB disease due to immunologic maturity.[72] In country with high TB burden as Indonesia, CI and systematic screening among children with household contacts to TB are suggested as routine in TB control and prevention program.[16,47]

However, previous studies and the NTP reports indicate low detection rate and high number of missing cases in childhood TB in Indonesia.[73,74] By implementing decentralization TB care, Puskesmas play a significant role in doing CI and systematic screening in Indonesia. Unfortunately, most of Puskesmas in Indonesia does have limited resources, both man and machine to activate the CI and systematic screening program.[17]

The 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. While microbiological examination with sputum becomes impractical for childhood TB since

most of children cannot produce sputum easily. 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 nasogastric aspiration and sputum induction.[18] This referral system is time-consuming and costly, which leads to delayed TB diagnosis and increasing risk of developing active or severe TB in children.[20]

3.2 Potential solutions and knowledge gaps

In 2020, to close the gap in detection rate, WHO started to recommends stool-Xpert testing as initial TB diagnostic among children with signs and symptoms of pulmonary TB. Studies show that stool-Xpert provide moderate evidence in TB diagnosis and highly feasible in lower-level healthcare such as Puskesmas in Indonesia.[24,47,68]

Therefore, there is a lack of information on how the stool-Xpert perform as a routine systematic screening method among children with household contact. A study conducted in high TB prevalence and primary healthcare as same as the Puskesmas will fill the gap to obtain the knowledge of the properties and feasibility of implementing stool-Xpert MTB/RIF Ultra as part of effective CI and systematic screening in lower-level healthcare.

Furthermore, children with presumptive TB in hospital will be recruited to estimate the properties of stool-Xpert MTB/RIF Ultra as diagnostic method, and determine the feasibility of its implementation in Puskesmas as primary healthcare and higher-level healthcare. The findings and recommendation from this study will present to local policymakers and health workers to state an advance CI and systematic screening workflow in Puskesmas to strengthen childhood TB detection and increase the childhood TB detection rate.

4. Research questions

1. What is the sensitivity and specificity of stool-Xpert MTB/RIF Ultra for childhood TB screening and diagnosis?
2. What is the feasibility of stool-Xpert MTB/RIF Ultra for childhood TB screening and diagnosis in primary and higher-level healthcare centers?

5. Objectives

1. To estimate sensitivity and specificity of stool-Xpert MTB/RIF Ultra for childhood TB screening and diagnosis in primary and higher-level healthcare centers.
2. To examine the feasibility of stool-Xpert MTB/RIF Ultra for childhood TB screening and diagnosis in primary and higher-level healthcare centers.

CHAPTER 2
METHODS

6. Conceptual framework

Children, particularly in younger children, tend to unable to expectorate sputum. Stool is a potential sample that can be easily collected and non-invasively for children with high-risk of TB or children with presumptive TB. In addition to provide a suitable TB screening program for children, healthcare providers were expected to implement stool-Xpert alongside with the childhood TB screening and diagnosis algorithm in Indonesia. The conceptual framework of the study is presented in Figure 3.

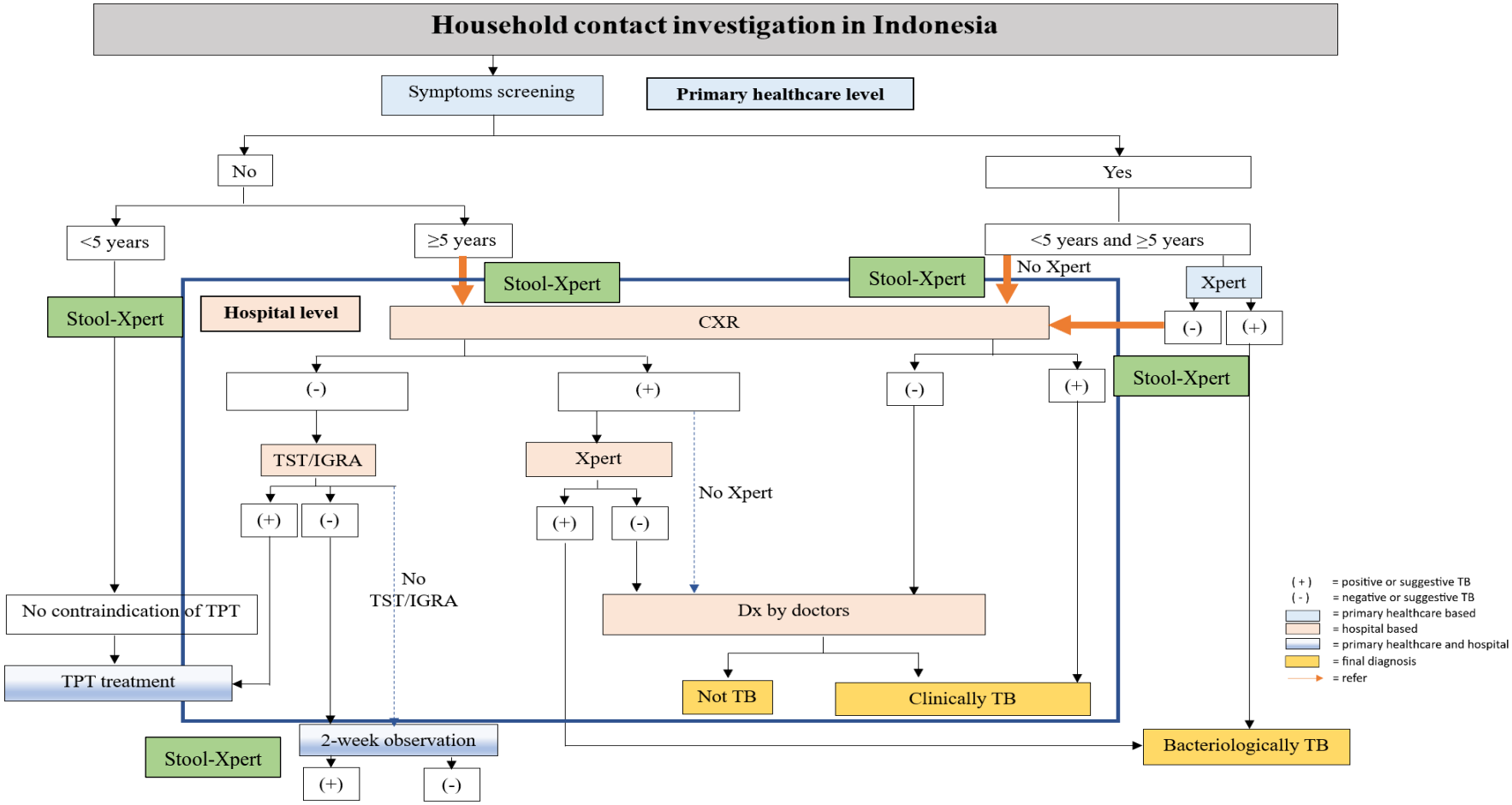

Figure 3. Conceptual framework

7. Methodology

7.1 Study design

A stool-Xpert MTB/RIF Ultra community screening program was conducted from September 2023 to April 2024 in Padang Municipality, Indonesia. Key informants who were health workers from each healthcare and eligible primary caretakers interviewed to assess the feasibility of stool-Xpert MTB/RIF procedure in healthcare.

7.2 Study setting

The study was conducted in Padang Municipality, Sumatera Barat Province, Indonesia, which has the highest prevalence of TB in the province. We approached 13 Puskesmas to provide stool-Xpert screening for children with TB household contact but only 6 Puskesmas able to do contact investigation actively. As a comparison for assessing the stool-Xpert performance, this study also took place in childhood TB clinic in 2 hospitals with outpatient or inpatient children with presumptive TB.

8. Stool-Xpert MTB/RIF Ultra community screening program

8.1 Study Sample

8.1.1 For children with tuberculosis household contact in Puskesmas

Inclusion criteria

1. Children who is family members of index TB case, live under the same household with index TB case for one or more nights or for frequent or extended daytime periods during 3-months before the start of current treatment.
2. Children ≤15 years.
3. Children whose parents have signed an informed consent form.

Exclusion criteria

Children who had received TPT or fixed-dosed combination (FDC) of anti-TB therapy for more than 72 hours.

8.1.2 For children with presumptive tuberculosis in hospital

Inclusion criteria

1. Children with TB signs and symptoms or suspected TB who is inpatient or outpatient in hospital under pediatrician supervision of childhood TB clinic.
2. Children ≤15 years.
3. Children whose parents have signed an informed consent form.

Exclusion criteria

Children who had received TPT or fixed-dosed combination (FDC) of anti-TB therapy for more than 72 hours.

8.2 Sample size

Based on previous literature, the sensitivity and specificity of stool-Xpert were 0.7 and 0.9, respectively. Using infinite population proportion formula as shown below, 81 and 139 children with and without TB were required. We targeted two groups of children aged ≤15 years who were children with TB household contact investigated in Puskesmas and children with presumptive TB referred to hospital. Here, children with presumptive TB were "positive control" group to avoid bias and increase the yield of stool-Xpert MTB/RIF Ultra in analysis and interpretation process.

Considering the efficiency and feasibility of the research, we used ratio 1:3 for children in primary healthcare and children in hospital. Eventually, 60 contact tracing investigation should be done in primary healthcare to get 81 children with TB while 243 children with TB in hospital expected to enrolled to stool-Xpert.

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

n = calculated sample size

Z = the standard normal value

α = 95% confidence interval

p = estimated sensitivity and specificity → 0.7 and 0.9

d = the desired precision → 0.1 and 0.05

8.3 Study procedures

8.3.1 Preparatory phase

1. The study proposal was submitted and approved by the Human Research Ethics Committee of Faculty of Medicine, Prince of Songkla University, Thailand and the Health Research Ethics Committee (HREC) of M. Djamil General Hospital, Padang, Indonesia. Permission obtained from the Health Office of Padang Municipality, Sumatera Barat Province.
2. A case report form (CRF) was translated from English to Bahasa version. The CRF developed based on the national TB-CRF and assessed by expert (pediatrician and TB data officer).
3. The final CRF was printed and distributed to each healthcare.
4. The variables in the CRF were entered into Excel for data collection.
5. The research team worked together with PT Medquest Jaya Global and TB laboratory services for stool-Xpert MTB/RIF Ultra training for laboratory staff in hospital.
6. The research team worked together with the Health Office of Padang Municipality, pediatrician and microbiologist for socialization and kick-off meeting related with (a) early TB screening for children and (b) practicing stool-Xpert MTB/RIF Ultra for pediatricians, resident doctors, general practitioners, TB officers, and laboratory staff in Puskesmas and hospital.
7. The research team prepared pamphlet contained with steps of stool specimen collection information for TB officers and primary caretakers or child patients.

8.3.2 Invitation process for child patients

a. For children with tuberculosis household contact in Puskesmas

We consecutively enrolled children ≤15 years old who visited Puskesmas for seek help after have TB household contact. The TB officer from each Puskesmas and research team reviewed the CI form and invited eligible children with their primary caretakers to follow signs and symptoms screening and physical examination by general practitioner and TB officer in Puskesmas. TB officer introduced

stool-Xpert and asked primary caretakers or patients who were young adolescents with TB household contact to collect stool specimen. Health workers notified the research team if home visit need to be applied or child patients need help to deliver stool specimen to laboratory in hospital.

b. For children with presumptive tuberculosis in hospital

Research team worked together with pediatrician and resident doctor from each hospital to screened TB signs and symptoms among child inpatient and outpatient in hospital aged ≤15 years old. Children referred to hospital mostly came with various severity of clinical signs and symptoms (i.e., cough more than two weeks, weight loss, fever, malaise, malnutrition). Pediatrician and resident doctor notified the research team if there were eligible child patients screened. Primary caretakers or young adolescent patients were informed about the stool collection by the pediatrician or resident doctor.

8.3.3 Child patients' enrollment and specimen collection

1. Written parental consent was taken if they agreed to their child's participation in the study alongside with routine TB screening and diagnosis (i.e., TST, radiological exam, blood exam with interferon gamma release assay (IGRA) test, anatomical pathology exam and sputum/GA/liquor cerebrospialis (LCS) Xpert/acid-fast bacillus (AFB) smear/culture). Children aged 7-15 years old have their consent asked, if applicable. Demographic data of children enrolled to the study recorded by TB officers from each healthcare.
2. Primary caretakers or patients who were young adolescents were provided with a pamphlet contained with steps of stool specimen collection information and stool container with child patients' unique ID.
3. Primary caretakers with inpatient children referred to pediatric intensive care unit (PICU) or high care unit (HCU) helped by a trained nurse to collect the stool specimen from children.
4. The stool specimen will be filled to the container with spoon provided. Only a small amount of stool required (0.8 g solid stool or thumbnail size or 2ml liquid stool). The container will be placed in sealable plastic bag.

5. The stool specimen will be sent back to healthcare 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.

8.3.4 Laboratory procedures

Laboratory staff received the stool specimen and checked the data in e-TB system. Sample processing and testing was performed with Xpert MTB/RIF Ultra machine. The stool specimen processing adopted the simple one-step (SOS) method.

Briefly, 0.8 g of solid or 2ml of liquid stool specimen will be transferred into liquid sample reagent (SR) bottle which available in Xpert MTB/RIF Ultra cartridge package. The bottle vigorously shaken for 30 seconds with hands and then incubated for 10 minutes in room temperature; this step is repeated once. This process formed solid particles, assumed that this allowed bacteria of TB float to the top of liquid SR. As much as 2 ml of the supernatant was transferred from to Xpert MTB/RIF Ultra cartridge and analysed using the Xpert machine.

The Xpert machine run molecular test automatically for 2 hours. The existence of *M. tuberculosis* showed up in monitor connected to the machine with several semi-quantitative levels that were not detected (negative), trace (call positive), very low, low, medium or high. The non-determinate Xpert MTB/RIF Ultra results (invalid, no result and errors) were repeated once to define the final test outcome.

8.3.5 Referral process for children with tuberculosis household contact in Puskesmas

After finished the routine screening process and stool-Xpert MTB/RIF Ultra screening in Puskesmas, each general practitioner or TB officer may refer children which allowed by their primary caretakers to get further examination in hospital under pediatrician supervision. The final diagnosis of TB disease decided by pediatrician based on national algorithm of childhood tuberculosis management in Indonesia. Transportation and accompaniment needed during the health procedure in referral healthcare were provided by the research team. For children who were not allowed to examined by pediatrician in hospital by the primary caretakers, result of TB screening and diagnosis from Puskesmas decided by trained general practitioner.

8.4 Study variables

8.4.1 Main outcomes

The main outcomes of the study were the result of stool-Xpert MTB/RIF Ultra exam against definitive diagnosis by doctor or pediatrician, as additional evidence on the scalability of stool-based exam using Xpert MTB/RIF Ultra to address the screening difficulty in childhood TB in a high TB burden settled in primary and higher-level healthcare setting.

Table 6. Main outcomes of the study

Variable name	Description
Prevalence	Proportion of children with positive TB results among children
Sensitivity	Percentage of participants who test positive for TB among a group who do have the disease
Specificity	Percentage of participants who test negative for TB among a group who do not have the disease
Positive predictive value (PPV)	Proportion of participants giving positive test results who truly have the TB disease
Negative predictive value (NPV)	Proportion of participants with negative test results who truly do not have the TB disease
False-negative rate (FN rate)	Probability of a true positive will be missed by the test
Positive likelihood ratio (LR+)	Probability of expected positive test in a patient divided by the probability that a positive test would be expected in a patient without a disease
Negative likelihood ratio (LR-)	Probability of negative tested patient has a disease divided by the probability of a patient testing negative who does not have a disease

8.4.2 Characteristics of children

1. Socio-demographic status
   1.1 Age: age in year of child patient by TB screening date and date of birth
   1.2 Sex: type of sex divided into male or female
   1.3 Marital status: current status of marriage
   1.4 Religion: religion group as written in family registration certificate
   1.5 Ethnicity: ethnic group of the child patient
   1.6 Education level: current level of education from child patient categorized into non-school age, kindergarten or primary school and high school
   1.7 Occupation: current occupation from child patient categorized into non-school or work age and student
   1.8 Monthly household income: total income in one household per month in rupiah then categorized into low-middle income and high-income using monthly minimum wage in Padang Municipality

2. Risk of tuberculosis identification
   To identify risk factors including environmental risk of TB infections among children with following aspects:
   2.1 HIV status: HIV status of child patient
   2.2 Children with immunocompromised condition: children with HIV, immunodeficiency, cancer or regular dialysis therapy
   2.3 Children living in prison, dorm or camp: children reside in prison, dorm or camp
   2.4 History of BCG vaccination: history of children with BCG-induced for TB prevention
   2.5 Number of people living under the same household: number of people reside in the same house
   2.6 Number of people sleeping in the same bedroom: number of people sleeps in the same indoor shared space
   2.7 History of tuberculosis household contact: history of living in the same house with bacteriologically confirmed TB patient

2.8 History of sharing room with index tuberculosis: history of shares the same indoor shared space with bacteriologically confirmed TB patient

2.9 History of sharing bedroom with index tuberculosis: history of shares the same bedroom with bacteriologically confirmed TB patient

2.10 History of taking tuberculosis drug: history of taking any kind of tuberculosis drug such as TB preventive therapy or anti-TB drug

2.11 Having AC in bedroom: having AC in bedroom

2.12 Opening window in bedroom: having window and daily behavior of opening window in bedroom

2.13 Having active smoker in household: having active tobacco smoker in the same house

3. Investigation of index tuberculosis case

To investigate risk of TB infection among children and index TB case who are living under the same household which determined by following aspects:

3.1 Age: age in year of index TB case by TB diagnosis date and date of birth

3.2 Sex: type of sex divided into male or female

3.3 Marital status: current status of marriage

3.4 Religion: religion group as written in family registration certificate or national ID card

3.5 Ethnicity: ethnic group of the index TB case

3.6 Highest education level: highest level of education from index TB case categorized into primary school, high school and diploma degree or above

3.7 Occupation: current occupation from index TB case categorized into low-middle income job and high-income job

3.8 Monthly personal income: personal income in one household per month in rupiah then categorized into low-middle income and high-income using monthly minimum wage in Padang Municipality

3.9 Relation with child patient: relation of index TB case with children categorized into parents and non-parents (sibling, relative or caretaker)

3.10 Type of TB diagnosis: type of TB disease of index TB case based on the evidence of TB diagnosis categorized into clinically TB and bacteriologically confirmed TB

3.11 Anatomical classification of TB: site of TB disease of index TB case categorized into pulmonary TB (PTB) and extrapulmonary TB (EPTB)

3.12 Type of TB drug: type of TB drug suggested by doctor to index TB case categorized into anti-TB drug for drug-sensitive TB and drug-resistant TB

4. Clinical assessment by general practitioners or/and pediatrician

To screen for signs and symptoms related with TB and physical examination to observe any abnormalities caused by TB throughout several assessment as follows:

4.1 Signs and symptoms screening: screen the existence and duration of fever, cough, weight loss, malaise, shortness of breath, chest pain and blood in sputum towards children

4.2 Anthropometry measurements

4.2.1 Weight: body mass of children in kilograms (kg)

4.2.2 Height: vertical distance from the feet to the top of the head in centimeters (cm)

4.2.3 Body index mass (BMI): brief assessment of nutritional status by calculating body fatness using formula of weight in kilograms divided by the square of height in meters (kg/m^2)

4.2.4 Nutritional status: result of depth nutritional assessment by pediatrician, general practitioner and nutritionist with biochemical test if applicable categorized into normal and abnormal nutritional status

4.3 Head and neck examination: physical examination done by pediatrician or general practitioner or both towards eye, head, neck, nose and mouth parts

4.4 Thorax examination

4.4.1 Pulmonary: physical examination done by pediatrician or general practitioner towards abnormalities in lung by inspection, palpation, percussion and auscultation assessment

4.4.2 Cardiac: physical examination done by pediatrician or general practitioner towards abnormalities in cardiovascular by inspection, palpation, percussion and auscultation assessment

4.5 Abdominal examination: examination done by pediatrician or general practitioner towards abnormalities in abdomen by inspection, palpation, percussion and auscultation assessment

4.6 Extremity examination: examination done by pediatrician or general practitioner towards abnormalities in extremity

5. Result of tuberculosis screening and diagnosis

To early detect TB infection or TB disease among children with clinical tests or microbiology procedures such as:

5.1 Signs and symptoms screening: result of the existence of TB signs and symptoms screening categorized into suggestive TB and not suggestive TB

5.2 Tuberculin skin test (TST): result of injecting small amount of fluid called tuberculin into the skin on lower part of the arm to detect possible exposure of *M. tuberculosis* categorized into positive (induration $\geq$10 mm or $\geq$5 mm among immunocompromised children) and negative

5.3 Chest x-ray (CXR): result of radiological suspicion towards anteroposterior (AP) and lateral imaging of lung among children with presumptive TB categorized into suggestive and not suggestive TB

5.4 Computed tomography scan (CT scan): result of radiological suspicion towards brain neuroimaging among children with presumptive meningitis TB categorized into suggestive and not suggestive TB

5.5 Anatomical pathology: result of histological diagnosis categorized into suggestive and not suggestive TB

5.6 Interferon gamma release assay (IGRA): result of blood exam for cell-mediated immune towards *M. tuberculosis* categorized into positive and negative

5.7 Stool-Xpert: result of real-time rapid molecular test with stool specimen using disposable cartridge of Xpert MTB/RIF Ultra and examined by Xpert machine categorized into MTB detected and MTB not detected

5.8 Sputum-Xpert: result of real-time rapid molecular test with sputum specimen to detect *M. tuberculosis* and resistance of rifampin (RIF) using disposable cartridge of Xpert MTB/RIF Ultra and examined by Xpert machine categorized into MTB detected and MTB not detected

5.9 Sputum-AFB smear: result of microscopic identification of *M. tuberculosis* throughout stain of sputum specimen to detect *M. tuberculosis* and drug-resistance categorized into positive and negative

5.10 TB-culture: result of sputum, LCS or blood specimen culture to assess the existence of *M. tuberculosis* categorized into growth and no growth

5.11 Liquor cerebrospialis-Xpert (LCS-Xpert): result of real-time rapid molecular test with LCS specimen to detect *M. tuberculosis* and resistance of rifampin (RIF) using disposable cartridge of Xpert MTB/RIF Ultra and examined by Xpert machine categorized into MTB detected and MTB not detected

5.12 Gastric aspiration-Xpert (GA-Xpert): result of real-time rapid molecular test with gastric specimen to detect *M. tuberculosis* and resistance of rifampin (RIF) using disposable cartridge of Xpert MTB/RIF Ultra and examined by Xpert machine categorized into MTB detected and MTB not detected

6. Final diagnosis

To find positive case among children with household contact and children with presumptive TB and decide further implementation of standard care towards each child patient by ruled out following aspects:

6.1 Type of TB: type of TB based on the evidence of TB diagnosis categorized into clinically TB due to the absence of bacteriological confirmation of TB or bacteriologically confirmed TB with any biological specimen is positive-tested by smear microscopy, culture, or mWRDs.

6.2 Anatomical classification of TB: site of TB disease categorized into pulmonary TB (PTB) when TB affects the lungs and extrapulmonary TB (EPTB) when TB affects organs other than lung.

6.3 Type of TB drug: type of TB drug suggested by doctor categorized into anti-TB drug for drug-sensitive TB and drug-resistant TB while children without TB will be listed for intensive monitoring by health workers

8.5 Data management

Detailed demographic, clinical and contact investigation information from each child patient were collected using paper-based case report form used Bahasa then translated into English. The paper-based records were then entered using Excel sheet developed for this study. The information was validated by cross-checking for completeness, accuracy and consistency by rotating check among two of research team and a pediatrician involved in the study. Final review for data cleaning, missing data, and error was done using R software (version 4.2.3).

8.6 Data analysis

Descriptive analyses were used for participant characteristics. We used chi-square and Fisher's exact test to analyzed characteristics of child patients related to socio-demographic characteristics, risk of TB identification, investigation of index TB cases, result of clinical assessment, tuberculosis screening and diagnosis, and final diagnosis. Prevalence, sensitivity, specificity, PPV, NPV, LR+, and LR- with 95% CI will be applied as statistical measurements for performance of stool-Xpert exam. Concordance and discordance were showed to explained the agreement among stool-Xpert with other screening and diagnostic tests. All analysis were performed with R version 4.2.3 with 'epicalc', 'dplyr', 'epiR', and 'epitools' packages.

9. Key informant interviews

9.1 Study sample

9.1.1 For health workers

Inclusion criteria

1. Responsible for TB control (i.e., general practitioner, TB officer and laboratory staff)

2. Have worked for at least 6 months in current healthcare provider

Exclusion criteria

Not applicable

9.1.2 Primary caretakers of children

Inclusion criteria

1. Primary caretakers of children who invited to stool-Xpert MTB/RIF Ultra screening program.
2. Primary caretaker aged ≥18 years

Exclusion criteria

Not applicable

9.2 Sample size

9.2.1 For health workers

The rationale of health workers in healthcare included in this study was to know the acceptability and experience of implementation of stool-Xpert MTB/RIF Ultra from the health workers perspective based on the current situation analysis, characteristics of children, convenience and resources aspects to answered objective 2. The research team recruited health workers from Puskesmas and hospitals to compare the experience of implementing stool-Xpert MTB/RIF Ultra in two different level of healthcare with different resources and work surfaces. Each healthcare had at least 1 key informant who were working for TB control and prevention program from different background such as TB officer, general practitioner, nurse and laboratory staff.

9.2.2 For primary caretakers

The research team recruited primary caretakers of child patients who have been invited to collect stool specimen for stool-Xpert exam and signed the informed consent as key informant to increase the saturation of information related to the feasibility of stool-Xpert screening. The research team recruited primary caretakers from primary and higher-level healthcare to compare barriers faced by both primary caretakers in different level of healthcare and how primary caretakers coped during

stool specimen collection. The research team also recruited primary caretakers who showed interest during recruitment process then could not adhered due to several specific reasons to analyze factors related to non-adherence.

9.3 Study procedures

9.3.1 Preparatory phase

1. The study proposal was submitted and approved by the Health Research Ethics Committee of Faculty of Medicine, Prince of Songkla University, Thailand and . the Health Research Ethics Committee (HREC) of M. Djamil General Hospital, Padang, Indonesia. Permission obtained from the Health Office of Padang Municipality, Sumatera Barat Province
2. Two semi-structured interview guidelines were developed for health workers and primary caretakers from literature review. Each interview guideline was translated from English to Bahasa version.
3. The semi-structure interview guidelines were printed and distributed to the research team.
4. The research team worked together with health worker from each healthcare to provide interview room and arranged appointment with key informants.

9.3.2 Key informants enrollment

a. For health workers

The research team recruited health workers from healthcare providers as key informants for the acceptability and implementation of stool-Xpert exam. The research team identified health worker who provided TB services for children in and got involved in stool-Xpert screening in their healthcare as informant. Written consent was taken from each health worker to showed agreement for participating in the interview.

b. For primary caretakers

The research team informed primary caretakers about the interview process alongside when their children invited to stool-Xpert screening. The research team recruited two groups of primary caretakers whose children enrolled to stool-Xpert exam and primary caretaker whose children could not adhere to stool-Xpert exam due

to several reasons. Written consent was taken from each primary caretaker to showed agreement for participating in the interview.

9.3.3 Interview process

Each interview was conducted among health worker used semi-structured interview guideline with open and closed-ended questions. Health workers were asked several questions such as “What challenges or difficulties have you faced while performing stool exam?” and “Would you consider handling and performing stool exam rather than referring children to higher-level healthcare?” Some of the interview questions that primary caretakers were asked included “Could you please provide brief description of how you performing stool collection from your children?” and “What challenges or difficulties have you faced while collecting stool specimen?”.

The interviews were conducted in each informant’s preferred method (face-to-face or by telephone) and language (Bahasa or Minangnese). There were no non-informants presents during interviews. The interviews lasted between 15-20 minutes and were audio and written-recorded with informant permission.

9.4 Study variables

9.4.1 Key informant interviews outcomes

Key informant interviews aimed to assessed the feasibility through adherence and implementation of stool-Xpert MTB/RIF Ultra screening from health workers and primary caretakers’ perspectives.

a. Adherence is how primary caretakers and children agree or not agree to participate due to the idea of appropriateness and suitable method offer by healthcare provider or health worker, and complete all procedures of stool-Xpert with a valid result.
b. Implementation is how informants participate in all procedures of stool-Xpert due to factors affecting the ease or difficulty and resources needed resulted to pros and cons of further implementation of stool-Xpert.

9.4.2 Independent variables

1. Characteristics of health workers
   1.1 Position of health workers: current role of health workers at healthcare provider, divided into clinical staff (general practitioner, TB officer and nurse) and non-clinical staff (laboratory staff and TB data officer).
   1.2 Working period: length of time in year since health worker started to work in current healthcare
   1.3 Work responsibility: type of TB services and other healthcare' program provided by health worker in healthcare

2. Characteristics of primary caretakers
   2.1 Socio-demographic status
      a. Age: age in year of primary caretaker by interview date and date of birth
      b. Sex: type of sex divided into male or female
      c. Highest education level: highest level of education from primary caretaker categorized into primary school, high school and diploma degree or above
      d. Occupation: current occupation from primary caretaker categorized into low-middle income job and high-income job
   2.2 Relation with child patient: relation of primary caretaker with child patient categorized into father and mother.

9.5 Data management

Data saturation was achieved after interviewing 29 primary caretakers and 11 health workers. Therefore, there was no follow-up interviews. Trustworthiness and accuracy of the data were validated by restating and summarizing all informants' responses.

Informants recorded were transcribed verbatim and none were returned to informants for comments or corrections. Findings were reported and discussed with co-authors for insights drawn and promote confirmability of the findings. The credibility of the study was maintained with prolonged engagement with informants resulted with a good rapport for data collection process.

9.6 Data analysis

The key informant interviews with health workers and primary caretakers from Puskesmas as primary healthcare and hospitals as higher-level healthcare were reviewed and the findings were summarised. Audio-records were transcribed and translated to English. The quality of data was checked before the coding and analysis. Thematic analysis was conducted with ATLAST.ti 24.

The codebook was developed and applied to a specimen of transcript; cross-checked codes; resolved discrepancies; and refined the codes. This process was repeated until the codebook adequately captured the interview content. The final codebook was applied to all transcripts. Author discussed all trends and patterns of the informations collected, then refined several themes with co-authors. Similar information was revealed from all 40 interviews reflected the data saturation was reached.

10. Ethics considerations

The study was approved by the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University, Thailand (REC. 66-295-18-1), and the Health Research Ethics Committee (HREC) of M. Djamil General Hospital, Padang, Indonesia (Ref. No. LB.02.02/5.7/444/2023), and the permission obtained from Padang Municipality Government, Indonesia (No. 070.7290/DPMPTSP-PP/VIII/2023) (Appendix 1). All proposed participants had a right to agree or disagree to participate in the study using the informed consent. The anonymity and confidentiality were stringently maintained throughout the study.

CHAPTER 3
RESULTS

11. Stool-Xpert MTB/RIF Ultra community screening program

There was total 125 child patients who were met the eligible criteria from primary healthcare and hospital, and their primary caretakers approached to collect stool specimen. All of primary caretakers from 125 child patients showed interest but 2 child patients from hospital passed away before stool collection procedure done due to critical illness, 31 child patients could not adhere due to several reasons and 6 child patients lost to follow-up.

Therefore, a total of 86 child patients (69%) including 42 children with TB household contact from Puskesmas and 44 children with presumptive TB from hospitals enrolled in the study and adhered to stool-Xpert exam. After stool collection procedure was done, 3 child patients passed away due to severity of TB.

All both child patients from Puskesmas and hospitals were investigated for history of TB contacts. All of child patients from Puskesmas have a clear history of household contact with family while only 6 (10%) child patients from hospital could rule the history of TB contact with their family.

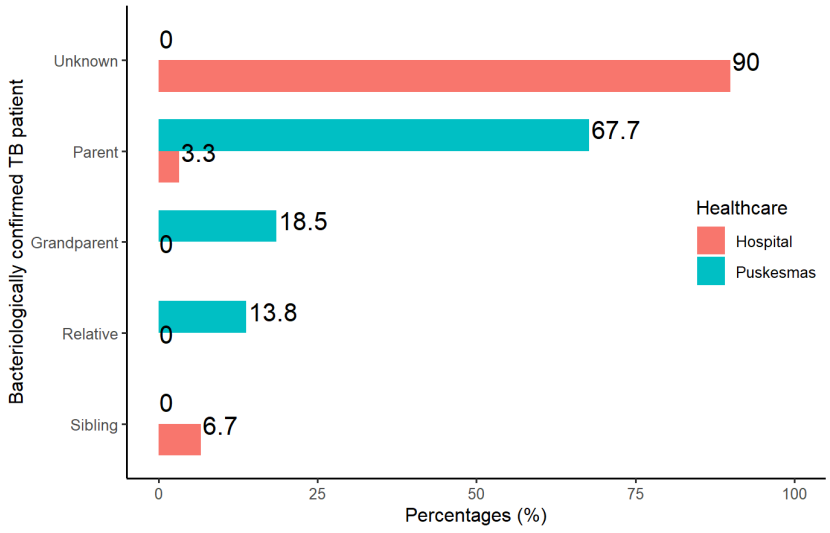

Figure 4. History of TB household contact reported among children

Based on follow-up of final diagnosis, from 125 child patients invited from both healthcare levels, we found that total there were 34 (39.5%) children who adhered to stool-Xpert diagnosed with clinically TB and 6 (7%) had bacteriologically confirmed TB, while 46 (35.5%) diagnosed with other disease or not TB. From children who non-adhered, there were 12 (30.8%) children had clinically TB, 2 (5.1%) had bacteriologically confirmed TB, and 25 (64.1%) with not TB.

Final diagnosis was made and category of TB drug were decided based on standard care aside of the result of stool-Xpert. In this study, final diagnosis for child patients from Puskesmas who referred to hospital as research participants were decided by pediatrician and radiologist while others who are not referred were diagnosed by general practitioners based on signs and symptoms screening, and result of TST if available. In hospital, diagnosis for child patients were decided by pediatrician.

11.1 Performance of stool-Xpert for childhood tuberculosis

In total, 54 children (43.2% of 125) were diagnosed with TB, of whom, 8 (15%) had bacteriological confirmation of TB whether with sputum-AFB, sputum-Xpert, or culture with any specimen. A valid stool-Xpert test was obtained for 86/125 children with sensitivity of 15% (95% CI: (5.7-29.8) and specificity of 100% (95% CI: 92.2-100.0) compared to definitive diagnosis made by pediatrician. The corresponding PPV and NPV were 100% (95% CI: 54.1-100.0) and 57.5 % (95% CI: 54.3-60.1), with estimated prevalence was 47%.

Investigation in Puskesmas also found high specificity of stool-Xpert against definitive diagnosis by pediatrician with 100% (95% CI: 88.1-100.0). However, we could not calculate the sensitivity, PPV, and LR+ due to none positive result of stool-Xpert among children with TB household contact in Puskesmas. The corresponding NPV were 69.1% (95% CI: 69.1-69.1), with LR- 1 and estimated prevalence was 31%.

The sensitivity was increased to 18.2% (95% CI: 6.9-35.5) among children with presumptive TB who screened in hospital with various severity of signs and symptoms of TB. The corresponding specificity, PPV, and NPV 100% (95% CI: 71.5-100.0), 100% (95% CI: 54.1-100.0), and 51.8% (95% CI: 47.8-55.8). The LR- was 0.82 with estimated prevalence was 75%.

All six children with positive result or MTB detected for stool-Xpert were children with presumptive TB from hospital. Out of six children, only one child was from 0-4 years age group while others were young adolescents. Two of them have history of TB household contact with their father and older brother.

All of children with positive stool-Xpert results were got BCG vaccination at 1 month old. All of them have abnormal nutritional status, five were experienced prolonged fever, four with prolonged cough, four had weight loss for the last one to three months, and two examined with abnormality of their lung function.

Out of six children with positive stool-Xpert results, three of them were diagnosed with pulmonary TB and other three were diagnosed with meningitis TB with bacteriological confirmation. These children started treatment for DS-TB based on their sputum-Xpert result.

The sensitivity was decreased when stool-Xpert against signs and symptoms screening for only up to three signs and symptoms. The sensitivity was dropped to 8.0% (95% CI: 1.0-26.0) for overall children, and 14.3% (95% CI: 2.0-43.0) for children with presumptive TB in hospital. However, the sensitivity was increased when stool-Xpert against signs and symptoms screening for more than three signs and symptoms to 26.6% (95% CI: 8.0-55.0) for overall children and 30.8% (95% CI: 9.0-61.0) for children with presumptive TB in hospital.

Table 7. Comparison of stool-Xpert Ultra results and definitive diagnosis among children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital by pediatrician

Stool-Xpert	Definitive diagnosis		Sn	Sp	PPV	NPV	Prev	FN	LR+	LR-
	TB disease (n)	Non-TB disease (n)	%, (95% CI)							
Overall (N=86)										
Positive	6	0	15.0 (5.7-29.8)	100.0 (92.2-100.0)	100.0 (54.1-100.0)	57.5 (54.3-60.1)	46.5 (35.7-57.6)	0.85	Inf	0.85
Negative	34	46								
Children with tuberculosis household contact in primary healthcare (Puskesmas) (n=42)										
Positive	0	0	NA	100.0 (88.1-100.0)	NA	69.1 (69.1-69.1)	30.9 (17.6-47.1)	1.0	NA	1.0
Negative	13	29								
Children with presumptive tuberculosis in hospital (n=44)										
Positive	6	0	18.2 (6.9-35.5)	100.0 (71.5-100.0)	100.0 (54.1-100.0)	51.8 (47.8-55.8)	75.0 (59.7-86.8)	0.82	Inf	0.82
Negative	27	11								

NA, not applicable. Inf, infinite. CI, confidence interval. PPV, positive predictive value. NPV, negative predictive value. LR+, likelihood ratio positive. LR-, likelihood ratio negative.

Table 8. Comparison of stool-Xpert Ultra results and signs and symptoms ≤3 among children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital by pediatrician

Stool-Xpert	Signs and symptoms ≤3		Sn	Sp	PPV	NPV	Prev	FN	LR+	LR-
	+	-	%, (95% CI)							
Overall (N=58)										
Positive	2	0	8.0 (1.0-26.0)	100.0 (89.0-100.0)	100.0 (16.1-100.0)	58.9 (56.0-62.1)	43.1 (30.2-57.0)	0.92	Inf	0.92
Negative	23	33								
Children with tuberculosis household contact in primary healthcare (Puskesmas) (n=36)										
Positive	0	0	NA	100.0 (87.1-100.0)	NA	69.4 (69.2-70.0)	30.5 (16.4-48.1)	1.0	NA	1.0
Negative	12	25								
Children with presumptive tuberculosis in hospital (n=22)										
Positive	2	0	14.3 (2.0-43.0)	100.0 (63.0-100.0)	100.0 (16.1-100.0)	40.3 (35.4-45.0)	63.6 (41.0-83.0)	0.86	Inf	0.86
Negative	12	8								

NA, not applicable. Inf, infinite. CI, confidence interval. PPV, positive predictive value. NPV, negative predictive value. LR+, likelihood ratio positive. LR-, likelihood ratio negative.

Table 9. Comparison of stool-Xpert Ultra results and and signs and symptoms >3 among children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital by pediatrician

Stool-Xpert	Signs and symptoms ≤3		Sn	Sp	PPV	NPV	Prev	FN	LR+	LR-
	+	-	%, (95% CI)							
Overall (N=28)										
Positive	4	0	26.6 (8.0-55.0)	100.0 (75.0-100.0)	100.0 (39.7-100.0)	54.2 (32.0-74.0)	53.6 (33.9-72.5)	73.0	Inf	73.0
Negative	11	13								
Children with tuberculosis household contact in primary healthcare (Puskesmas) (n=6)										
Positive	0	0	NA	100.0 (39.2-100.0)	NA	66.7 (66.6-66.7)	33.3 (4.33-77.7)	1.0	NA	1.0
Negative	2	4								
Children with presumptive tuberculosis in hospital (n=22)										
Positive	4	0	30.8 (9.0-61.0)	100.0 (66.1-100.0)	100.0 (39.7-100.0)	50.0 (41.0-59.0)	59.1 (36.4-79.3)	69.2	Inf	69.0
Negative	9	9								

NA, not applicable. Inf, infinite. CI, confidence interval. PPV, positive predictive value. NPV, negative predictive value. LR+, likelihood ratio positive. LR-, likelihood ratio negative.

Stool-Xpert results, both in Puskesmas and hospitals, showed low agreement with final TB diagnosis made by pediatrician while it showed high agreement with another laboratory exam such as sputum-Xpert and sputum-AFB. It also highly agreed with the result of culture with several specimen such as sputum, blood, and LCS. Unfortunately, stool-Xpert also showed low agreement with other TB screening method of signs and symptoms screening, TST, and CXR. However, in this report, not all children went through the same TB investigation procedures due to limited resources in each healthcare.

Table 10. Documentation of TB investigation' results for children with tuberculosis household contact in Puskesmas adhered to stool-Xpert (N=42)

		S&S (n=42)		TST (n=24)		CXR (n=11)		Stool-Xpert (n=42)		Sputum-Xpert (n=9)		Final diagnosis (n=42)	
		+	-	+	-	+	-	+	-	+	-	+	-
S&S	+			7	6	5	NA	0	18	0	0	8	10
	-			4	7	6	NA	0	24	0	9	5	19
TST	+					6	NA	NA	11	NA	3	9	2
	-					4	NA	NA	13	NA	4	2	11
CXR	+							NA	11	5	6	9	2
	-							NA	0	NA	NA	NA	NA
Stool-Xpert	+									0	0	0	0
	-									33	9	13	29
Sputum-Xpert	+											NA	NA
	-											5	4
Final diagnosis	+												
	-												

Table 11. Documentation of TB investigation' result for children with presumptive tuberculosis in hospital adhered to stool-Xpert (N=44)

		S&S (n=44)		TST (n=37)		CXR (n=43)		Stool-Xpert (n=44)		Sputum-Xpert (n=23)		Sputum-AFB (n=7)		Culture (n=9)		IGRA (n=5)		LCS-Xpert (n=2)		GA-Xpert (n=1)		AP (n=5)		Final diagnosis (n=44)	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
S&S	+			18	18	27	15	6	37	6	16	1	6	2	7	1	4	NA	2	NA	1	5	NA	27	16
	-			0	1	0	1	0	1	0	1	0	0	0	0	0	0	NA	0	NA	0	0	NA	0	1
TST	+					12	6	2	16	2	4	0	3	0	4	1	0	NA	0	NA	0	1	NA	16	2
	-					10	8	2	17	2	12	1	2	2	1	0	3	NA	1	NA	0	2	NA	6	13
CXR	+							4	23	4	9	1	4	2	5	1	2	NA	2	NA	1	2	NA	19	8
	-							2	14	2	7	0	2	0	2	0	2	NA	0	NA	0	3	NA	8	8
Stool-Xpert	+									6	0	1	0	2	1	0	0	NA	0	NA	0	0	NA	6	0
	-									0	17	0	6	0	6	1	4	NA	2	NA	1	5	NA	21	17

		S&S (n=44)		TST (n=37)		CXR (n=43)		Stool-Xpert (n=44)		Sputum-Xpert (n=23)		Sputum-AFB (n=7)		Culture (n=9)		IGRA (n=5)		LCS-Xpert (n=2)		GA-Xpert (n=1)		AP (n=5)		Final diagnosis (n=44)	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Sputum-Xpert	+											1	0	2	1	0	0	NA	0	NA	0	0	NA	6	0
	-											0	2	0	3	0	1	NA	0	NA	0	3	NA	7	10
Sputum-AFB	+													1	0	0	0	NA	0	NA	0	0	NA	1	0
	-													0	2	0	0	NA	2	NA	1	1	NA	6	0
Culture	+															0	0	NA	0	NA	0	0	NA	2	0
	-															0	0	NA	0	NA	0	2	NA	7	0
IGRA	+																	NA	0	NA	0	0	NA	1	0
	-																	NA	0	NA	0	0	NA	0	4
LCS-Xpert	+																			NA	0	0	NA	0	0
	-																			NA	1	0	NA	2	0

		S&S (n=44)		TST (n=37)		CXR (n=43)		Stool-Xpert (n=44)		Sputum-Xpert (n=23)		Sputum-AFB (n=7)		Culture (n=9)		IGRA (n=5)		LCS-Xpert (n=2)		GA-Xpert (n=1)		AP (n=5)		Final diagnosis (n=44)	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
GA-Xpert	+																					0	NA	0	0
	-																					1	NA	1	0
AP	+																							4	1
	-																							0	0
Final diagnosis	+																								
	-																								

From 86 children adhered to stool-Xpert, 32 (37.2%) went through sputum-Xpert. All positive result in stool-Xpert reflects all positive result in sputum-Xpert and vice versa. The corresponding sensitivity, specificity, PPV, and NPV among stool-Xpert against sputum-Xpert were 100% (95% CI: 54.1-100.0), 100% (95% CI: 86.8-100.0), 100% (95% CI: 54.1-100.0), and 100% (95% CI: 86.8-100.0).

Table 12. Comparison of stool-Xpert Ultra and sputum-Xpert Ultra results from children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital (N=32)

Stool-Xpert	Sputum-Xpert		
	Positive	Negative	Total
Positive	6	0	6
Negative	0	26	26
Total	6	26	**32**

Invalid and error results were documented in 11.6% (10/86) at initial testing. Due to aim of research, we repeated the tests in invalid and error cases led to valid results. There was no sputum-Xpert with invalid or error results. Only one difference was found in semi-quantitative result where one MTB detected very low in sputum-Xpert showed MTB trace in stool-Xpert. Rifampicin resistance was not detected in the sputum or stool specimens. Three of Rifampicin not detected results had "trace" semi-quantitative values in their stool-Xpert test.

Table 13. Semi-quantitative categories of stool-Xpert Ultra and sputum-Xpert Ultra among bacteriologically confirmed TB patients (N=32)

Sputum-Xpert result	Stool-Xpert result					
	Negative	Trace	Very low	Low	Medium	High
Negative	26	0	0	0	0	0
Trace	0	2	0	0	0	0
Very low	0	1	0	0	0	0
Low	0	0	0	2	0	0
Medium	0	0	0	0	1	0
High	0	0	0	0	0	0

11.2 Adherence of stool-Xpert MTB/RIF Ultra among children with tuberculosis household contact in Puskesmas

There was total 136 children investigated with tuberculosis household contact in Puskesmas included as our study settings during September 2023 to April 2024 with only 65 eligible child patients to be invited to stool-Xpert. About 65% of children from Puskesmas who investigated after TB household contact adhered to stool-Xpert. None of eligible children excluded due to exclusion criteria since children were recruited to study before the final diagnosis and treatment suggested by the doctor or pediatrician.

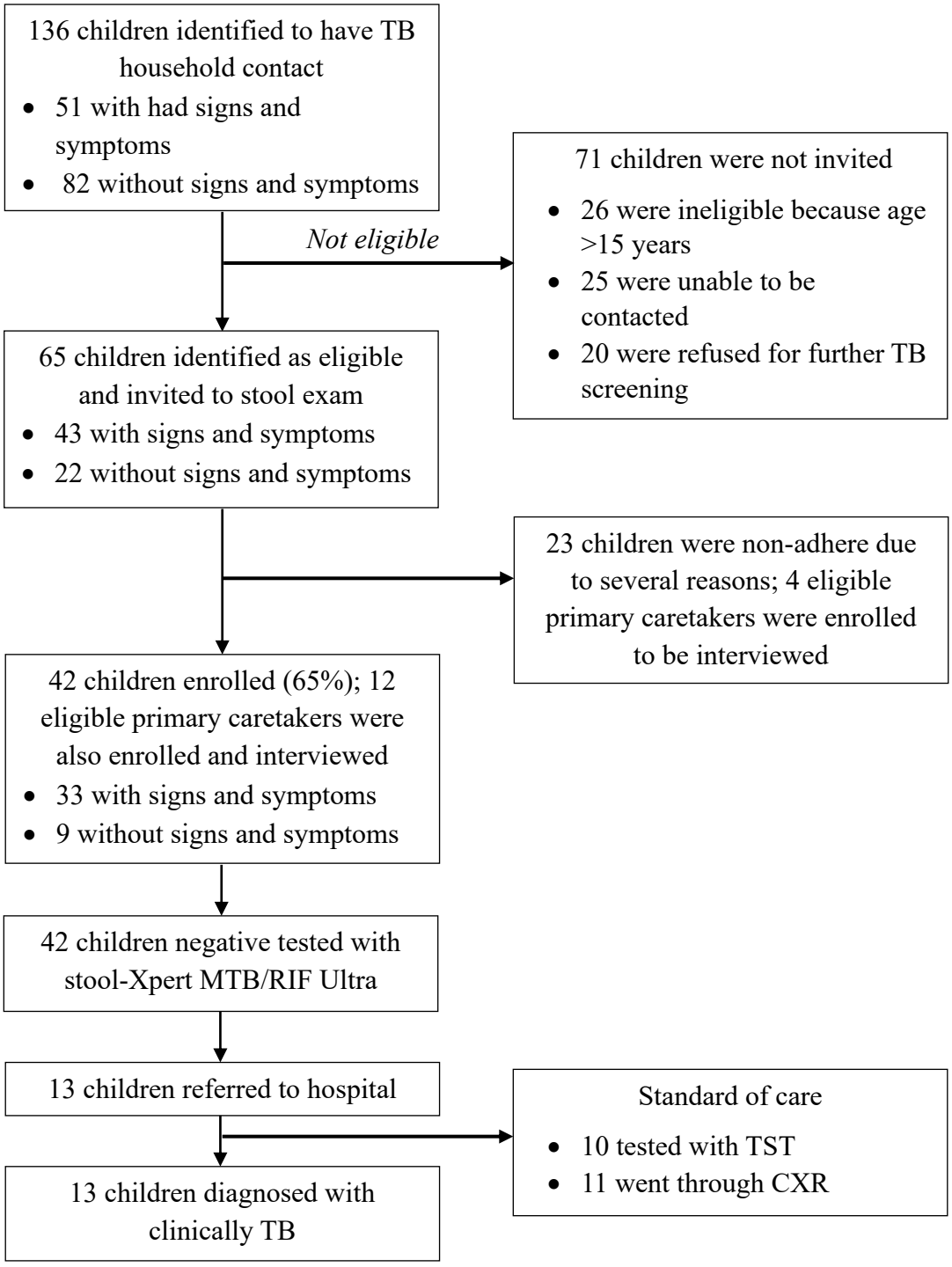

Figure 5. Children' screening, recruitment, and enrollment process in Puskesmas

11.2.1 Socio-demographic characteristics of children with tuberculosis household contact in Puskesmas

The socio-demographic characteristics of children investigated in Puskesmas are shown in Table 8. Most of child patients invited to stool-Xpert were children from children aged ≤5 years group which found to be more adhered to stool-Xpert (*p* value=0.014) more than older age groups. All of children were Muslim and most of them were female from Minangnese ethnicity while a few of them came from Mentawai and Melayu ethnicities. Most of them were non-school age children which had higher adherence rate to stool-Xpert (*p* value=0.017) then followed by children from primary school or kindergarten. We found that higher average monthly household income predicted the decision to adhere to stool-Xpert by primary caretakers and children in Puskesmas (*p* value=0.002), but most of them lived with low monthly household income compared to average monthly household expenses in Padang Municipality.

Table 14. Comparison of adherence to stool-Xpert by socio-demographic characteristics in Puskesmas (N=65)

Socio-demographic characteristics	Children investigated in Puskesmas (N=65)		*p* value[a]
	Adherence (n=42)	Non-adherence (n=23)	
Age (years), median (IQR)	5 (2-7)		
Age group (years)			0.014
0-4	26 (61.9)	6 (26.1)	
5-12	15 (35.7)	15 (65.2)	
13-15	1 (2.4)	2 (8.7)	
Sex			0.783
Male	23 (54.8)	11 (47.8)	
Female	19 (45.2)	12 (52.2)	
Ethnicity			0.174
Minangkabau	40 (95.2)	19 (82.6)	
Others	2 (4.8)	4 (17.4)	

Current education			0.017
Non-school age	29 (69.0)	9 (39.1)	
Primary school or lower	13 (31.0)	12 (52.2)	
High school	0 (0)	2 (8.7)	
Average monthly household income (USD)			0.002
<62	5 (11.9)	11 (47.8)	
62-123	6 (14.3)	5 (21.7)	
123-185	13 (31)	6 (26.1)	
185-247	11 (26.2)	0 (0)	
247-309	4 (9.5)	0 (0)	
>309	3 (7.1)	1 (4.3)	

NA, not applicable. [a]Chi-squared test or Fisher's exact test. [b]1 USD=16,162 Indonesian Rupiah.

11.2.2 Risk of tuberculosis investigation, signs and symptoms screening, and physical examination of children with tuberculosis household contact in Puskesmas

All children invited from Puskesmas were having household contact with TB patients who is their parents (67.7%), grandparents (18.5%), and other relatives (13.8%) (Table 9). Several risk to TB infection among household related with daily activities and health behavior have statistically significant association with adherence rate to stool-Xpert were having >7 people sleep in one bedroom (*p* value=0.041) and opening the window in the bedroom (*p* value=0.015).

Besides the risk of TB investigation by nurse or TB officer, child patients in Puskesmas also screened for signs and symptoms of TB and physical examination done by general practitioner. There were 14 children had fever with 12 of them were prolonged fever ≥2 weeks, and 15 children had cough with 14 of them were prolonged cough ≥2 weeks. However, weight loss symptom was the only statistically significant predictor of the adherence of primary caretakers and children to stool-Xpert (*p* value=0.023). General practitioner in each Puskesmas reported no abnormalities during physical examination among children with TB household contact in Puskesmas.

Table 15. Comparison of adherence to stool-Xpert by risk of tuberculosis investigation, signs and symptoms screening, and physical examination in Puskesmas (N=65)

Risk of tuberculosis	Children investigated in Puskesmas (N=65)		*p* value[a]
	Adherence (n=42)	Non-adherence (n=23)	
Investigation of TB risk			
Had history of immunocompromised disease	0 (0)	0 (0)	NA
Living in dorm or camp	0 (0)	0 (0)	NA
Not having BCG vaccination	10 (23.8)	7 (30.4)	0.775
Having >7 household member	16 (38.1)	4 (20.0)	0.257
Having >7 people sleep in one room	0 (0)	3 (13.0)	0.041
Had history of household contact	42 (64.6)	23 (35.4)	NA
Had shared room with TB patient	36 (85.7)	23 (100)	0.082
Had shared bedroom with TB patient	16 (38.1)	11 (47.8)	0.618
History of taking TB drug			1
Ever	4 (9.5)	2 (8.7)	
Currently	1 (2.4)	1 (4.3)	
Never	37 (88.1)	20 (87.0)	
Having AC in the bedroom	11 (26.2)	6 (26.1)	1
Opening the window in the bedroom			0.015
Have no window	2 (4.8)	6 (30.0)	
Never open	4 (9.5)	0 (0)	
Frequently open	36 (85.7)	14 (70.0)	
Having smoker	31 (73.8)	17 (73.9)	1
Signs and symptoms screening			
Fever	11 (26.2)	3 (13.0)	0.345
Prolonged fever ≥2 weeks	10 (90.9)	2 (66.6)	0.188
Cough	15 (35.7)	4 (17.4)	0.225

Prolonged cough ≥2 weeks	14 (93.3)	4 (100)	0.279
Weight loss	12 (28.6)	1 (4.3)	0.023
Malaise	1 (2.4)	0 (0)	1
Chest pain	0 (0)	(0)	NA
Shortness of breath	1 (2.4)	0 (0)	1
Blood in sputum	0 (0)	0 (0)	NA
Abnormal nutritional status	22 (52.4)	9 (39.1)	0.445
Any abnormalities in physical examination			
Lung	0 (0)	0 (0)	NA
Heart	0 (0)	0 (0)	NA
Abdomen	0 (0)	0 (0)	NA
Extremity	0 (0)	0 (0)	NA

NA, not applicable. [a]Chi-squared test or Fisher's exact test.

11.2.3 Comparison of diagnosis uptakes of children with tuberculosis household contact in Puskesmas

Several children adhere and non-adhere to stool-Xpert were getting tested by laboratory standard care with sputum specimen, culture with any specimen, and Xpert test with any specimen. Other clinical exam and testing were used such as CXR, TST, anatomical pathology with any tissue specimen, IGRA, and CT scan for children with suggestive meningitis TB. However, all of these standards were not applied to all child patients depend on the availability of test equipment during the time, severity of signs and symptoms, healthcare levels, and anatomical of suggestive TB (pulmonary TB or extrapulmonary TB).

In standard care, several Puskesmas and hospital are providing sputum-Xpert service but due to limited number of Xpert-cartridge, not all children were advised to went through sputum-Xpert. For culture, not only sputum specimen was used but also blood and LCS specimens used to detect the growth of MTB. Culture for *M. tuberculosis* is also available in both Puskesmas and hospital but culture for childhood TB is very rare to be done except when children have severe signs and symptoms of TB or have indications of MDR-TB. AFB is also provided in Puskesmas and hospital

but the use of AFB for childhood TB diagnosis was started to replace by rapid molecular test by Xpert.

LCS and GA-Xpert were the least TB tests used since the procedure to collect specimens were invasive and lengthy. All LCS-Xpert and GA-Xpert in this study were done in hospital. Other clinical exam and testing besides signs and symptoms screening and TST were not supported in Puskesmas since it was lower-level or primary healthcare with limited resources. Therefore, CXR, anatomical pathology, IGRA, and CT scan were done in hospital.

In this study, only 11 children in Puskesmas went through sputum collection for sputum-Xpert which only children from non-adhere group also got positive result after sputum-Xpert, sputum-AFB, and sputum-culture done (Table 12). About 43% children adhered to stool-Xpert in Puskesmas were having signs and symptoms suggestive to TB, while only 17% children from non-adhere group were having signs and symptoms of TB. These children at least have cough, fever, or weight loss for several days.

Several children in Puskesmas with moderate or severe signs and symptoms were referred to hospital to went through CXR or IGRA and supervision by pediatrician. There were 12 children got suggestive TB with CXR features and 1 positive infected by TB by IGRA test. Besides that, 24 children got TST whether in Puskesmas or hospital during the referral procedure, resulted to 13 children got positive TB proven by appearance of bump in the area of injection.

These TB screening and diagnosis were done first before stool-Xpert was done or result of stool-Xpert reported to the primary caretakers. Therefore, we assumed that result of sputum-Xpert, result of CXR, and TST done to children were statistically significant predictors of adherence rate of stool-Xpert among primary caretakers and child patients.

Table 16. Comparison of adherence to stool-Xpert by screening and diagnosis uptakes for children with tuberculosis household contact in Puskesmas (N=65)

Tuberculosis screening and diagnosis method	Children investigated in Puskesmas (N=65)		*p* value[a]
	Adherence (n=42)	Non-adherence (n=23)	
Specimen collected and testing			
Sputum collected	9 (21.4)	2 (8.7)	0.302
Sputum-Xpert done	9 (100)	2 (100)	0.302
Sputum-Xpert positive	0 (0)	2 (100)	0.018
Sputum-AFB done	0 (0)	2 (8.7)	0.122
Sputum-smeared positive by AFB	0 (0)	0 (0)	NA
Culture with any specimen			
Culture done	0 (0)	2 (8.7)	0.122
MTB growth detected by culture	0 (0)	2 (100)	NA
LCS collected	0 (0)	0 (0)	NA
LCS-Xpert positive	0 (0)	0 (0)	NA
GA collected	0 (0)	0 (0)	NA
GA-Xpert positive	0 (0)	0 (0)	NA
Other clinical exam and testing			
Signs and symptoms: suggestive TB	18 (42.9)	4 (17.4)	0.072
CXR			
CXR done	11 (26.2)	5 (21.7)	0.923
Suggestive TB CXR features	11 (100)	1 (20.0)	0.003
TST			
TST done	24 (57.1)	6 (26.1)	0.032
TST positive with bump	11 (45.8)	2 (33.3)	0.672
Anatomical pathology			

Anatomical pathology done	0 (0)	0 (0)	NA
Suggestive TB by anatomical pathology exam	0 (0)	0 (0)	NA
IGRA			
IGRA done	1 (2.4)	0 (0)	1
TB infection detected by IGRA	1 (100)	0 (0)	NA
CT scan			
CT scan done	0 (0)	0 (0)	NA
Suggestive TB CT scan features	0 (0)	0 (0)	NA

NA, not applicable. [a]Chi-squared test or Fisher's exact test.

11.2.4 Final diagnosis of TB and treatment for children with tuberculosis household contact in Puskesmas

In Puskesmas, 14 children diagnosed to have TB disease without bacteriological confirmation of TB where 13 of them were adhered to stool-Xpert and referred to hospital. None of them have MDR-TB. Fifty-one children diagnosed to have no TB and advised to get TB preventive treatment or 2-weeks intensive monitoring for older children without any signs and symptoms of TB.

Table 17. Comparison of final diagnosis and suggested treatment for children with tuberculosis household contact in Puskesmas (N=65)

TB diagnosis and treatment	Children investigated in Puskesmas (N=65)	
	Adherence (n=42)	Non-adherence (n=23)
TB diagnosis		
Clinically TB	13 (31.0)	1 (4.3)
Bacteriologically TB	0 (0)	0 (0)
Not TB	29 (69.0)	22 (95.7)
Site of TB		
Pulmonary TB	13 (31.0)	1 (4.3)

Extrapulmonary TB	0 (0)	0 (0)
Not TB	29 (69.0)	22 (95.7)
TB treatment		
Fixed-dose TB treatment	13 (31.0)	1 (4.3)
Preventive treatment	23 (54.8)	20 (87.0)
Monitoring	6 (14.2)	2 (8.7)

11.3 Adherence of stool-Xpert MTB/RIF Ultra among children with presumptive tuberculosis in hospital

There was total 138 children with presumptive TB investigated in a secondary and tertiary hospitals that included as our study settings. However, only 60 child patients were invited to the stool-Xpert exam with 73% of them adhered resulted with valid result of stool-Xpert. None of eligible children excluded due to exclusion criteria since children were recruited to study before the final diagnosis and treatment suggested by the pediatrician.

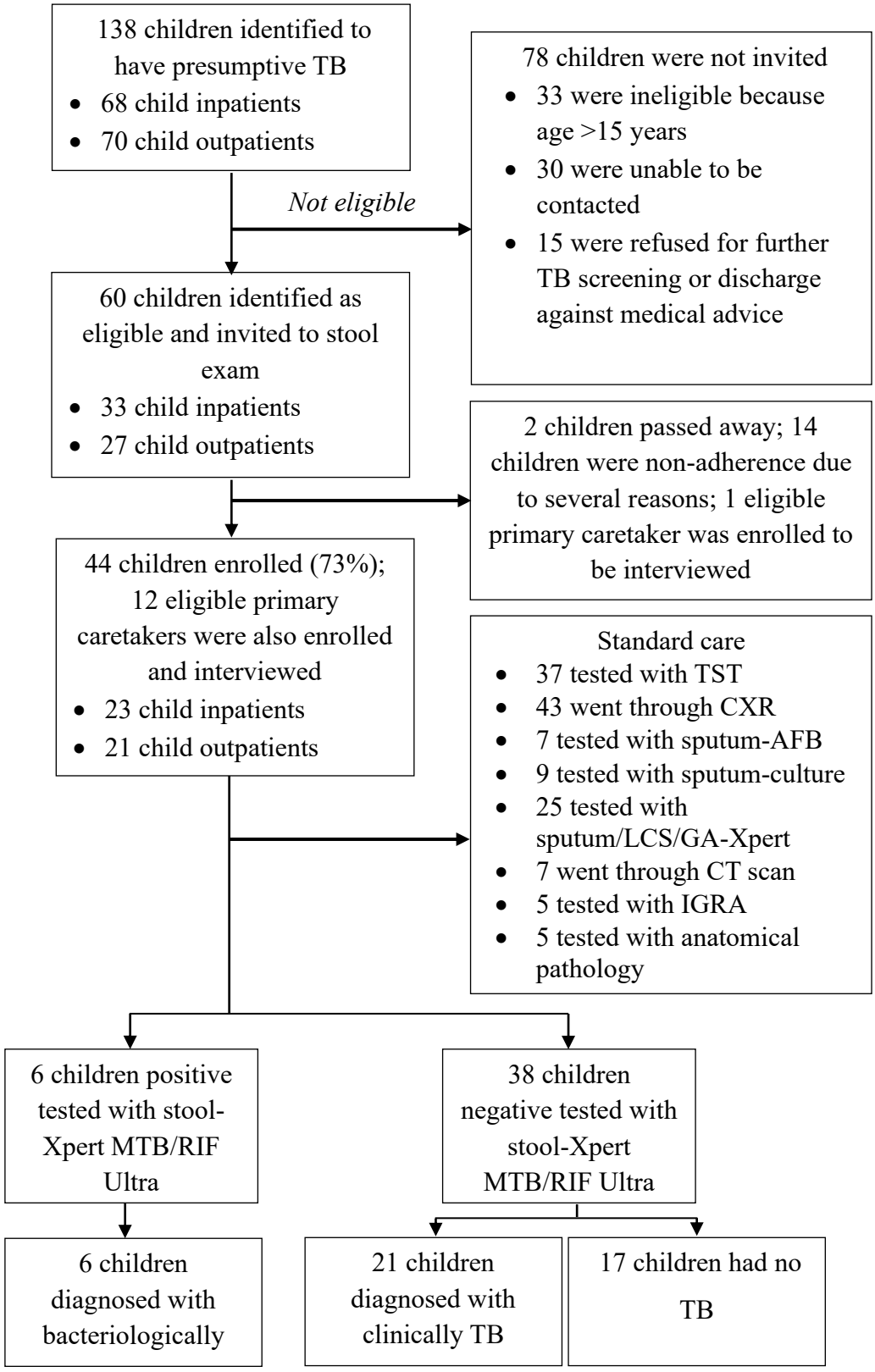

Figure 6. Children' screening, recruitment, and enrollment process in hospital

11.3.1 Socio-demographic characteristics of children with presumptive TB in hospital

Children in hospital were dominated with school-aged children and young adolescents. There was no socio-demographic characteristics which statistically significant could predict the adherence rate of stool-Xpert among primary caretakers and child patients in hospital. Overall, the socio-demographic characteristics were not different from children in Puskesmas: children in hospital were dominated with female and Minangnese, while others were coming from Melayu and Javanese ethnicities.

Table 18. Comparison of adherence to stool-Xpert by socio-demographic characteristics in hospital (N=60)

Socio-demographic characteristics	Children with presumptive TB in hospital (N=60)		*p* value[a]
	Adherence (n=44)	Non-adherence (n=16)	
Age (years), median (IQR)	11 (3-15)		
Age group (years)			0.344
0-4	10 (22.7)	6 (37.5)	
5-12	16 (36.4)	3 (18.8)	
13-15	18 (40.9)	7 (43.8)	
Sex			0.258
Male	20 (45.5)	4 (25.0)	
Female	24 (54.5)	12 (75.0)	
Ethnicity			1
Minangkabau	35 (79.5)	13 (81.2)	
Others	9 (20.5)	3 (18.8)	
Current education			0.252
Non-school age	11 (25.0)	7 (43.8)	
Primary school or lower	13 (29.5)	2 (12.5)	
High school	20 (45.5)	7 (43.8)	
Average monthly household income (USD)			0.064
<62	4 (9.1)	1 (6.2)	

62-123	16 (36.4)	6 (37.5)
123-185	7 (15.9)	8 (50.0)
185-247	4 (9.1)	1 (6.2)
247-309	8 (18.2)	0 (0)
>309	5 (11.4)	0 (0)

NA, not applicable. [a]Chi-squared test or Fisher's exact test. [b]1 USD=16,162 Indonesian Rupiah.

11.3.2 Risk of tuberculosis investigation, signs and symptoms screening, and physical examination of children with presumptive TB in hospital

Results of risk of TB investigation, signs and symptoms of TB screening, and physical examination among children in hospital were more various than children in Puskesmas. There were 6 child patients came with immunocompromised disease such as cancer and immunodeficiency disorders, but there were no children with HIV disease found in this study (Table 13).

About 9.1% children adhered to stool-Xpert were living in dormitory for school or military residential with confined environment. Fifteen (34%) of children adhered had living with more than 7 household members with 1 child need to shared bedroom with other 7 household members. These facts showed housing condition among child patients in hospital were diverse. However, in contact investigation, only 6 (10%) children in hospital can recalled their history of TB household contact who is their parents (3.3%) and sibling (6.7%) while others had unknown contact history (90%).

In risk of TB investigation, unlike children in Puskesmas, history of not having BCG vaccination (p value=0.017) and housing condition of having AC in the bedroom (p value=0.046) predicted the higher adherence rate of stool-Xpert among children in hospital. History of BCG vaccination may relate with seeking care behavior of primary caretakers of children, while having AC is related with socio-economic and housing condition of primary caretakers and children. Children who got BCG vaccination and having AC have higher adherence rate.

Most of children in adhered to stool-Xpert from hospital came with moderate or severe signs and symptoms of TB. About sixty-sixth have fever where 24

of them was prolonged cough, 25 (56.8%) had cough with 22 of them was prolonged cough, 30 (68.2%) experienced weight loss, malaise (36.4%), shortness of breath (40.9%), and abnormal nutritional status (86.4%) with most of them experienced severe anemia and malnutrition.

Several signs and symptoms such as chest pain and blood in sputum which not found among children in Puskesmas were found among both of children adhered and non-adhere of stool-Xpert in hospital. Several abnormalities with different severities also detected during physical examination where child patients experienced heart abnormalities have higher tendency to not adhere to stool-Xpert.

Table 19. Comparison of adherence to stool-Xpert by risk of tuberculosis investigation, signs and symptoms screening, and physical examination in hospital (N=60)

Risk of tuberculosis	Children with presumptive TB in hospital (N=60)		*p value*[a]
	Adherence (n=44)	Non-adherence (n=16)	
Investigation of TB risk			
Had history of immunocompromised disease	5 (11.4)	1 (6.2)	1
Living in dorm or camp	4 (9.1)	0 (0)	0.565
Not having BCG vaccination	4 (9.1)	6 (37.5)	0.017
Having >7 household member	15 (34.1)	2 (12.5)	0.120
Having >7 people sleep in one room	1 (2.3)	0 (0)	1
Had history of household contact	6 (13.6)	0 (0)	0.179
Had shared room with TB patient	6 (13.6)	0 (0)	0.179
Had shared bedroom with TB patient	5 (11.4)	0 (0)	0.311
History of taking TB drug			0.052
Ever	7 (15.9)	0 (0)	
Currently	11 (25)	1 (6.2)	

Never	26 (59.1)	15 (93.8)	
Having AC in the bedroom	15 (34.1)	1 (6.2)	0.046
Opening the window in the bedroom			0.711
Have no window	3 (6.8)	2 (12.5)	
Never open	1 (2.3)	0 (0)	
Frequently open	40 (90.9)	14 (87.5)	
Having smoker	31 (70.5)	15 (93.8)	0.086
Signs and symptoms screening			
Fever	29 (65.9)	11 (68.8)	1
Prolonged fever ≥2 weeks	24 (82.7)	11 (100)	0.490
Cough	25 (56.8)	7 (43.8)	0.545
Prolonged cough ≥2 weeks	22 (88.0)	7 (100)	0.892
Weight loss	30 (68.2)	10 (62.5)	0.918
Malaise	16 (36.4)	4 (25)	0.606
Chest pain	1 (2.3)	0 (0)	1
Shortness of breath	18 (40.9)	4 (25)	0.408
Blood in sputum	3 (6.8)	1 (6.2)	1
Abnormal nutritional status	38 (86.4)	11 (68.8)	0.143
Any abnormalities in physical examination			
Lung	16 (36.4)	3 (18.8)	0.326
Heart	1 (2.3)	4 (25.0)	0.015
Abdomen	6 (13.6)	0 (0)	0.179
Extremity	7 (15.9)	6 (37.5)	0.088

[a]Chi-squared test or Fisher's exact test.

11.3.3 Comparison of diagnosis uptakes of children with presumptive TB in hospital

There were about 33 children in hospital collected their sputum by conventional coughing or sputum induction in hospital (Table 14). From there, 23 children from adhered group and 5 children from non-adhere to stool-Xpert were tested positive or MTB detected. Sputum-AFB, culture with any specimen, LCS-Xpert, and

GA-Xpert were done for several child patients. However, in this study, there was no positive results for children enrolled to culture and LCS-Xpert.

Anatomical pathology only done for total 9 child patients in hospital, with 5 resulted positive among children adhered to stool-Xpert and 3 resulted positive among children non-adhere. IGRA was done for 5 child patients, with 1 resulted positive for children in hospital. CT scan was done for total 10 children, 6 (85.7%) from children adhered to stool-Xpert and 2 (66.7%) from children non-adhere to stool-Xpert had resulted suggestive meningitis TB imaging by CT scan. However, there is no previous TB screening and diagnosis were predictors of adherence of stool-Xpert among primary caretakers and child patients in hospital.

Table 20. Comparison of adherence to stool-Xpert by screening and diagnosis uptakes for children with presumptive tuberculosis in hospital (N=60)

Tuberculosis screening and diagnosis method	Children with presumptive TB in hospital (N=60)		*p* value[a]
	Adherence (n=44)	Non-adherence (n=16)	
Specimen collected and testing			
Sputum collected	27 (61.4)	6 (37.5)	0.177
Sputum-Xpert done	23 (52.3)	5 (31.2)	0.250
Sputum-Xpert positive	6 (26.1)	2 (40.0)	0.093
Sputum-AFB done	7 (15.9)	4 (25.0)	0.462
Sputum-smeared positive by AFB	1 (14.3)	1 (25.0)	1
Culture with any specimen			
Culture done	9 (20.5)	0 (0)	0.096
MTB growth detected by culture	2 (22.2)	(0)	NA
LCS collected	2 (4.5)	0 (0)	1
LCS-Xpert positive	0 (0)	0 (0)	
GA collected	1 (2.3)	1 (6.2)	0.466
GA-Xpert positive	0 (0)	1 (100)	1

Other clinical exam and testing			
Signs and symptoms: suggestive TB	43 (97.7)	15 (93.8)	0.466
CXR			
CXR done	43 (97.7)	16 (100)	1
Suggestive TB CXR features	27 (62.8)	10 (62.5)	1
TST			
TST done	37 (84.1)	10 (62.5)	0.088
TST positive with bump	18 (48.6)	8 (80.0)	0.151
Anatomical pathology			
Anatomical pathology done	5 (11.4)	4 (25.0)	0.230
Suggestive TB by anatomical pathology exam	5 (100)	3 (75.0)	0.444
IGRA			
IGRA done	5 (11.4)	0 (0)	0.311
TB infection detected by IGRA	1 (20.0)	0 (0)	NA
CT scan			
CT scan done	7 (15.9)	3 (18.8)	1
Suggestive TB CT scan features	6 (85.7)	2 (66.7)	1

NA, not applicable. [a]Chi-squared test or Fisher's exact test.

11.3.4 Final diagnosis of TB and treatment for children with presumptive TB in hospital

About 47% from 44 child patients adhered to stool-Xpert in hospital were diagnosed with clinically TB, 13% diagnosed with bacteriological confirmation of TB, and 38% diagnosed with not TB. In non-adhered group, 68% of 16 child patients were having clinically TB, 12.4% were having bacteriological confirmation of TB, and 18.8% were having other disease. Several of them were diagnosed with extrapulmonary TB such as meningitis TB, intestinal TB, and lymphadenitis TB.

Child patients with TB disease were treated with fixed-dosed combination (FDC) for children or adult followed the weight and nutritional status of

each child patient. None of child patients with TB disease were diagnosed with MDR-TB. Child patients diagnosed with other disease were suggested to have TB preventive treatment or 2-weeks intensive monitoring for any possibility of signs and symptoms development.

Table 21. Comparison of final diagnosis and suggested treatment for children with presumptive TB in hospital (N=60)

TB diagnosis and treatment	Children with presumptive TB in hospital (N=60)	
	Adherence (n=44)	Non-adherence (n=16)
TB diagnosis		
Clinically TB	21 (47.7)	11 (68.8)
Bacteriologically TB	6 (13.7)	2 (12.4)
Not TB	17 (38.6)	3 (18.8)
Site of TB		
Pulmonary TB	19 (43.2)	7 (43.8)
Extrapulmonary TB	8 (18.2)	6 (37.5)
Not TB	17 (38.6)	3 (18.7)
TB treatment		
Fixed-dose TB treatment	27 (61.4)	13 (81.3)
Preventive treatment	2 (4.5)	1 (6.2)
Monitoring	15 (34.1)	2 (12.5)

11.4 Reasons of non-adherence from primary caretakers on stool collection

Research team were promoted the benefit and stool collection procedure for stool-Xpert by help from health workers included TB officer, general practitioner, and pediatrician. However, several primary caretakers and child patients who showed interest during invitation process but not perceived any benefit since no signs and symptoms perceived by primary caretakers, could not cope with the barriers faced during the stool collection procedure, or even lost to follow-up.

Table 16 shows having no signs and symptoms perceived by primary

caretakers or asymptomatic children was the most common reason for primary caretakers to finally decided to withdrawn from stool-Xpert. Other reasons were felt inconvenience to collect the stool specimen such as having bad odor or difficult to deliver the specimen to healthcare, constipation, and lost to follow-up primary caretakers and child patients by healthcare and research team. Moreover, two patients were passed away due to severity of signs and symptoms of TB before the process of stool collection was finished.

Table 22. Reasons of non-adherence from primary caretakers by healthcare (N=39)

Adherence	Reasons	Non-adherence of stool-Xpert N (%)	
		Children with TB household contact in Puskesmas n=23	**Children with presumptive TB in hospital n=16**
Primary caretakers' perspective			
No attempt	Asymptomatic child	11 (100.0)	0
Attempted but could not adhere	Disagreement among parents	2 (40.0)	3 (60.0)
	Inconvenience	6 (66.6)	3 (33.3)
	Had constipation	0	6 (100.0)
	Death	0	2 (100.0)
Health providers' perspective			
No attempt	Lost to follow-up	4 (66.6)	2 (33.3)

11.5 Patterns of adherence to tuberculosis investigation among children and total tuberculosis cases recorded by healthcare

There were several patterns which can be used to describe adherence of stool-Xpert among primary caretakers and children. In Puskesmas, from 11 patterns of TB investigation followed by primary caretakers and children, three patterns could not include stool-Xpert. However, 'only done the signs and symptoms screening' pattern had highest number of children examined of children invited to stool-Xpert (17/65).

These children were only taking signs and symptoms screening as follow-up of their household contact with bacteriologically TB patients.

In hospital, 14 from 19 patterns of TB investigation followed by primary caretakers and children were including stool-Xpert. None of children only went through signs and symptoms since children in hospital were presenting signs and symptoms related with TB, showed the necessary of further examinations to decide the TB diagnosis.

Table 23 and Table 24 only showed results from standard care practiced in each healthcare and stool-Xpert for the aimed of this study. Other screening and diagnostic methods done after previous standard care applied and show no suggestive TB while children showed signs and symptoms related with TB, or done to support the result of previous standard care.

Table 23. Patterns of adherence to tuberculosis investigation among children with tuberculosis household contact in primary healthcare (Puskesmas) (N=65)

Tuberculosis examinations in Puskesmas							Number of people examined	Number of suggestive TB		TST*	Results of further examinations**				
S&S	TST	CXR	Stool -Xpert	Sputum -Xpert	Sputum -AFB	Culture		-	+		CXR	Stool-Xpert	Sputum-Xpert	Sputum-AFB	Culture
												n			
+			+				15	15	0			0			
+	+		+				13	8	5	5		0			
+	+	+	+	+			6	0	6	3	6	0			
+	+	+	+				4	0	4	3	4	0			
+			+	+			2	2	0			0			
+		+	+				1	0	1		1	0			
+	+		+	+			1	1	0			0			
+							17	17	0						
+	+	+					3	1	2	1	1				
+	+	+		+	+	+	2	0	2	0			2		2
+	+		+				1	0	1	1		0			
Total							**65**	**44**	**21**	**13**	**12**	**0**	**2**	**0**	**2**

TST*, TST as first test completed. Results of further examinations**, suggestive TB cases captured by further examinations.

Table 24. Patterns of adherence to tuberculosis investigation among children with presumptive tuberculosis in hospital (N=60)

Tuberculosis examinations in hospital							Number of children examined	Number of suggestive TB		TST*	Results of further examinations**				
S&S	TST	CXR	Stool-Xpert	Sputum-Xpert	Sputum-AFB	Culture		-	+		CXR	Stool-Xpert	Sputum-Xpert	Sputum-AFB	Culture
													n		
+	+	+	+				13	2	11	10	8	0			
+	+	+	+	+			13	5	8	3	6	2	2		
+	+	+	+	+		+	3	0	3	1	2	1	1		1
+		+	+				2	1	1		1	0			
+	+	+	+		+		2	1	1	0	1	0		0	
+		+	+	+			2	0	2		2	1	1		
+	+	+	+	+	+	+	2	0	2	1	2	1	1	1	1
+		+	+		+		1	0	1		1	0		0	
+		+	+			+	1	0	1		1	0			0
+	+	+	+			+	1	0	1	1	1	0			0
+	+	+	+		+	+	1	0	1	1	1	0		0	0
+	+		+	+			1	1	0	0	0	0	0		
+	+	+	+	+	+		1	0	1	1	0	0	0	0	
+		+	+	+		+	1	0	1		1	1	1		0
+	+	+					4	0	4	4	0				
+	+	+			+		4	0	4	3	3			1	
+		+					3	0	3		3				
+		+		+			3	0	3		3		2		
+	+	+		+			2	0	2	1	1		0		
Total							**60**	**10**	**54**	**26**	**37**	**6**	**8**	**2**	**2**

TST*, TST as first test completed. Results of further examinations**, suggestive TB cases captured by further examinations.

12. Key informant interviews

12.1 Feasibility assessment of stool-Xpert screening among health workers

Health workers from Puskesmas and hospital were recruited as informants after several months of implementation of stool-Xpert in their healthcare. Health workers were asked about their experiences in introducing stool-Xpert, collecting stool specimen from child patients and primary caretakers and stool-Xpert exam according to their role background as general practitioner, TB officer, nurse and laboratory staff.

Table 25. Background characteristics of the primary caretakers (N=11)

Characteristics of the participants	Number of participants n (%)
Female	9 (81.8)
Length of working in TB program (years)*	
1-5	10 (90.9)
6-10	1 (9.1)
Healthcare	
Puskesmas	6 (54.5)
Hospital	5 (45.5)
Occupation	
General practitioner	1 (9.1)
TB officer	6 (54.5)
Nurse	2 (18.2)
Laboratory staff	2 (18.2)

Note: *Length of working in TB program (years) in current healthcare

12.1.1 Situation analysis

Currently, childhood TB screening and diagnosis in Padang Municipality, Indonesia faced lack of detection rate due to limitation of health resources and education. Even though contact investigation and screening and diagnosis algorithm built, the recommendations were not applicable on the field. Both healthcare providers faced problem with limited equipment in Puskesmas as lower-settings of

healthcare provider caused several screening and diagnosis method prioritized for children with signs and symptoms, or high-TB risk only.

“Actually, all children with household contact need to be screened with tuberculin skin test (TST). However, due to limited stock of tuberculin liquid, we only can do TST to children with signs and symptoms or children with malnutrition. If the parents with children with household contact still want to examine their children, we can do it depends on the availability of TST or refer them to hospital for chest X-ray.” (H11)

“We prioritize children with signs and symptoms related to TB, like cough and fever >14 days, and malnutrition; and children with HIV-positive.” (H6)

Both healthcare providers also faced refusal from primary caretakers whose asymptomatic children. Primary caretakers may refuse screening test and TB preventive treatment (TPT) was suggested by health workers.

“However, in the field, there are often challenges as families may refuse examination due to the absence of symptoms and reluctance to take medication.” (H10)

“Many parents refuse to give medicine to their children if there are no signs and symptoms.” (H3)

When children with signs and symptoms already screened and suggested to be referred to have sputum exam, but younger children cannot produce sputum resulted to low quality of sputum exam procedure.

“… (sputum) specimen sent should precisely fit to the given criteria to rise the quality of TB exam … it must be sputum sent, not only saliva.” (H2)

12.1.2 Rationale

Children from both populations, children with TB household contacts in Puskesmas and children with presumptive TB in hospital due to TB signs and symptoms were having similar problem with inability to expectorate sputum. Children referred or admitted to hospital would have sputum induction which invasive and painful for children. Using stool specimen was given opportunity for health workers to do early screening for children without delayed.

“It's the first time I've heard of TB testing using stool samples. It is promising since most of the case, children cannot produce sputum but defecating every day. The hardest part is to ensure parents to join the screening program.” (H5)

Stool exam also had higher adherence among primary caretakers in Puskesmas since stool exam not required children to be refer to hospital, except the specimen itself. While to do sputum induction, children need to be referred to hospital and children with specific signs and symptoms, and negative screening result need to be referred to hospital. Screening method available in Puskesmas such as tuberculin skin test (TST) was also invasive. Therefore, stool collection may had higher possibility to be implemented in further settings.

“It's more effective with stool examinations. Compared to referrals, it's somewhat challenging, as sometimes patients don't have health insurance, and not everyone can go directly to the hospital … Initially, there was concern that the parents may refuse, but so far, they are willing to undergo the TB testing with stool.” (H4)

“It is more convenient for children then tuberculin skin test which invasive for children.” (H3)

12.1.3 Health condition of children-related

Asymptomatic children showed positive adherence of doing contact investigation for a long time. The primary caretakers assumed that the absence of signs and symptoms caused children not to suspect TB therefore they refused to undergo TB household contact screening and stool-Xpert screening.

“However, on the field, there are often challenges as families may refuse examination due to the absence of symptoms and reluctance to take medicine.” (TB officer, H10)

It usually happened in Puskesmas when children came without signs and symptoms. While in higher-level healthcare, health workers would not found primary caretakers’ refusal due to asymptomatic children since children already referred with various level of severity. This health condition also leads to delayed in stool collection since suspected TB children were having constipation or severe signs and symptoms.

“… some patients do not have a regular constipation schedule each day, and when they do defecate, it may be only in a small amount. ” (Nurse, H8)

"… patients here are mostly bedridden and lack of movement (children admitted to intensive care unit (ICU) or high care unit (HCU))." (Nurse, H8)

12.1.4 Human resources-related

Health worker who responsible as TB officer, both in Puskesmas and hospital face multiple work burden due to limited human resources in each healthcare. TB officer in Puskesmas need to divide their work to other program such as immunization and rabies program. These led to health worker cannot do proper contact investigation among children with TB household contact with home visit, regular monitoring, or help children to do specimen delivery.

"… expanding number of TB officer for simultaneous visits to multiple locations would be advantageous, enabling proactive specimen collection as some patients may face challenges in personally delivering samples back to Puskesmas." (TB officer, H9)

While TB-related officer in higher-level healthcare face high amount of specimen examination requests from hospital and patients or specimen referred from other cities and provinces. Sometimes specimen examination is requested, but none of specimen arrived to laboratory. Miscommunication among nurse, laboratory staff, and residents led the specimen which was collected not delivered to laboratory but storage in specimen cabinet in each ward for long time, and not suitable for the examination.

"The request form was submitted to the e-TB system, but the sample is not arrived yet to laboratory." (Laboratory staff, H1)

"The difficulty arises when the sample does not align with the appropriate criteria for examination." (Laboratory staff, H2)

Thus, a comprehensive training for stool-Xpert need to be done for all TB-related health worker. This aim to help each health worker have the same perception about why they do stool collection, principle and use of stool specimen, how to do stool collection and examination.

"All health worker related to TB need to be included and learn about stool specimen collection and examination, then all will have the same perception about the method and have ability to explain it properly to responsible health worker and primary caretaker from each ward." (Nurse, H7)

12.1.5 Tools or equipment-related

Stool examination will be done with GeneXpert machine which available in several Puskesmas in Padang Municipality. However, to process and examine stool specimen, unlike sputum specimen, advanced biocontainment equipment with high cost and complex instalment is needed. Currently, Puskesmas as a primary healthcare provider is not covering this area of laboratory specification. Therefore, stool specimen needs to be referred to hospital with high level of protection against biological hazards laboratory.

"It is applicable only in hospital since Puskesmas have no biosafety cabinet." (Laboratory staff, H1)

"… stool collection can be adapted to all healthcare level, but for stool exam, the equipment in Puskesmas is not suitable … we need biosafety cabinet if we want to do stool exam in the future." (TB officer, H11)

Most of the time, TB screening and diagnostic equipment in both healthcare is available in limited stock. It restricts other utilization of TB screening and diagnostic equipment with other specimen which is not prioritized by the NTP but suggested by the international TB forum. Recently, sputum specimen is the only specimen acknowledged by the NTP.

"It is possible to conduct stool exam, but it requires legal instruction from the NTP. If we use reagents for other specimen than sputum, they won't provide the same number of reagents in the following month." (Laboratory staff, H2)

"Even though we are a referral hospital, but in fact, we are still running out of stock (Xpert cartridge) every time." (TB officer, H6)

12.1.6 Technical-related

There are several technical issues arises during the stool collection, process, and examination. However, there are also positive feedbacks from health worker after implementing stool-Xpert algorithm in their healthcare.

"… stool specimen has to be delivered to hospital due to limited equipment in Puskesmas." (TB officer, H3)

"Stool specimens tend to have a stronger odor, which make me dizzy. The specimen must be weighted precisely to ensure the accuracy." (Laboratory staff, H2)

“Collecting stool is easier than collecting sputum from children … since not all children can produce sputum, especially children aged <5 years.” (TB officer, H9)
“Stool collection is very easy and applicable. As a nurse, it is common for me to collect stool specimen although not for TB testing.” (Nurse, H7)
“Stool and sputum processing are similar. None is easier or difficult.” (Laboratory staff, H1)

To ensure the accuracy of the whole stool-Xpert process, laboratory staff implies the urgency of health education within health workers related with TB and primary caretakers or child patients, and provide and extensive communication with primary caretakers in how to collect appropriate specimen.
“Doctors and nurses who directly involved with patients are expected to educate patients in how to collect specimen properly.” (Laboratory staff, H1)

Sensitivity and specificity issue after not provided stool exam instruction from the NTP is intense. Even though stool specimen for TB diagnostic already suggested by the WHO, health worker related with TB is still waiting for further notification from the NTP, especially stool exam as a TB screening method.
“I remain unsure about stool-Xpert due to numerous negative results. I do not know if it is applicable for screening.” (TB officer, H11)

12.1.7 Primary caretakers-related

Primary caretakers’ involvement is crucial for childhood TB screening and diagnosis. Primary caretakers who mostly parents of children with TB household contact or suspected TB children will decide further TB screening and diagnosis method and TB treatment received by children. Primary caretakers’ refusal appears with asymptomatic children, compounded by TB stigma within the community. Therefore, benefit of stool as non-invasive method can be promoted.
“Parents refuse to take their children for screening or treatment due to the stigma associated with TB or the lengthy treatment regimen.” (TB officer, H11)
“Parents feel afraid of using stool specimens (as they perceive it as indicating a serious disease). They question why it is necessary for a child with no symptoms.” (TB officer, H3)

“When compared to tuberculin injection (tuberculin skin test), parents would likely prefer stool exam while obtaining sputum can be challenging.” (GP, H4)

“In the initial stage, it is challenging because there are still many questions from parents as there has not been mass health promotion related with stool examination for TB screening (which is unfamiliar).” (TB officer, H5)

“Challenges may arise when parents initially show enthusiasm and willing to undergo the examination but later fail in returning the sample for several reasons.” (TB officer, H10)

12.1.8 Health system-related

The existence of legal instruction or guideline to use stool specimen in TB screening and diagnosis algorithm by the NTP is a must. This will provide assurance in doing stool-Xpert for health workers and primary caretakers related to its effectiveness, efficiency, and public health impact.

“Once the guidelines for stool-Xpert establish, a well-planned procedure will be implemented specifically for child patients in Puskesmas. Assuming the accuracy meets expectations and the equipment is suitable, there is a strong imperative to proceed with stool-Xpert implementation.” (TB officer, H3)

“… a national standardized stool-Xpert guideline is necessary, start from the collection process, storage, and examination to ensure the accuracy of stool-Xpert result.” (Nurse, H7)

Table 26. Stool-Xpert implementation experiences of health workers in Puskesmas and hospital

Aspects	Puskesmas			Hospital		
	Supporting factors	**Barriers**	**Facilitators**	**Supporting factors**	**Barriers**	**Facilitators**
Health condition of children	NA	Children is asymptomatic	NA	NA	Having constipation	NA
	NA	NA	NA	NA	Children with severe TB signs and symptoms	NA
Human recourses	Health workers joined stool-Xpert training	None health workers to do home visit, screening, and specimen delivery from house or to hospital	Comprehensive training for health workers	Trained health worker available 24 hours	Limited health workers to deliver specimen from ward to laboratory	Comprehensive training for health workers
	Health workers explained and suggested stool-Xpert to primary caretakers	NA	NA	NA	Miscommunication among health workers for specimen collection and delivery time	NA

	NA	No proper biosafety cabinet (BSC) available for stool-Xpert	NA	Advanced laboratory equipment	Lack of Xpert cartridge	NA
Tools or equipment						
Technical parts	NA	Stool specimen needs to refer to hospital	NA	Stool is common for other disease diagnosis	Bad odor of the specimen	NA
	Unsure about the accuracy of stool specimen	NA	Extensive communication among doctor or nurse with primary caretakers	NA	Unsure about the accuracy of stool specimen	Extensive communication among doctor or nurse with primary caretakers
	NA	NA		Stool processing is similar with sputum	Complicated specimen processing [e.g. specimen must be weighted]	NA
Primary caretaker involvement	Children with symptoms [e.g. cough >14 days, malnutrition]	Children is asymptomatic leads to parents' refusal	NA	NA	NA	NA
	NA	Unfamiliar method	NA	NA	NA	NA
	NA	Not clearly understood how to	NA	NA	NA	NA

	NA	prevent contamination TB stigma	NA	NA	NA	NA
Health system	NA	Stool is not standardized by the Ministry of Health	NA	NA	Stool is not standardized by the Ministry of Health	NA

12.2 Adherence, barriers, and coping mechanism assessment of stool-Xpert screening among primary caretakers

During the study period, we interviewed a total of 29 primary caretakers from two sources of population. The first group included 16 primary caretakers of the children exposed to TB based on household contact investigation in Puskesmas where children exposed to a family member diagnosed with tuberculosis in 16 different households. The second group included 13 primary caretakers whose children were sick and presumptive with TB based on screening by the pediatrician at the hospital.

The research team recruited primary caretakers from primary and higher-level healthcare to compare the experience of implementing stool collection in two different level of healthcare with different characteristics and severity of signs and symptoms of TB. The research team also interviewed 5 primary caretakers who expressed interest but did not show up to deliver stool specimen back to the healthcare provider. Of 29 primary caretakers, 93.1% of them are mothers of child patients; their median age was 41 (IQR: 46.5-32). All of them showed interest at the first time and agreed to do stool collection. However, only 24 of them were able to deliver the stool specimen.

Table 27. Number of primary caretakers interviewed

No	Criteria	Puskesmas	Hospital
1	Primary caretakers with children enrolled to stool-Xpert	12	12
2	Primary caretakers with children non-adhered to stool-Xpert	4	1
	Total	16	13

12.2.1 Difficulties and solution of stool collection for children with tuberculosis household contact experienced by primary caretakers in Puskesmas

Of 12 from 16 primary caretakers recruited from Puskesmas, despite those difficulties and barriers, all of them done the stool collection. All of the specimen delivered and referred to hospital's laboratory to be examine with valid results. While 4 primary caretakers had withdrawn and refuse to adhere from the research due to health problem related to their status as index TB case, health condition of children such as asymptomatic children and having constipation, and health behavior where children and primary caretakers could not cope with the inconvenience stool specimen collection procedure.

12.2.1.1 Acceptability

Two main reasons for parents to accept the stool-Xpert were first, it was recommended by the health workers such as TB officers or general practitioners in Puskesmas. Second, it was also easy to do.

"I just followed the suggestion for doing stool collection from TB officer and general practitioner in Puskesmas when I took my son for general check-up about a week ago." (P21)

"This is my first time to do the stool collection and I feel no difficulties to do it." (P1)

We also met primary caretaker with medical education background and knowing that possible stool exam for intestinal TB. It was easier for primary caretaker to accept the stool exam for children.

"Initially, I thought that stool exam is only for intestinal TB. Can it also be used for PTB? However, I think it is easy to do; and based on journals I have read, it is more accurate than tuberculin skin test (TST) (for diagnosis)." (P23)

When children had no signs and symptoms of tuberculosis, most parents perceived their children were well even exposed to TB, Moreover, asking them to do some investigation was perceived as their children were sick. This two conflicting information could be confusing for both parents and children to agree and make consensus. Explanation about justification for screening from health workers could increase acceptability of the test.

“My husband did not agree to continue the examination since he was think there is no need to do that since my son was asymptomatic. However, I tried to explain the aim of stool exam like explained by the TB officer…” (P24)
“He (my son) was afraid to be examined or suggested to take more drugs … I need to explain to my son that none injection or invasive examination will be done to him ...” (P16)

In some cases, even TB officer and one side of parents helped to explain the aims of stool-Xpert to others parent, it is not always work out.
“I told his mother that it was only took the stool, but his mother was not agreed since our son have no signs and symptoms.” (P26)

12.2.1.2 Specimen collection

Clear instructions in how to do specimen collection from health workers to primary caretakers is a key success of stool collection. Health workers and researchers need to provide clear instructions on amount of stool specimen needed, how to collect stool specimen from toilet bowel or diaper (for young children), and how to prevent cross contamination between stool and urine, or stool with other bacteria inside toilet bowl. If there is any hesitation among primary caretakers in doing stool collection, health workers and researchers were opened to discuss with primary caretakers.
“This is my first time in doing stool collection ..., it was easy to be done since the health worker also gave a clear explanation.” (P23)
“I asked my daughter to pee first before to make sure that the stool is not contaminated by the urine.” (P3)

Older children who asked to collect stool by themselves may feels inconvenience. However, accompaniment and clear instructions from parents will be help.
“I need to explain to my son to help collect the stool specimen. It is inconvenience for him due to bad odor.” (P16)

There also several children who felt inconvenience since they thoughts it is disgusting then the parents were asked to withdrawn from the stool exam procedure.

“He said it is disgusting and he could not do it.” (P28)

12.2.1.3 Health condition of children

Stool collection is practically easier for younger children who still use diaper. Primary caretakers with children who have regular defecation also have positive experience in collecting stool.

“I did not have any difficulties since my son still use diaper and have regular defecation.” (P21)

However, several children also have problem with constipation. It some cases, it would delay the specimen delivery back to healthcare, while others chose to withdrawn from the stool exam procedure.

“It's not that difficult to collect the stool, but my children have a problem with their defecation schedule. Therefore, it took a long time to collect the stool sample and deliver it back to the TB officer in Puskesmas.” (P3)

“My children had constipation for a week now. I think I will only take the preventive treatment from Puskesmas.” (P27)

12.2.1.4 Availability

Assurance of the availability of primary caretakers or another guardian to collect and deliver stool specimen back to Puskesmas is needed. Primary caretakers may have tight working time and won’t be available to collect stool specimen in the targeted time, caused delay to stool exam procedure.

“My family help us (I and my husband) to collect the stool specimen (since we were both working) …” (P2)

Primary caretakers with more than one child usually takes longer time to collect all specimen together from all children. There is an urgency to explain how to store stool specimen at home to prevent decreased quality of specimen, in case there is delay in stool delivery.

“Challenge that I experienced is my (three) kids’ defecation schedules are different.” (P23)

Other than that, we found children with TB household contact had primary caretakers who was infected by TB and under medical treatment. Due to side effects of anti-TB drug, they struggled on following daily task, including collecting stool sample for the children.

“I was unable to continue since I had taken anti-TB medication. I was less focused and fatigued, making it difficult to collect stool samples from my two children. Additionally, my legs and hands have been slightly painful until now.” (P29)

Table 28. Stool collection experiences among children with TB household contact in Puskesmas

Aspects	Reasons to adherence			Reasons to not adherence
	Supporting factors	**Difficulties**	**Solutions**	**Barriers or constraints**
Acceptability	Easy to do	No signs and symptoms	NA	Disagreement among parents
	Non-invasive	Fear exhibited by children to undergo further health procedure	NA	NA
	Advices from TB officer	Disagreement among both parents	Recommends by TB officer	NA
	Stool exam is not new		Further discussion about the aim of stool exam with family	NA
Specimen collection	Understand how to do it	Not clearly understood how to do it	Discussed and received more information from the health worker	Having constipation
	NA	Not clearly understood how to prevent contamination	Prevent specimen for contamination: children aged ≤2 years take specimen from the upper side of stool on diaper; for children ≥3 years to urine first then defecate	Inconvenience due to bad odor

	NA	NA	Assisting by TB officer	NA
	NA	Inconvenience for older children to collect by themselves	Accompaniment by primary caretakers	NA
	NA	Inconvenience due to bad odor	NA	NA
Health condition of children	Use diaper	NA	NA	NA
	Regular defecation	NA	NA	NA
Availability	NA	Working primary caretaker	Ask for family' help	NA
	NA	Number of children	Specimen can be store in room temperature without direct sun light for one day	NA
	NA	NA	NA	Primary caretaker is an index TB case

12.2.2 Difficulties and solution of stool collection for children with presumptive tuberculosis experienced by primary caretakers in hospital

Of 12 from 13 primary caretakers recruited to the interview have collected the stool specimen to be examined. Two children from primary caretakers who participated in this interview passed away after they collected stool specimen and received clinically TB as final diagnosis, while one child did not finish stool collection due to severe signs and symptoms, as well as constipation.

12.2.2.1 Acceptability

Similar to primary caretakers in Puskesmas, those in hospital also experienced easy-to-do and non-invasive stool specimen collection. Primary caretakers also have direct communication with pediatrician who suggested the stool exam, increased the adherence of doing stool collection for further examination for child patients with TB signs and symptoms. Pediatrician also educated primary caretakers that stool exam is common for other disease though it is still rare in TB diagnosis. Family relation within parents and children also increase primary caretakers' adherence towards stool collection.

"I have done sputum collection for my daughter; the pediatrician and nurse also did blood collection before. As a parent, I think stool collection is way easier and non-invasive since there is no tube-inserting or injection procedure which may hurt the children …" (P17)

"This is not my first time to heard about stool exam. The doctor already explained to me about several kind of specimen can be used to do TB examination including stool." (P12)

"I did not have any problem … I only thought that this is my own children, so why I need to feel inconvenience about it?" (P6)

12.2.2.2 Specimen collection

Primary caretakers whose child inpatients in hospitals have direct access for nurses or pediatricians' accompaniment, made it easier for primary caretakers to asked for assistance of health workers or more specific information on how to done stool collection.

“We just followed the steps informed by the researcher. We just made sure that the sample is not contaminated by urine.” (P6)

“For the sample collection, I did not have any problem. But, in the first time, I thought we only can use stool from morning defecation. I have confirmed it to the nurse and researcher, we can the sample from other time. Therefore, it is easier for me to do the stool collection and gave it as soon as possible to the nurse and researcher to examine.” (P12)

“We a little bit misinformed about how to store it. Therefore, the sample was lost and we need to collect it for the second time. Still, there is not difficulties in doing it.” (P7)

12.2.2.3 Health condition of children

In hospital, child inpatients admitted with severe signs and symptoms with several health problem which required them to use diaper. However, due to disease severity, children experienced several conditions such as lack of movement and constipation which may hinder the stool collection procedure.

“It is easy to do the sample collection since they will only take the sample from my daughter's diaper.” (P9)

“There is no difficulties for me and my children also defecating regularly. I only concerned about the contamination with urine.” (P20)

“However, my children have problem with his defecating process, the stool is in liquid form and it is uneasy to collect it. Therefore, we failed to collect the stool until my son is discharged from the hospital.” (P10)

12.2.2.4 Availability

Primary caretakers who child inpatients stayed in pediatric intensive care unit (PICU) or high care unit (HCU) will be helped by a trained nurse to collect the stool specimen, since primary caretakers were not allowed to enter the wards. While primary caretakers of child inpatients in acute and chronic wards, or child outpatients would have the responsibility to collect the stool specimen.

“For my case, the sample collection was done with help from the nurses in hospital.” (P4)

“It is easier for me to do the stool collection and gave it as soon as possible to the nurse and researcher to examine.” (P13)

12.2.2.5 Logistic

Primary caretakers whom collect stool specimen would be informed how to collect an appropriate stool specimen by the nurse or residents or research team. Therefore, several primary caretakers also provided with personal protective equipment such as gloves.

“I took the sample by myself. The researcher gave us a pair of hand gloves, then I think it is safe and easy.” (P15)

Table 29. Stool collection experiences among children with presumptive TB in hospital

Aspects	Reasons to adherence			Reasons to not adherence
	Supporting factors	**Difficulties**	**Solutions**	**Barriers or constraints**
Acceptability	Easy to do	NA	NA	NA
	Non-invasive	NA	NA	NA
	Advices from pediatrician	NA	NA	NA
	Severity of signs and symptoms	NA	NA	NA
	Stool exam is common for disease diagnosis	NA	NA	NA
	Family relation with the children	NA	NA	NA
Specimen collection	Understand how to do it	Not clearly understood how to do it	Discussed and received more information from the health workers	NA
	NA	NA	Assisting by a nurse or public health officer	NA
	NA	Not clearly understood how to prevent contamination	Prevent specimen for contamination: children aged ≤2 years take specimen from the upper side of stool on diaper; for	NA

			children ≥3 years to urine first then defecate	
	NA	Unknown time to collect a specimen	Understand the principle of stool specimen collection: not strictly require morning stool	NA
	NA	NA	Accompaniment by nurse or resident doctor	NA
Health condition of children	Use diaper	NA	NA	Having constipation
Availability	Nurse is available 24 hours to help	NA	NA	NA
Logistic	Hand gloves is available	NA	NA	NA

12.3 Feasibility of further implementation of stool-Xpert in Puskesmas and hospital

Most of the informants agreed that stool-Xpert have chance to be implement. This chance came after the benefits of stool is out such as applicable for younger children or asymptomatic children who cannot produce sputum and no need referral process. Others still unsure about the referral specimen mechanism from Puskesmas to hospitals.

“I think it can be used for further implementation … since not all of children have cough or cough with sputum …” (P25)

“Stool specimen collection is good considering that referrals are not for everyone since not everyone have resources to go there. It's easier to conduct examinations initially at the Puskesmas, and if necessary, then refer.” (H9)

“I do not understand about the difference of screening and diagnosis. I think to make it safe; we still need to combine it with doctor or pediatrician opinion.” (P21)

Stool collection found to be more acceptable for primary caretakers since it was non-invasive than TST that commonly used for early screening. However, implementation of stool-Xpert is still debatable since there is no standardized guideline provided from the Ministry of Health, specimen cannot be assessed at Puskesmas to limited biocontainment equipment. It was also notified by the primary caretakers.

“Yes, it's the first time I've heard about it during this research. When compared to tuberculin skin test, parents would likely prefer stool testing if the results are accurate, as obtaining sputum also can be challenging.” (H4)

“No injection, no cry.” (P16)

“We need a standardize guideline about each step of collection, storage, and examination to ensure the accuracy of our test result.” (H7)

“Stool collection is possible to be done in Puskesmas or hospital but for stool exam, we are still lack of safety equipment in Puskesmas, right?” (H6)

“Since the stool collection part is easy to do, I think it is applicable to do for the next cases. The thing maybe since it is not the Puskesmas right to do the (laboratorium) examination? It is the hospital. Then, the health workers need to make sure that the result will also come fast or on time.” (P11)

Therefore, several recommendations come from primary caretakers and health workers if stool-Xpert will be implemented further in Puskesmas and hospital: need to be done alongside with other screening and diagnosis method, comprehensive training for all health workers related with TB , clear instructions or guideline, health promotion related with TB and stool-Xpert, availability of the tools or equipment, expansion on health workers number, and children aged under-5 years.

“I think we need to look up at the signs and symptoms too, and the suggestion from the pediatrician.” (P11)

“We may need do further training for laboratory staff in Puskesmas if we want to implement it in Puskesmas.” (H4)

“First, we need to educate our patient that contact investigation is important. We need to investigate close and household contact, and it is important to prevent severe TB in any possible contact, especially for children. Second, we need to try to minimize the TB stigma like doing health promotion in World TB Day.” (H7)

“Regularly making sure of the availability of tools or equipment. Even though we are a referal hospital, but in fact, we are still running out of stock almost every time. Then, all health worker related with TB need to have the same perception about the screening and diagnosis order; to prevent misunderstanding or mis method that already plan. Then, maximize education process to patients, especially about each screening or diagnostic method, and each result.” (H6)

“If possible, expanding the TB team for simultaneous visits to multiple locations would be advantageous, enabling more proactive sample collection as some patients may face challenges in personally delivering samples back to Puskesmas.” (H9)

“It would be nice to have stool-Xpert for children, especially for children <5 years. And maybe wider health promotion about the existence and use of stool-Xpert is needed.” (H11)

Table 30. Recommendation from primary caretakers and health workers for further implementation of stool-Xpert in Puskesmas and hospital

	Supporting factors	Difficulties	Recommendations
Primary caretakers	1. Applicable for children who cannot produce sputum 2. Non-invasive	1. Ensure about the accuracy 2. Refer specimen to hospital or higher-setting laboratory	1. Alongside with other diagnostic and screening method, and final decision must be made by pediatrician.
Health workers	1. Applicable for younger children 2. No need referral process 3. Primary caretakers' acceptance is higher	1. Stool specimen is not preferred yet by the Ministry of Health, Indonesia 2. No standardize guideline 3. Lack of equipment in lower-settings healthcare such as Puskesmas	1. Comprehensive training for health workers 2. TB-related stigma and health education 3. Expansion of TB officers

Primary caretakers who withdrawn or could not adhere had interest to participate in stool exam. However, after explanation from TB officer, there was several challenges which came out after primary caretakers' personal opinion about TB and health condition of children. We asked primary caretakers about what was possible solution of their condition and how to increase their adherence toward stool collection

and stool exam but it was very personal reasons that primary caretakers only asked time to process whole TB education and possible procedure. Health workers suggested to have a massive promotion for TB education, screening, and diagnosis working together with cross sectors such as local leaders and organization to introduce and review stool exam for larger mass.

“For now, it is just about my physical condition. I think there is no solution needed from external.” (P29)

“There should be an emphasis on screening for suspected TB cases, enhancing collaboration across sectors to reduce the negative stigma associated with TB patients.” (H9)

“In the initial stages, it's a bit challenging because there are still many questions from patients. This happens because there hasn't been mass testing yet related with stool examination for TB. But with education and promotion, it may become easier.” (H5)

CHAPTER 4
DISCUSSION AND CONCLUSION

13. Screening performance of stool-Xpert for children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital

There are several key findings in stool-Xpert MTB/RIF Ultra community screening. First, the stool-Xpert results had low sensitivity against the final diagnosis by pediatrician while it had high concordance with sputum-Xpert. Second, there was a high rate of non-determinate stool-Xpert specimens related with stool processing and durability of Xpert MTB/RIF Ultra cartridges. Third, stool-Xpert showed similar results with sputum-Xpert with one different semi-quantitative result. Fourth, stool-Xpert proved ability to detect *M. tuberculosis* among child patients with extrapulmonary TB. Fifth, stool-Xpert have low or negative correlation with other TB screening method and final diagnosis by pediatrician while it had high correlation with TB diagnosis method with bacteriological confirmation.

Used of stool specimen was planned to improve case detection rate and decrease 80% of incidence rate of TB by 2030 worldwide. Studies have shown stool as alternative specimen for *M. tuberculosis diagnosis* for children who cannot expectorate sputum.[75] However, in this study, we found lower sensitivity of stool-Xpert results against final diagnosis by pediatrician was 15% (95% CI: 6.0-30.0) than we hypothesized based on previous research and recommendation. High false-negative rate (82-100%) with only 0.19 probability of success (95% CI: 0.07-0.36) in stool-Xpert may increase missing cases among children who were not went through standard screening and diagnosis procedure. However, several researches with stool-Xpert against clinical diagnosis for HIV-positive children also showed low sensitivity result raging between 9-11%.[25,50,52,53] This may relate with nature of childhood TB that children have pauci-bacillary TB.

One research in Zimbabwe showed different result with sensitivity of

53% against clinical diagnosis for children aged 5-16 years with TB symptoms or investigated for close contact with bacteriologically confirmed TB patients. This difference may be happened due to different severity of children enrolled to this study and children in Zimbabwe.[23] In this study, child patients with TB household contact in Puskesmas were invited regarding the existence of signs and symptoms. The differences of sample size and age range also may predict the sensitivity of the test. These findings further emphasize stool-Xpert MTB/RIF Ultra is more suitable as initial diagnosis method for children with presumptive TB than as screening method.[46]

The rate of non-determinate, both "invalid" and "error" stool-Xpert was found to be in higher rate than other study. Even repeated testing applied to error results led to a valid result, the need to maintain the quality of test procedure comprehensively is there. Each laboratory staff is eager to discuss with microbiology experts and research team to improve performance of the test and prevent non-determinate result during regular monitoring program.

Laboratory staff were using the simple one-step (SOS) method which promoted by WHO.[76] One possible reason for non-determinate results related with stool processing is high load of solid particles in stool specimen caused high chance that the bacteria in supernatant is not well isolated, blocking the micro fluid filter in the Xpert MTB/RIF Ultra cartridge.[77] It may happen since the laboratory staff have minimum experience in doing stool-Xpert other than the one-time training before the research started. Another reason is at one time, stool-Xpert tests was using nearly expired cartridges and reagents marked with color-changing reagents liquid from transparent into yellow which leads to failure in producing concentrated specimen and separating bacteria.

Previously, Xpert-Ultra reported to produce less non-indeterminate results than Xpert assay.[78] A study in Southern Ethiopia had found low rate of 2.4% (9/373) non-determinate results with stool-Xpert related with stool processing and cartridge failure.[77] Instead, study in Southwest Ethiopia showed higher error rate in Xpert assay with stool specimen (4.6%, 7/152 specimens). Study by de Haas et al. stated that error results of stool-Xpert will be decreased by time due to increasing experience of using SOS stool method among laboratory staff.[79]

Another important finding in our study was that stool-Xpert MTB/RIF

showed similar result with sputum-Xpert. Out of six bacteriologically confirmed TB diagnosed among child patients, all of them have positive result for both stool-Xpert and sputum-Xpert. However, we found one different result in semi-quantitative Xpert-Ultra results where there were three "MTB trace" result in stool-Xpert while only two "MTB trace" showed in sputum-Xpert.

A report from Bangladesh showed the proportion of "trace" results was higher in stool specimens compared to induced sputum.[80] Other findings reported by Andriyoko in Indonesia, Sun in China, and Babo in Southern Ethiopia with high correlated semi-quantitative scale among stool-Xpert with sputum-Xpert and GA-Xpert.[77,81,82] Detecting *M. tuberculosis* from swallowed sputum in the stool frequently showed lower semi-quantitative scale (low, very low, and trace) since the load of MTB DNA is dependent on volume of *M. tuberculosis* infected sputum swallowed by children. Characteristics of diluted stool specimen mixed with food in intestines might also prevent *M. tuberculosis* swallowed released from stool easily.[77,83]

In this study, we observed several results as indeterminate rifampicin results, both in stool and sputum specimens, similar with trace semi-quantitative results. "MTB trace" in Xpert will automatically produce Rif indeterminate result. In "trace" result, the RpoB gene, which sequenced to indicate any mutation related with Rif-resistant, is not detected. Thus, there is no way the test can give any interpretation on the sample due to insufficient signal of MTB detection.[46]

In Indonesia, final diagnosis after "MTB trace" will be decided by comprehensive TB screening and investigation by doctor such as the existence of signs and symptoms, history of TB, and history of close-contact with bacteriologically confirmed TB. Patients diagnosed with TB disease after "MTB trace" were advised to DS-TB treatment. Therefore, alternative specimen exam with Ultra MTB/RIF or other TB diagnosis method may need to be done in children with high likelihood of RR-TB or MDR-TB.

Out of six child patients got positive stool-Xpert, three of them were diagnosed with meningitis TB. In previous recommendation from WHO, stool-Xpert is only advised to children with signs and symptoms of pulmonary TB.[46] There is very limited information (published) on stool-Xpert test for extrapulmonary TB. A study among adults aged >18 years in Pakistan found 20% positive-tested by stool-Xpert from

100 patients suspected with intestinal TB. Finding in this study may prove the ability of stool-Xpert to detect *M. tuberculosis* among child patients with extrapulmonary TB.

We documented the result of other TB screening and diagnosis methods which also emphasized performance of stool-Xpert as diagnosis method for childhood TB. It showed low performance to screened TB compare to other screening method. This may due to low loads of *M.* tuberculosis assessed during stool examined while signs and symptoms were already present and suggestive to TB disease. In this case, final diagnosis will be made by doctors based on clinical assessment to answer the probability of LTBI or clinically TB among child patients.[28,29,46]

14. Adherence of stool-Xpert among children with tuberculosis household contact in Puskesmas and children with presumptive tuberculosis in hospital

In total, there is about 69% of 125 child patients invited to stool-Xpert adhered and got valid stool-Xpert test. About 65% of 65 children from Puskesmas and 75% of 60 child patients from hospital invited to stool-Xpert adhered. There are several possible explanations for this finding. First, child patients in 0-4 years age group and child patients with higher household income in Puskesmas were predicted to adhere more to stool-Xpert since primary caretakers of children aged 0-2 years could collect stool specimen from their children's diaper, while older children may be asked to collect stool specimen by themselves. Higher household income also reflected the readiness of getting further treatment since TB screening, diagnosis, and treatment procedures takes time and resources to complete such as working time used to picking up children to healthcare and transportation. In hospital, none of socio-demographic related to adherence rate of stool-Xpert.

In risk of tuberculosis investigation, health worker and researcher were investigated any health behavior which may increase the risk of TB infection to child patients. In child patients from Puskesmas, only behavior of opening the window predicted the adherence of stool-Xpert. While among child patients in hospital, primary caretakers whose children were having BCG vaccination and having AC in the bedroom adhered more to stool-Xpert than the others who are not. This study also found that child patients without abnormality in heart will tend to adhere to stool-Xpert. However,

none of child patients in Puskesmas reported to have abnormality in any chest, abdomen, and extremity examinations. This may due to skills of pediatrician or medical doctors in hospital for clinical assessment may account for higher TB signs than that done by general practitioners and TB officer in Puskesmas.[84] Despite training and clinical mentoring which done before the research started, general practitioners and TB officer in Puskesmas may have not been empowered enough to initiate further assessment for childhood TB due to no signs and symptoms, limited equipment of clinical and bacteriological tests, and huge burden of work in Puskesmas aside of TB prevention and control program.[84,85]

Result from previous TB screening and diagnosis method also predicted higher adherence to stool-Xpert among child patients in Puskesmas. Primary caretakers whose child patients had sputum-AFB negative, suggestive TB imaging by CXR, and were having TST before were tend to adhere to stool-Xpert. While none of similar predictors related with adherence of stool-Xpert among child patients in hospital.

Primary caretakers in Puskesmas interested to refer stool-Xpert specimen after results of previous screening and diagnosis method to get second opinion of TB diagnosis for their children. These primary caretakers already aware with risk of TB infection after TB household contact for their children. Several of them with children aged 0-4 years whose suggestive TB by CXR also felt anxious to take TB-drug for their children. Therefore, they were looking for fixed diagnosis from stool-Xpert. The health worker and research team explained that the result of stool-Xpert should be combined with another test to finalized the TB diagnosis of children. We also provided consultation with pediatrician for primary caretakers for discussion about TB-drug for children.

The severity of disease among child patients with presumptive TB may explained the situation of adherence of stool-Xpert in hospital.[84] Most of child patients in adhered and non-adhere groups had similar socio-demographic and clinical characteristics. Primary caretakers got informed to do stool-Xpert by pediatrician in hospital and understood the stool collection assignment as systematic TB screening and diagnosis procedure in hospital. For several inpatients in PICU or HCU rooms, nurse also helped primary caretakers to collect stool specimen to be examined. However,

several child patients with severe signs and symptoms experienced malaise and constipation which led to uncomplete stool collection procedure among child patients.

Other than constipation, no signs and symptoms perceived by primary caretakers also prevented adherence of stool-Xpert. At the first time, parents as primary caretakers showed interest and willing to participate but withdrawn after several follow-ups due to found no signs and symptoms in their children. Several primary caretakers denied the information of risk of TB infection among children by health workers, and assumed the symptoms found such as cough or fever were only 'light' cough or fever which not related with TB. Health promotion for one side of parents (only to mother or only to father) also increased different perception among both parents as primary caretakers of their children. Disagreement about the urgency of doing stool-Xpert for children increased the non-adherence number of children.

Inconvenience procedure mostly came from cases of older children who asked to collect stool specimen by themselves. Children felt disgusting to collect their stool due to its smell. Several primary caretakers who got informed about the possibility of cross-contamination between stool, urine, or other bacteria in toilet bowl also felt confused in completing stool collection procedure. However, the majority of primary caretakers from both adhered and non-adhere to stool-Xpert agreed that this method is non-invasive for children than TST or sputum-Xpert.

Those reasons led to increasing number of patients who lost to follow-up for collecting their stool specimen to healthcare. Contextual factors probably played a role for this reason such as limited access to deliver stool specimen back to healthcare since child patients were lived in another city or districts, working primary caretakers, or even primary caretakers who also patients of TB disease.[86]

15. Pros and cons of stool-Xpert MTB/RIF implementation

This key informant interviews revealed that feasibility of stool-Xpert for early childhood TB screening was predicted by the attitude of primary caretakers and health workers towards stool collection and stool exam procedures. The primary caretakers reported to be agreed on stool collection when children have TB signs and symptoms, while they tend to refuse since children was asymptomatic reinforces findings from previous studies aimed to assessed challenges in identifying and

diagnosing childhood TB. Most of primary caretakers associated TB with cough which is an pulmonary TB, while children also had risk to have extrapulmonary TB.[36] This study highlighted that this may be caused primary caretakers were lack of TB-related knowledge.

Perceived benefits among informants strengthened the trust in the existing screening and diagnosis algorithm. The benefits can be knowing the final diagnosis or health status of the child, and have a clue for further TB prevention or medication suggested for children. Primary caretaker whose children with severe signs and symptoms such as cough more than 14 days and extreme weight loss will be strictly adhered to stool collection suggested by pediatrician in hospital or TB officer in Puskesmas because of fear of TB complications.[87,88]

Informants had trust to health workers as they seeking for appropriate medical assistance after realizing the risk of TB disease within their children. Primary caretakers found to done stool collection since it was directly suggested to them by pediatrician in hospital or TB officer in Puskesmas, they also seek for assistance and discussion with health worker to complete stool collection appropriately. It showed that health workers performed an essential role in giving health education related with TB, its risk, screening and diagnosis, and plan treatment. Studies found that comprehensive information and positive advice among primary caretakers and health workers will increase treatment adherence of the patients.[87–89]

One of the key findings is that family support is valuable in deciding further participation in stool collection then plan of treatment for children. Primary caretakers are mostly parents who is the decider on children's healthcare seeking behavior. Good communication for decision making among family members was important. It was demonstrated by disclosure to the spouse (among parents) and other family members concerning the TB risk, its transmission, and prevention of the children. This study faced several situations when both parents have disagreement about TB screening plan for their children, then it solved by further discussion. Family support also can provide help to collect stool specimen for working primary caretakers. This meant family understand about the importance of TB risk of the children.[88,90–92]

In other case, family support is needed when primary caretaker was the index TB case of the household. Primary caretakers might could not help children to

collect the specimen due to side effects of anti-TB drug such as fatigue, dizziness, feeling tired or weak, and vomiting.[93] Then support from other family member to complete child's screening and diagnosis procedures is very important.[93,94]

Several children from informants exhibited inconvenience in doing stool collection. Older children feel afraid in doing stool exam, thinks that stool exam indicating they have serious illness. They also felt inconvenience due to bad odor and disgusting with stool specimen. The commitment of primary caretakers should be shown. Primary caretakers should apply health behavioral skills in communicating with children and coping with inconvenience to carry out the actions needed for done stool collection. Children and adolescent have limited ability to acquire, comprehend, and effectively use health information. Therefore, primary caretakers accompaniment will ensure proper stool collection completion.[95–97]

This study also revealed that several primary caretakers expressed interest but did not complete the stool collection due to unclearly understand how to do stool collection. Even though primary caretakers already provided with picture and equipment [e.g. stool container, plastic sheeting, and hand gloves], and discussion session. Previous studies show the urgencies of health providers positioning in providing proper health education and home-based program to increase adherence of TB screening and treatment.[88,97–99] Both primary caretakers and health workers recommended to promote issues related to TB and TB screening with stool-Xpert as a new method. Additional health workers and utilization of trained health volunteers are needed to build a home-based approached in educating primary caretakers, it can be used to encourage primary caretakers to do stool collection which is non-invasive and easy-to-do, thus increasing the completion of stool collection among children with household contact.

Given the enthusiasm for non-invasive and easy-to-do method, especially for children aged under-5 years with diapers and regular defecation, both child population in Puskesmas and hospital also experienced delayed in specimen collection or withdrawn due to personal health condition such as constipation suggest a missed opportunity which also happened with other specimen and method such as sputum and tuberculin skin test.[98,100] In previous study with collecting the sputum specimen, TB officers could increase rate of sputum collection by doing direct

supervision in community collection points, showed the urgency in providing home-based and community-based program for TB mass screening and investigation.[101]

Efforts to improve stool collection should therefore on eliminating barriers that originate from personal condition. In order to reduce losses during stool collection, we suggest that general practitioner and pediatrician from Puskesmas and hospital to prescribe stool softener if applicable. Moreover, advocacy of new stool-Xpert method should be sounded to stakeholder and decision-maker thus a clear and standardized guideline could be provided for all health workers related with TB.

Another key challenge from the providers' side was that the availability of free screening and diagnostic equipment test with Xpert machine is still limited thus sputum examination is preferred in limited settings, while most of child patients cannot expectorate sputum or need to be referred to hospital while not all primary caretakers and family have resourced to pick-up their children to hospitals (e.g. none insurance, pediatric pulmonologist is far away) caused children continue to be unidentified. Notably, stool collection is a promising aspect, therefore advocacy with decision maker related with laboratory and TB diagnosis equipment improvement must be done. Another plus point is pulmonary hospital in West Sumatera (outside of our research settings) tried to do stool exam to diagnosed their patients after the news of stool exam implementation in our research settings.

Besides that, health workers should receive continuous training to bring their skills up to the standards of laboratory staff. The critical point of doing laboratory work is the quality of stool specimen. Despite all the challenges, stool-Xpert is a promising method. Most of primary caretakers and health workers shared positive experience indicate the possibility of further implementation of stool-Xpert for children. Such an expansion would efficiently and effectively identify more child TB patients within a shorter time.

TB stigma is one of challenges faced by health workers on the field. Primary caretakers who refused soon after the index TB case got diagnosed may have been apprehensive and concerned about TB stigma cause negative opinions about stool exam and childhood TB.[102,103] TB stigma has been recognized by the WHO and the United Nations as a key barrier to eliminating TB.[104,105] TB stigma associated with challenges to treatment adherence, which can reduce TB treatment success, and

increase the risk of TB transmission and the development of drug-resistant TB.[97,106] Primary caretakers refuse to bring their children to be screened due to stigma of TB [e.g. infectious disease, long regimen disease, fear of stigma]. Health workers suggested to have mass health promotion related with TB and TB prevention to raise awareness about TB stigma and risk of TB working with local leaders, organizations, and health volunteers.

From the laboratory side, stool storage, processing, and exam with Xpert machine almost have no differences with sputum specimen. Stool storage is not complicated since primary caretakers can save it in room temperature without direct sun exposure before they deliver it to hospital.

For inconvenience due to bad odor, innovation such as perfume patch or aromatherapy patch could be shared and used to the mask of laboratory staff while doing stool processing and exam. Nowadays, stool processing already simplified by using simple one-step method which required nothing than available equipment from Xpert package (e.g. reagent and cartridges) and laboratory's default.[21,25]

Children usually have pauci-bacillary tuberculosis cause children TB screening and diagnosis thorough assessment of all the evidence derived from a careful history of exposure, clinical examination, and relevant investigation.[38,46] Therefore, childhood TB screening rests heavily on doctor or pediatrician decision. Bacteriological confirmation and other testing have full range of test, to have stool-Xpert alongside with other screening and diagnosis method is a must.[107] The development of affordable and effective algorithm for TB in children in low-resource settings should be a priority for researchers and policy-makers.

16. Strength and limitation

In this study, we observed children with diverse health condition: children with TB household contact with and without TB signs and symptoms, and children with presumptive TB with various severity of TB signs and symptoms. This possibly contributed to assess benefit of stool-Xpert among several different populations of children. Second, we also able to document routine TB screening and diagnosis done to each child patient including contact investigation, risk of TB and signs and symptoms screening and clinical and radiological suspicion. Thus, we could

assess the agreement among the result of stool-Xpert and routine practices. Third, the positive results among child patients with extrapulmonary TB in this study may increase more evidence of the effectiveness of further use of stool-Xpert for extrapulmonary TB.

To date, this study is the first study uncovered pros and cons of the feasibility of stool-Xpert from both perspectives: primary caretakers and health workers. This study also recruited primary caretakers and health workers with diverse attitude from several healthcare. We reached thematic saturation from each group of primary caretakers: primary caretakers who were willing to joined and easily done stool collection; were willing to joined and experienced several difficulties in done stool collection; and were willing then withdrawn after several difficulties.

However, our study has several limitations. First, we had a sample size less than anticipated as we were not able to achieve the planned sample size of 243 due to unforeseen external factors which may reduce the significance of our study. We also went through previous studies which showed lower sensitivity among stool-Xpert with clinical diagnosis as reference standard and do blinding in deciding the final diagnosis of childhood TB aside from stool-Xpert.

Second, we were unable to enroll children with HIV due to a challenging enrolment process for children living with HIV while they may have higher benefited from the stool-Xpert than other population. However, we maximize external validity of our findings by selected two different healthcare levels with different severity of child patients enrolled, and documented the result of screening and diagnosis method in standard care.

Unfortunately, we were unable to interview primary caretakers who were refused to take their children in further TB screening and diagnosis procedures. Thus, we ameliorated the findings by invited health workers to share their experiences in inviting primary caretakers to do stool collection during contact investigation and TB screening program. The primary caretakers recruited were also dominated by mother, which may not reflect factors and barriers experienced by father of child patients.

17. Implication and recommendation

17.1 For practice

There is a tendency from primary caretakers and health workers to accept stool collection than other kind of TB screening method. However, it cannot guarantee the stool-Xpert' performance as a screening method but diagnosis which also recommended by WHO for children with signs and symptoms. To improve future implementation and adherence of stool-Xpert, several strategies may improve the adherence such as:

1. Emphasize on the benefit of stool exam in the broader community;
2. Integrate stool-Xpert with home visit program for index TB case, primary caretakers and others family members for TB screening and counselling session;
3. Adopt multi-pronged approach to address TB stigma; and
4. Provide a comprehensive capacity building for human resources including laboratory staff and health volunteer in healthcare.

17.2 For research

Further research is warranted for children living with HIV and severe malnutrition, as these children benefit most from the non-invasive and innovative method. Hence, stool-Xpert have an opportunity to increase case detection of children with severe signs and symptoms who expected to loads high number of *M. tuberculosis*, especially for them who cannot produce sputum.

18. Conclusion

Stool collection for stool-Xpert screening is highly feasible in both at Puskesmas and hospital. However, use of stool-Xpert for childhood TB screening faced limitations of performance in sensitivity. The result of stool-Xpert MTB/RIF Ultra show no yield for childhood TB screening.

In general, the main barriers of further implementation of stool-Xpert in Padang Municipality is limited resources available in each healthcare. Puskesmas as primary healthcare is the unavailability of biosafety cabinet (BSC) required for stool specimen processing; while both primary and higher-level healthcare struggles with

limited stock of Xpert equipment and responsible TB officer with multiple work burden. In the other hand, primary caretakers and health workers who done stool collection and stool exam believe that stool specimen can be used as an alternative for respiratory specimen and was shown to be non-invasive test for children who cannot expectorate sputum.

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APPENDIXES

Appendix 1. Documentary proof of ethical clearance and research permission

PEMERINTAH KOTA PADANG
DINAS PENANAMAN MODAL DAN PELAYANAN TERPADU SATU PINTU
Jl. Jendral Sudirman No.1 Padang Telp/Fax (0751)890719
Email : dpmptsp.padang@gmail.com Website : www.dpmptsp.padang.go.id

REKOMENDASI
Nomor : 070.7290/DPMPTSP-PP/VIII/2023

Kepala Dinas Penanaman Modal dan Pelayanan Terpadu Satu Pintu Kota Padang setelah membaca dan mempelajari :

1 Dasar :

a. Peraturan Menteri Dalam Negeri Republik Indonesia Nomor 7 Tahun 2014 tentang Perubahan atas Peraturan Menteri Dalam Negeri Republik Indonesia Nomor 64 Tahun 2011 tentang Pedoman Penerbitan Rekomendasi Penelitian;
b. Peraturan Walikota Padang Nomor 11 Tahun 2022 tentang Pendelegasian Wewenang Penyelenggaraan Pelayanan Perizinan Berusaha Berbasis Risiko dan Non Perizinan Kepada Kepala Dinas Modal dan Pelayanan Terpadu Satu Pintu;
c. Surat dari Prince of Songkla University/ Universitas Andalas Nomor : 68104.8/66-00225;

2. Surat Pernyataan Bertanggung Jawab penelitian yang bersangkutan tanggal 31 Juli 2023

Dengan ini memberikan persetujuan Penelitian / Survey / Pemetaan / PKL / PBL (Pengalaman Belajar Lapangan) di wilayah Kota Padang sesuai dengan permohonan yang bersangkutan :

Nama	:	Chairunnisa Athena Pelawi
Tempat/Tanggal Lahir	:	Kisaran / 16 September 1999
Pekerjaan/Jabatan	:	Mahasiswa
Alamat	:	Komplek Pasaman Baru Indah, Nagari Lingkuang Aua, Kecamatan Pasaman, Kabupaten Pasaman Barat
Nomor Handphone	:	082389994444
Maksud Penelitian	:	Tesis
Lama Penelitian	:	2023 s.d. November 2023
Judul Penelitian	:	Skrining Tuberkulosis pada Anak dengan Kontak Serumah menggunakan Xpert MTB/RIF dengan Sampel Feses (Stool) di Puskesmas dan Rumah Sakit di Kota Padang.
Tempat Penelitian	:	Puskesmas Andalas, Puskesmas Lubuk Buaya, Puskesmas Padang Pasir, Puskesmas Pegambiran, Puskesmas Koto Panjang Ikua Koto, Puskesmas Nanggalo, RS Yos Sudarso, RS BMC Bunda, dan RS Universitas Andalas
Anggota	:	-

Dengan Ketentuan Sebagai berikut :

1. Berkewajiban menghormati dan mentaati Peraturan dan Tata Tertib di Daerah setempat / Lokasi Penelitian.
2. Pelaksanaan penelitian agar tidak disalahgunakan untuk tujuan yang dapat mengganggu kestabilan keamanan dan ketertiban di daerah setempat/ lokasi Penelitian
3. Wajib melaksanakan protokol kesehatan Covid-19 selama beraktifitas di lokasi Penelitian
4. Melaporkan hasil penelitian dan sejenisnya kepada Wali Kota Padang melalui Kantor Kesbang dan Politik Kota Padang
5. Bila terjadi penyimpangan dari maksud/tujuan penelitian ini, maka Rekomendasi ini tidak berlaku dengan sendirinya.

Padang, 31 Juli 2023

Balai Sertifikasi Elektronik

Telah ditandatangani secara elektronik oleh :
Plt. KEPALA DINAS PENANAMAN MODAL DAN PELAYANAN TERPADU SATU PINTU
Ir. Corri Saidan, M.Si
Pembina Utama Muda
NIP.19661023 199202 2 002

Tembusan :
1. Head of Department of Epidemiology, Director of WHO-CC for Research and Training on Epidemiology, Prince of Songkla University
2. Kepala Dinas Kesehatan Kota Padang
3. Kepala Kantor Kesbangpol Kota Padang

HEALTH RESEARCH ETHICS COMMITTEE
RSUP Dr. M. DJAMIL PADANG

KETERANGAN LOLOS KAJI ETIK
DESCRIPTION OF ETHICAL APPROVAL
"ETHICAL APPROVAL"

Nomor : LB.02.02/5.7/444/2023

Protokol penelitian yang diusulkan oleh :
The research protocol proposed by

Peneliti utama : Chairunnisa Athena Pelawi
Principal Investigator

Nama Institusi : Master of Science in Epidemiology (International Program)
Name of the Institution Prince of Songkla University

Dengan Judul :
Title

" Skrining Tuberkulosis pada Anak dengan Kontak Serumah dan Pasien Suspek TB menggunakan Xpert MTB/RIF dengan Sampel Feses (Stool) di Puskesmas dan Rumah Sakit di Kota Padang, Indonesia"
"Stool-Xpert MTB/RIF for Tuberculosis Screening among Children with Household Contact and Suspected TB Patients in Primary and Secondary Healthcare Facilities of Padang Municipality, Indonesia"

Dinyatakan layak etik sesuai 7 (tujuh) Standar WHO 2011, yaitu 1) Nilai Sosial, 2) Nilai Ilmiah, 3) Pemerataan Beban dan Manfaat, 4) Risiko, 5) Bujukan/Eksploitasi, 6) Kerahasiaan dan Privacy, dan 7)Persetujuan Setelah Penjelasan, yang merujuk pada Pedoman CIOMS 2016. Hal ini seperti yang ditunjukkan oleh terpenuhinya indikator setiap standar.

Declared to be ethically appropriate in accordance to 7 (seven) WHO 2011 Standards, 1) Social Values, 2) Scientific Values, 3) Equitable Assessment and Benefits, 4) Risks, 5) Persuasion/Exploitation, 6) Confidentiality and Privacy, and 7) Informed Concent, referring to the 2016 CIOMS Guidelines. This is as indicated by the fulfillment of the indicators of each standard.

Pernyataan Laik Etik ini berlaku selama kurun waktu Agustus 2023 sampai dengan Agustus 2024

This declaration of ethics applies during the period August 2023 until August 2024

Padang, 8 Agustus 2023
Chairperson

RSUP DR. M. DJAMIL KOMITE ETIK PENELITIAN & KESEHATAN PADANG

Dr. dr. Qaira Anum, SpKK(K), FINSDV FAADV
NIP. 19681126 200801 2 014

Appendix 2. Participant information sheet children

Informed Assent Form (Children aged 7-13 years)

Hi! My name is Chairunnisa Athena Pelawi. I am Master Student in Epidemiology International Program, Faculty of Medicine, Prince of Songkla University, Thailand under support of the Fogarty International Center, National Institutes of Health

I want to invite you to take part in **tuberculosis screening among children with tuberculosis household contact and suspected TB program** of the research entitled "Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia".

After you have read and understood all information about this research, you can say "No" if you do not want to join this program.

- ***Why am I invited?***

  We would like to invite you to participate in the program by following a few health procedures listed since you may have risks to get infected by a bacteria called *Mycobacterium tuberculosis* and got TB disease. The total time to complete all procedures is about 2 days.

- ***What am I going to face if I join this study?***

  If you decide to join this research, you will enlist to a few health procedures.

  a. We will ask you some questions about your health and daily activities. We will ask you some questions about your health and daily activities. There are also several sensitive questions about your HIV status and your parents monthly income. Do not worry, you will be helped by your parents to answer the questions.
  b. We will check your height and weight, examine your head, and other parts of your body, like your respiratory system.
  c. We will ask your parents or guardians to help you collect a stool sample for the health worker.
  d. You and your parents or guardians will receive the TB test results from the stool sample within one day after you submit it to the health worker.

e. If necessary, you will be referred to a pediatric specialist at the hospital for further examination.

Your caregivers will be allowed to accompany you during those procedures. Your anonymity will be protected and none of your friends or family have access to know your health condition without you and your caregiver consent.

- ***Any risk or discomforts?***

  The health procedures may take about 2 days long. It may time-consuming and make you tired. First, the health worker will ask you and your caregiver about the existing TB signs and symptoms in your body. Then, the health worker will describe about stool-Xpert MTB/RIF procedure and ask to collect your stool specimen. The health worker in Puskesmas will also suggest you to take further clinical assessment. Do not worry, research team will accompany you during all the health procedures.

  The health procedure after referral process in hospital you may join several medical procedures. Things you should know are,

  a. Tuberculin test, like your peers, the injection from the tuberculin test can cause itching and swelling at the injection site; and
  b. Chest X-ray, which uses X-ray radiation. Typically, there are no side effects from X-ray radiation during TB examination due to its short duration. However, you may feel dizzy or nauseous after the examination.

  Please feel free to refuse to follow the health procedure that discomfort you and to withdraw from the program at any time. Your refusal to participate, discontinuance or failure to complete the procedures will not affect your future health services experience in any healthcare.

- ***Any benefits to me?***

  If the *Mycobacterium tuberculosis* is detected inside your body, you will be benefited to take early anti-TB drug under health professional supervision to avoid severe-form of disease.

  When you complete the health procedures, you may consider that you probably have a TB infection or disease that you do not know before. Please understand

that the result is confirmed by professional health worker, and not only by the researcher. You may be suggested to take regular drug and supervision in healthcare nearby. If you need specific advice on this problem, please discuss with your caregivers to visit any of the following nearby Puskesmas or hospitals.

- Pediatrics Department, Dr. M. Djamil Central Public Hospital, Padang
- Pediatrics Department, BMC Bunda Private Hospital, Padang
- Puskesmas Nanggalo
- Puskesmas Lubuk Buaya
- Puskesmas Andalas
- Puskesmas Rawang
- Puskesmas Kuranji
- Puskesmas Air Tawar

- ***What will happen to the information I gave?***

  None of your information will be shared to anyone outside of the research team, including your school, neighbors, or friends. Your identified information will not be reported anywhere. When we are going to present the research data by publication or in any other way, there will be no name or other information that can be linked to you.

- ***What will happen if I say "No"?***

  Please feel free to refuse or stop joining anytime, no one will be angry at you about this. I assure you that there will be no punishment if you do not want to join. Your refusal will not affect your future health services experience in Puskesmas.

- ***Contact person***

  If you have any questions, please ask Ms. Chairunnisa Athena Pelawi by telephone +6282389994444, email: chairunnisaathena.pelawi@gmail.com at any time. I will be happy to answer to all your questions.

After you read and understood the study with its procedure involved, if you are willing to participate in the study, please tick the box and sign your name.

I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction and was given 7 days to discuss and decide my participation with my parents. To compensate the time lost I experienced, I accept the transportation fee as much as IDR 50,000 after I complete the research process.

☐ I AGREE to participate ☐ I DON'T AGREE to participate

Child's signature

_____

(_____)

Date (Day/ Month/ Year)

_____

Researcher's signature

_____

(_____)

Date (Day/ Month/ Year)

_____

Please make a photocopy of this form for participant after signing.

This form is valid only when parent(s) has signed a separate consent form for their permission.

Appendix 3. Participant information sheet for health workers

Participant Information Sheet for Health Worker

Title: Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia

Research team: Chairunnisa Athena Pelawi, Dr. dr. Finny Fitry Yani, Sp. A(K), Associate Professor Rassamee Chontipanvithayakul, M.D., Professor Virasakdi Chongsuvivatwong, M.D.

Research site: Padang Municipality

Funding: TB/MDR TB research training program at the Epidemiology Unit, Faculty of Medicine, Prince of Songkla University under the support of the Fogarty International Center, National Institutes of Health (Grant number: D43TW009522)

It is important for you to know that this is a research project, NOT a routine procedure. Please feel free to refuse to participate or withdraw your consent anytime.

In this document, there may be some statements that you do not understand. Please ask the principal investigator or her representative to give you explanations until you are clearly understood. You will have sufficient time and information to make the decision to participate. You may also bring this document and consult to your relatives or someone you trust.

Introduction of the study

Children with household contacts to TB infectious adult or adolescent are having a high-risk for developing TB disease due to immunologic maturity. However, previous studies and the NTP reports indicate low detection rate and high number of missing cases in childhood TB in Indonesia. By implementing decentralization TB care, Puskesmas as PHC play a significant role in doing CI and systematic screening in Indonesia. Unfortunately, most of Puskesmas in Indonesia does have limited resources, both man and machine to activate the CI and systematic screening program.

Thus, suspected children need to be referred to higher-level healthcare, go through further clinical assessment, and do invasive method of sample collection procedure. This referral system is time-consuming and costly, which leads to delayed TB diagnosis

and increasing risk of developing active or severe TB in children. While, studies show that stool-Xpert provide moderate evidence in TB diagnosis and highly feasible in lower-levels healthcare such as Puskesmas in Indonesia. Therefore, there is a lack of information on how the stool-Xpert perform as a routine systematic screening method among children with household contact. The findings and recommendation from this study will present to local policymakers and health workers to state an advance CI and systematic screening workflow in Puskesmas to strengthen childhood TB detection and increase the childhood TB detection rate.

Purpose of the research

This study aims to (i) identify the properties of using stool-Xpert MTB/RIF screening among children with tuberculosis household contact, and (ii) determine the feasibility of using new strategy of screening program among children with tuberculosis household contact by using stool-Xpert MTB/RIF in primary health care.

Procedures of the study

If you agree to participate, we will interview you about some basic characteristics, personal experience, and perception about childhood TB screening and contact investigation in your healthcare for about 45 minutes in an empty room in your office. The interview will be guided by a written list of questions and your answer will be recorded. The interview will be held on private setting where in your office, there are only you as health worker and a member of research team.

Risk and discomforts

The questionnaire interview has no greater than minimal harm or discomfort. You may withdraw or ask to stop the interview any time if you feel it.

Benefits

You will not get direct benefit from the interview. However, the results of this study may help to improve and strengthen the policy of childhood TB screening and contact investigation in the future which can provide indirect benefit for you.

Compensation

You will not get any compensation. However, you will get a little souvenir for contribution of your time.

Confidentiality

We will comply with relevant data privacy laws during this research. For documentation purposes, we will note your name and phone number when we ask you for your informed consent to participate in the research. However, this is only for higher-up offices to check our work. The signed forms will be kept in a locked cabinet, and only the project head (principal investigator) knows the location of the cabinet and has the key. We will not include your name or personal details in the data that we collect during the research, or in the publication of the survey results. None of school, friends, neighbors, or other family will have access to the information related with the interview such as medical record without your permission.

Right to refuse or withdraw

You have right to withdraw from the study at any time by directly purposing to the research team. You still can change your mind even after the data collection process finish. If you request withdrawal, your information will not be used and your participation will be terminated.

Contact for further information and emergency use

If you have any questions or further information, please feel free to contact Ms. Chairunnisa Athena Pelawi (telephone +6282389994444, email: chairunnisaathena.pelawi@gmail.com) at any time or Department of Epidemiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, Thailand (Tel: +66 74-451165-6) at working hours. If you receive anything that is not as indicated above, you can consult/complain to the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University, Thailand at +66 74-45-1157 or mail to medpsu.ec@gmail.com OR Health Research Ethics Committee (HREC) RSUP Dr. M. Djamil, Jalan Perintis Kemerdekaan, Sawahan Timur, Kota Padang, Sumatera Barat, Tel +62751-8956666, e-mail: kepkmdjamil@yahoo.com.

Informed Consent Form

This Informed Consent Form is for those who are invited to participate in the research entitled **"Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia"**.

I have been invited to take part in the research on "*Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia*". I have been told about this research as follows:

- **The purpose of the research** is to identify the properties and the feasibility of using stool-Xpert MTB/RIF screening procedure among children by using stool-Xpert MTB/RIF in primary health care.
- **Procedures,** if you agree to participate, we will interview you about some basic characteristics, personal experience, and perception about childhood TB screening and contact investigation in your healthcare.
- **Risk and discomforts,** the questionnaire interview has no greater than minimal harm or discomfort. You may withdraw or ask to stop the interview any time if you feel it.
- **Benefits** of the research, will not directly affect to you. However, the results of this study may help to improve and strengthen the policy of childhood TB screening and contact investigation in the future which can provide indirect benefit for you.
- **Confidentiality** of all information will be kept strictly confidential. Information will not be released to anyone who is not associated with the research.
- **Contact information, for further information or any questions about the research project,** please feel free to contact Ms. Chairunnisa Athena Pelawi (telephone +6282389994444, email: chairunnisaathena.pelawi@gmail.com) at any time.
- **Complaints**

  On the condition that you are not treated as indicated in this information sheet, you can contact the Chair of Human Research Ethics Committee (HREC), Office of HREC, 4th floor, Administrative Building, Faculty of Medicine, Prince of Songkla

University, Thailand, Tel +66-7-4451157, e-mail: medpsu.ec@gmail.com OR Health Research Ethics Committee (HREC) RSUP Dr. M. Djamil, Jalan Perintis Kemerdekaan, Sawahan Timur, Kota Padang, Sumatera Barat, Tel +62751-8956666, e-mail: kepkmdjamil@yahoo.com.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction and was given 7 days to decide my participation. I consent voluntarily to be a participant in this study and understand that I have the right to withdraw at any time without in any way affecting my medical care. I confirm that the individual has given consent freely. To compensate the time lost I experienced, I accept the transportation fee as much as IDR 50,000 after I complete the research process.

Signature of participant : _____

Name of participant : _____

Date (dd/mm/yyyy) : _____

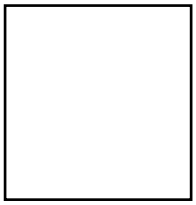
If illiterate, I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Signature of impartial witness: _____

Name of witness : _____

Date (dd/mm/yyyy) : _____

Thumb print of a participant



Name of researcher : Chairunnisa Athena Pelawi

Signature of researcher : _____

Date (dd/mm/yyyy) : _____

Appendix 4. Participant information sheet for primary caretakers

Participant Information Sheet for Contact Cases and Caregivers

Title of research project: Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia

Research team: Chairunnisa Athena Pelawi, Dr. dr. Finny Fitry Yani, Sp. A(K), Associate Professor Rassamee Chontipanvithayakul, M.D., Professor Virasakdi Chongsuvivatwong, M.D.

Research site: Padang Municipality

Source of fund: TB/MDR TB research training program at the Epidemiology Unit, Faculty of Medicine, Prince of Songkla University under the support of the Fogarty International Center, National Institutes of Health (Grant number: D43TW009522)

It is important for you to know that this is a research project, NOT a routine procedure. Please feel free to refuse to participate or withdraw your consent anytime.

In this document, there may be some statements that you do not understand. Please ask the principal investigator or her representative to give you explanations until you are clearly understood. You will have sufficient time and information to make the decision to participate. You may also bring this document and consult to your relatives or someone you trust.

Introduction of the study

Children with household contacts to TB infectious adult or adolescent are having a high-risk for developing TB disease due to immunologic maturity. However, previous studies and the NTP reports indicate low detection rate and high number of missing cases in childhood TB in Indonesia. By implementing decentralization TB care, Puskesmas as PHC play a significant role in doing CI and systematic screening in Indonesia. Unfortunately, most of Puskesmas in Indonesia does have limited resources, both man and machine to activate the CI and systematic screening program.

Thus, suspected children need to be referred to higher-level healthcare, go through further clinical assessment, and do invasive method of sample collection procedure. This referral system is time-consuming and costly, which leads to delayed TB diagnosis

and increasing risk of developing active or severe TB in children. While, studies show that stool-Xpert provide moderate evidence in TB diagnosis and highly feasible in lower-levels healthcare such as Puskesmas in Indonesia. Therefore, there is a lack of information on how the stool-Xpert perform as a routine systematic screening method among children with household contact. The findings and recommendation from this study will present to local policymakers and health workers to state an advance CI and systematic screening workflow in Puskesmas to strengthen childhood TB detection and increase the childhood TB detection rate.

Purpose of the research

This study aims to (i) identify the properties of using stool-Xpert MTB/RIF screening among children with tuberculosis household contact, and (ii) determine the feasibility of using new strategy of screening program among children with tuberculosis household contact by using stool-Xpert MTB/RIF in primary health care.

Procedures of the study

If you and your children agree to participate, we will register your children into a few health procedures to do early detection of TB infection or TB disease after household contact or TB signs and symptoms. After that, we will interview you about some basic characteristics, personal experience, and perception about childhood TB screening and contact investigation that you and your children have done in Puskesmas. The interview will hold for about 45 minutes in an empty room in your office. The interview will be guided by a written list of questions and your answer will be recorded. The interview will be held on private setting where in your office, there are only you as health worker and a member of research team. However, there may be several sensitive information required such as HIV status of your children as contact case and your household income.

Risk and discomforts

If you and your children agree to participate, the health procedures may take about 2 days long. It may time-consuming and make you tired. Your children may also feel some discomfort after several clinical or physical examination such as itching, swelling or irritation. Meanwhile, for your part, the questionnaire interview has no greater than minimal harm or discomfort. However, you may feel discomforts during the research team ask about your personal information or your medical history. The research team

will hold the interview in an empty room available in the healthcare to minimize this condition. You and your children may withdraw or ask to stop the study procedures any time if you feel it.

Benefits

If the *Mycobacterium tuberculosis* is detected in your children, you will be benefited to take early anti-TB drug under health professional supervision to avoid severe-form of disease in your children.

When you complete the health procedures, you may consider that your children probably have a TB infection or disease that you do not know before. Please understand that the result is confirmed by professional health worker, and not only by the researcher. Your children may be suggested to take regular drug and supervision in healthcare nearby. If you need specific advice on this problem, please visit any of the following nearby Puskesmas or hospitals.

- Pediatrics Department, Dr. M. Djamil Central Public Hospital, Padang
- Pediatrics Department, BMC Bunda Private Hospital, Padang
- Puskesmas Nanggalo
- Puskesmas Lubuk Buaya
- Puskesmas Andalas
- Puskesmas Rawang
- Puskesmas Kuranji
- Puskesmas Air Tawar

Compensation

You will get compensation for your travel fee and contribution of your time.

Confidentiality

We will comply with relevant data privacy laws during this research. For documentation purposes, we will note your name and phone number when we ask you for your informed consent to participate in the research. However, this is only for higher-up offices to check our work. The signed forms will be kept in a locked cabinet, and only the project head (principal investigator) knows the location of the cabinet and has the key. We will not include your name or personal details in the data that we collect during the research, or in the publication of the survey results. None of school, friends,

neighbors, or other family will have access to the information related without the permission of patient and caregivers.

Right to refuse or withdraw

You have right to withdraw from the study at any time by directly purposing to the research team. You still can change your mind even after the data collection process finish. If you request withdrawal, your information will not be used and your participation will be terminated

Contact for further information and emergency use

If you have any questions or further information, please feel free to contact Ms. Chairunnisa Athena Pelawi (telephone +6282389994444, email: chairunnisaathena.pelawi@gmail.com) at any time or Department of Epidemiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, Thailand (Tel: +66 74-451165-6) at working hours. If you receive anything that is not as indicated above, you can consult/complain to the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkla University, Thailand at +66 74-45-1157 or mail to medpsu.ec@gmail.com OR Health Research Ethics Committee (HREC) RSUP Dr. M. Djamil, Jalan Perintis Kemerdekaan, Sawahan Timur, Kota Padang, Sumatera Barat, Tel +62751-8956666, e-mail: kepkmdjamil@yahoo.com.

Informed Consent Form

This Informed Consent Form is for those who are invited to participate in the research entitled **"Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia"**.

I have been invited to take part in the research on "*Stool Xpert® MTB/RIF for tuberculosis screening among children with household contact and suspected TB patients in primary and secondary healthcare facilities of Padang Municipality, Indonesia*". I have been told about this research as follows:

- **The purpose of the research** is to identify the properties and the feasibility of using stool-Xpert MTB/RIF screening procedure among children by using stool-Xpert MTB/RIF in primary health care.
- **Procedures,** your children will be registered into a few health procedures to do early detection of TB infection or TB disease after household contact or TB signs and symptoms. After that, we will interview you about some basic characteristics, personal experience, and perception about childhood TB screening and contact investigation that you and your children have done in Puskesmas.
- **Risk and discomforts,** if you and your children agree to participate, the health procedures may time-consuming and make you tired. Your children may also feel some discomfort after several clinical or physical examination such as itching, swelling or irritation. Meanwhile, for your part, the questionnaire interview has no greater than minimal harm or discomfort. You and your children may withdraw or ask to stop the study procedures any time if you feel it.
- **Benefits** of the research, if the *Mycobacterium tuberculosis* is detected in your children, you will be benefited to take early anti-TB drug under health professional supervision. A souvenir for the time spent during the health procedures will be given to you and your children.
- **Confidentiality** of all information will be kept strictly confidential. Information will not be released to anyone who is not associated with the research.
- **Contact information, for further information or any questions about the research project,** please feel free to contact Ms. Chairunnisa Athena Pelawi

(telephone +6282389994444, email: chairunnisaathena.pelawi@gmail.com) at any time.

- **Complaints**

  On the condition that you are not treated as indicated in this information sheet, you can contact the Chair of Human Research Ethics Committee (HREC), Office of HREC, 4th floor, Administrative Building, Faculty of Medicine, Prince of Songkla University, Thailand, Tel +66-7-4451157, e-mail: medpsu.ec@gmail.com Health Research Ethics Committee (HREC) RSUP Dr. M. Djamil, Jalan Perintis Kemerdekaan, Sawahan Timur, Kota Padang, Sumatera Barat, Tel +62751-8956666, e-mail: kepkmdjamil@yahoo.com.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions I have been asked have been answered to my satisfaction and was given 7 days to decide my children and I participations. I consent voluntarily to be a participant in this study and understand that I have the right to withdraw at any time without in any way affecting my medical care. I confirm that the individual has given consent freely. To compensate the time lost we experienced, I accept the transportation fee as much as IDR 50,000 after we complete the research process.

Signature of the caregiver : _____

Name of the caregiver : _____

Date (dd/mm/yyyy) : _____

Signature of the children : _____

Name of the children : _____

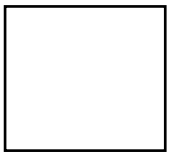
Date (dd//mm/yyyy) : _____

If illiterate, I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Signature of impartial witness: _____

Name of witness : _____

Date (dd/mm/yyyy) : _____

Thumb print of a participant 

Name of researcher : Chairunnisa Athena Pelawi

Signature of researcher : _____

Date (dd/mm/yyyy) : _____

Appendix 5. Data recording form for children

CASE REPORT FORM

Examination date: _____/_____/_____ Examiner code: _____	Children ID: [ ][ ][ ][ ][ ] Index case ID: [ ][ ][ ][ ][ ] Caregivers ID: [ ][ ][ ][ ][

A. Identity

1.	Date of birth (dd/mm/yyyy)	__/__/____
2.	Age (from last birthday)	[ ][ ]
3.	Sex	[ ] 1. Male [ ] 2. Female
4.	Marital status	[ ] 1. Single [ ] 2. Married [ ] 3. Widows/divorced [ ] 99. Refuse to answer
5.	Religion	[ ] 1. Islam [ ] 2. Catholic/ Christian [ ] 3. Buddhist [ ] 4. Hinduist [ ] 5. Konghucu [ ] 6. Other, _____ [ ] 99. Refuse to answer
6.	Ethnicity	[ ] 1. Minangkabau [ ] 2. Javanese [ ] 3. Batak/Mandailing [ ] 4. Other, _____ [ ] 88. Don't know [ ] 99. Refuse to answer
7.	Highest education level	[ ] 1. Never went to school [ ] 2. Kindergarten [ ] 3. Primary school [ ] 4. High school [ ] 5. Diploma/bachelor [ ] 6. Higher degree [ ] 88. Don't know [ ] 99. Refuse to answer
8.	Occupation	[ ] 1. Government employee [ ] 2. Private sector employee [ ] 3. Professional

		[ ] 4. Entrepreneur [ ] 5. Blue collar job [ ] 6. Homemaker [ ] 7. Student [ ] 8. Unemployed [ ] 9. None-school or work age [ ] 99. Refuse to answer
9.	Average monthly household income (IDR)	[ ] 1. ≤1.000.000 [ ] 2. 1.000.001-2.000.000 [ ] 3. 2.000.001-3.000.000 [ ] 4. 3.000.001-4.000.000 [ ] 5. 4.000.001-5.000.000 [ ] 6. >5.000.000 [ ] 88. Don't know [ ] 99. Refuse to answer
10.	Health provider	[ ][ ]

B. Identification of tuberculosis risk factor

No	Criteria	Answers
1.	Children with HIV	[ ] 1. Yes [ ] 2. No [ ] 88. Don't know
2.	Children under the immunocompromised treatment such as children living with HIV, cancer, or regularly taking dialysis treatment	[ ] 1. Yes [ ] 2. No [ ] 88. Don't know
3.	People living in prison, dormitory, or military camp	[ ] 1. Yes [ ] 2. No [ ] 88. Don't know
4.	History of BCG vaccine	[ ] 1. Yes [ ] 2. No [ ] 88. Don't know
5.	Number of people in the household	[ ] 1. <3 person [ ] 2. 3-4 person [ ] 3. 5-6 person [ ] 4. ≥7 person
6.	Number of people sleeping per room	[ ] 1. <3 person [ ] 2. 3-4 person [ ] 3. 5-6 person [ ] 4. ≥7 person

7.	Household contact with bacteriologically pulmonary TB patients	[ ] 1. Yes [ ] 2. No
8.	Are you sharing the same room with the TB patient before the diagnosis of TB?	[ ] 1. Yes, go to no. 9 [ ] 2. No, go to no. 11
9.	Currently, do you sleep in the same bedroom as index TB patient?	[ ] 1. Yes [ ] 2. No
10.	Do you ever take TB drug before?	[ ] 1. Yes [ ] 2. Currently on TB drug [ ] 3. Never
11.	Having an air conditioning in the bedroom	[ ] 1. Yes [ ] 2. No
12.	Opening the windows in bedroom	[ ] 1. No window [ ] 2. Never open [ ] 3. Open frequently
13.	Having people who smoke inside the house	[ ] 1. No one [ ] 2. Have active smoker

C. Contact investigation

No	**Sociodemographic**	
1.	Date of birth (dd/mm/yyyy)	__/__/____
2.	Age of index case	[ ][ ]
3.	Sex of index case	[ ] 1. Male [ ] 2. Female
4.	Marital status of index case	[ ] 1. Single [ ] 2. Married [ ] 3. Widows/divorced [ ] 99. Refuse to answer
5.	Religion of index case	[ ] 1. Islam [ ] 2. Catholic/ Christian [ ] 3. Buddhist [ ] 4. Hinduist [ ] 5. Konghucu [ ] 6. Other, _____ [ ] 99. Refuse to answer
6.	Ethnicity of index case	[ ] 1. Minangkabau [ ] 2. Javanese [ ] 3. Batak/Mandailing [ ] 4. Other, _____ [ ] 88. Don't know [ ] 99. Refuse to answer
7.	Highest education level of index case	[ ] 1. Never went to school [ ] 2. Kindergarten

		[ ] 3. Primary school [ ] 4. High school [ ] 5. Diploma/bachelor [ ] 6. Higher degree [ ] 88. Don't know [ ] 99. Refuse to answer
8.	Occupation of index case	[ ] 1. Government employee [ ] 2. Private sector employee [ ] 3. Professional [ ] 4. Entrepreneur [ ] 5. Blue collar job [ ] 6. Homemaker [ ] 7. Student [ ] 8. Unemployed [ ] 9. None-school or work age [ ] 99. Refuse to answer
9.	Average personal income (IDR) of index case	[ ] 1. ≤1.000.000 [ ] 2. 1.000.001-2.000.000 [ ] 3. 2.000.001-3.000.000 [ ] 4. 3.000.001-4.000.000 [ ] 5. 4.000.001-5.000.000 [ ] 6. >5.000.000 [ ] 88. Don't know [ ] 99. Refuse to answer
10.	Relation of index case to child patient	[ ] 1. Parents [ ] 2. Siblings [ ] 3. Grandparents [ ] 4. Family relatives [ ] 5. Caregivers [ ] 6. Others, _____ [ ] 99. Refuse to answer
	History of index case	
11.	Final diagnosis date (dd/mm/yyyy)	__/__/____
12.	Type of TB	[ ] 1. Clinical diagnosis [ ] 2. Bacteriological diagnosis [ ] 3. Not TB
13.	Site of TB	[ ] 1. Pulmonary TB [ ] 2. Extrapulmonary TB [ ] 3. Not TB

14.	Suggested anti-TB drug	[ ] 1. FDC, _____ [ ] 2. TB preventive treatment
15.	Treatment started date (dd/mm/yyyy)	__/__/____
16.	Stool-Xpert result (if applicable)	[ ] 1. Positive, _____ [ ] 2. Negative [ ] 3. Invalid [ ] 4. Error [ ] 5. No result [ ] 6. Indeterminate [ ] 7. Inadequate sample [ ] 8. Others, _____
17.	Stool-Xpert date (if applicable)	__/__/____

D. Behavioral assessment (for children aged 12-15 years)

1.	Do you have history of smoking?	[ ] 1. Never [ ] 2. Past [ ] 3. Current [ ] 4. Others, _____ [ ] 99. Refuse to answer
2.	How often do you smoke?	[ ] 1. Daily [ ] 2. Weekly [ ] 3. Monthly [ ] 4. Others, _____ [ ] 99. Refuse to answer
3.	Do you have history of alcohol drinking?	[ ] 1. Never [ ] 2. Past [ ] 3. Current [ ] 4. Others, _____ [ ] 99. Refuse to answer
4.	How often do you drink alcohol?	[ ] 1. Daily [ ] 2. Weekly [ ] 3. Monthly [ ] 4. Others, _____ [ ] 99. Refuse to answer

E. Clinical assessment (Fill by trained general practitioner or pediatrician)

Signs and symptoms	[1] Yes	[2] No	Duration of signs and symptoms (days)
Fever (>14 days)			
Cough (>14 days)			

Weight loss			
Malaise			
Shortness of breath			
Chest pain			
Blood in sputum			
Others, specify			
Physical examination			
Weight	[ ][ ][ ].[ ] kg	Height	[ ][ ][ ].[ ] cm
BMI	[ ][ ].[ ] kg/m^2	Status	[ ] Normal [ ] Abnormal, _____
Head and neck examination			
Eye	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Head	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Neck	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Nose	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Mouth	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Thorax examination			
Lung			
Inspection	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Palpation	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Percussion	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Auscultation	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Heart			
Inspection	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Palpation	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Percussion	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Auscultation	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Abdomen	[ ] 1. Normal	[ ] 2. Abnormal, _____	
Extremity	[ ] 1. Normal	[ ] 2. Abnormal, _____	

F. TB diagnosis (Fill ones which applicable)

Method	Result
Signs and symptoms	[ ] 1. Yes [ ] 2. No
Tuberculin skin test	[ ] 1. Positive [ ] 2. Negative [ ] 99. Not done
Chest X-ray	[ ] 1. Suggestive TB [ ] 2. Not suggestive TB [ ] 99. Not done
Culture with any specimen	[ ] 1. Yes [ ] 2. No [ ] 3. Indeterminate [ ] 4. Inadequate sample [ ] 99. Not done
Sputum-Xpert	[ ] 1. MTB detected, _____ [ ] 2. MTB not detected [ ] 3. MTB trace detected, _____ [ ] 4. Error [ ] 5. Invalid [ ] 6. No result [ ] 99. Not done
Stool-Xpert	[ ] 1. MTB detected, _____ [ ] 2. MTB not detected [ ] 3. MTB trace detected, _____ [ ] 4. Error [ ] 5. Invalid [ ] 6. No result [ ] 99. Not done
Others (if applicable)	

G. Final diagnosis

Latent tuberculosis infection (LTBI) : [ ] 1. Yes [ ] 2. No

Tuberculosis disease : [ ] 1. Yes [ ] 2. No

Clinically TB : [ ] 1. Yes [ ] 2. No

Bacteriologically TB : [ ] 1. Yes [ ] 2. No

Site of TB : [ ] 1. Pulmonary TB

[ ] 2. Extrapulmonary TB

Suggested anti-TB drug : [ ] 1. Fixed-dose combination

[ ] 2. Tuberculosis preventive treatment

[ ] 3. Monitoring

Examiner's signature

_____

(_____)

Date (Day/ Month/ Year)

_____

Appendix 6. Data recording form for health workers

Semi-structured interview guide on acceptability and implementation of stool-Xpert MTB/RIF among children with TB household contact in health workers in Puskesmas

General Information

Interviewer code: _____ Note-taker code: _____

Date: _____/_____/_____ Start time: _____

Description of place of interview: _____

A. Identity

1. Health Worker Code: _____
2. Sex: Male ☐ Female ☐
3. Profession: _____
4. Primary Healthcare Unit: _____

B. Experience in Tuberculosis Control and Prevention Program

1. How long have you been working at this health facility?
2. What role(s) do you play at this health facility?
3. What type of TB services are provided in your unit? (*probe for: education, diagnosis, laboratory, treatment, referral*)
4. How long have you been involved with TB control and prevention at this healthcare?
5. Have you had any training on TB diagnosis and treatment? (If yes, how many times have you been trained?) *(probe: how long ago was your last training on TB?)*
6. Have you had any training on TB diagnosis with stool-Xpert MTB/RIF? If yes, how many times have you been trained?
7. Do you have the guidelines on stool-Xpeert MTB/RIF available? (If yes, then look at the guidelines with the health worker and discuss about which aspect

can be implemented or not implemented on the settings. If no, show your guideline and go through the same procedure described above.)

C. Practices in Tuberculosis Contact Investigation (TB Officer only)

1. Do you have electronic TB register system and how often are entries made in it? (*look at the e-TB system with the health worker and discuss the gaps in the register, variables entered, last entry date)*
2. What do you do with the data entered in the e-TB system?
3. If a patient reports a close contact with children, what do you do? (*probe: if health worker does not mention the use of a symptom screening or home visit, then you ask about its use*).
4. How do you identify child patients needing a TB test? (*probe: for use of TB symptom screening or tuberculin skin test*)
5. If a patient is identified as requiring a sputum test, what do you do? *(probe: education on sputum, lab request form, provide sputum container, refer to the TB lab or hospital*)
6. What do you do when a patient who has been asked to do a sputum test return with
    a. a positive test results? (*probe: counselling, TB treatment*)
    b. a negative test results? (*probe: counselling, normal treatment*)
7. What infection prevention and control measures do you take in this primary healthcare to prevent spread of TB *(probe: promptly early diagnosis among children with TB household contact, promptly home visit to community)*
8. What guidelines do you follow in diagnosing TB in this health facility?
9. Do you have the guidelines available on contact investigation? (If yes, then look at the guidelines with the health worker and discuss about who aspect can be implemented or not implemented on the settings. If no, show your guideline and go through the same procedure described above)

D. Experience in Implementing Stool-Xpert MTB/RIF among Children with Tuberculosis Household Contact

1. Can you please briefly describe how you are performing the systematic screening with stool-Xpert MTB/RIF?
2. What challenges or difficulties have you faced when performing the test? Can you please give some specific examples?
3. When you first heard about the test, what was your initial impression? What is your opinion now?
4. Given your experience of the stool-Xpert MTB/RIF test and what you know about it, what is your perception of the test and the various aspects of its implementation? *(probe: may we can start in broader terms and then explore some specific aspects further? At what level of care do you think the test is most adapted? Why?)*
5. How do you think stool-Xpert MTB/RIF should fit in the TB screening algorithm? *(probe: should it be used with other screening or diagnostic methods? Why?)*
6. Do you consider that handling and performing the stool-Xpert MTB/RIF test using than following referral system to higher-level healthcare? (choose one alternative)

☐ *With stool-Xpert MTB/RIF and referral system are similar*
☐ *With stool-Xpert MTB/RIF is easier than referral system*
☐ *With stool-Xpert MTB/RIF is more difficult than referral system*

E. Experience in Processing Stool-Xpert MTB/RIF in Laboratory (Laboratory Staff only)

1. How many tests required until you feel comfortable to perform the test independently/confidently?
2. If you were training someone on performing the stool-Xpert MTB/RIF test: What are the most important things you would teach them?

3. If you use a scale that goes from ’Very easy’ to ‘Very difficult’ how would you rate your ability to interpret the stool-Xpert MTB/RIF test result as positive/negative/invalid? (choose one alternative)

☐	☐	☐	☐	☐
Very Easy	*Easy*	*Neutral*	*Difficult*	*Very Difficult*

4. Do you consider that handling and performing the stool-Xpert MTB/RIF test using than sputum-Xpert MTB/RIF? (choose one alternative)

   ☐ *With stool and sputum are similar*
   ☐ *With stool is easier than sputum*
   ☐ *With stool is more difficult than sputum*

5. Do you consider that handling and performing the stool-Xpert MTB/RIF test using than tuberculin skin test (TST)? (choose one alternative)

   ☐ *With stool-Xpert MTB/RIF and TST are similar*
   ☐ *With stool-Xpert MTB/RIF is easier than TST*
   ☐ *With stool-Xpert MTB/RIF is more difficult than TST*

F. Suggested Solutions

1. What do you think can be done to improve TB case detection in this primary healthcare?
2. What would be your recommendations to other research/setting regarding stool-Xpert MTB/RIF?

Interview end time: _____

Appendix 7. Data recording form for primary caretakers

Questionnaire on acceptability and implementation of stool-Xpert MTB/RIF among caregivers

General Information

Interviewer code: _____ Note-taker code: _____

Date: _____/_____/_____ Start time: _____

Description of place of interview: _____

No	Questions	Answers
1.	Interviewer code	[ ][ ]
2.	Date of interview (dd/mm/yyyy)	__/__/____
3.	Subject ID	[ ][ ][ ][ ][ ]
5.	Index case ID	[ ][ ][ ][ ][ ]
4.	Child patient ID	[ ][ ][ ][ ][ ]
6.	Primary healthcare code	[ ][ ]
A. Sociodemographic status		
1.	Sex	[ ] 1. Male [ ] 2. Female
2.	Date of birth (dd/mm/yyyy)	__/__/____
3.	Marital status	[ ] 1. Single [ ] 2. Married [ ] 3. Widows/divorced [ ] 99. Refuse to answer
4.	Religion	[ ] 1. Islam [ ] 2. Catholic/ Christian [ ] 3. Buddhist [ ] 4. Hinduist [ ] 5. Konghucu [ ] 6. Other, _____

		[ ] 99. Refuse to answer
5.	Ethnicity	[ ] 1. Minangkabau [ ] 2. Javanese [ ] 3. Batak/Mandailing [ ] 4. Other, _____ [ ] 88. Don't know [ ] 99. Refuse to answer
6.	Highest education level	[ ] 1. Never went to school [ ] 2. Kindergarten [ ] 3. Primary school [ ] 4. High school [ ] 5. Diploma/bachelor [ ] 6. Higher degree [ ] 88. Don't know [ ] 99. Refuse to answer
7.	Occupation	[ ] 1. Government employee [ ] 2. Private sector employee [ ] 3. Professional [ ] 4. Entrepreneur [ ] 5. Blue collar job [ ] 6. Homemaker [ ] 7. Student [ ] 8. Unemployed [ ] 9. None-school or work age [ ] 99. Refuse to answer
8.	Average monthly household income (IDR)	[ ] 1. ≤1.000.000 [ ] 2. 1.000.001-2.000.000 [ ] 3. 2.000.001-3.000.000 [ ] 4. 3.000.001-4.000.000 [ ] 5. 4.000.001-5.000.000 [ ] 6. >5.000.000

		[ ] 88. Don't know [ ] 99. Refuse to answer
9.	Relation to child patient	[ ] 1. Parents [ ] 2. Siblings [ ] 3. Grandparents [ ] 4. Family relatives [ ] 5. Caregivers [ ] 6. Others, _____ [ ] 99. Refuse to answer

B. Outline for in-depth interview: Experience in implementing stool specimen collection among primary caretakers

1. Can you please briefly describe how you are performing the stool collection from your children?
2. What challenges or difficulties have you faced when collect the stool? Can you please give some specific examples?
3. When you first heard about the test, what was your initial impression? What is your opinion now?
4. Given your experience of the stool-Xpert MTB/RIF test and what you know about it, what is your perception of the test and the various aspects of its implementation? *(probe: is it convenience? Do you feel strange to collecting the stool from your kids?)*
5. How do you think stool-Xpert MTB/RIF should fit in the TB screening algorithm? *(probe: should it be used with other screening or diagnostic methods? Why?)*

Interview end time: _____

Appendix 8. Practical manual of processing stool specimen for childhood tuberculosis

1. Stool collection and storage

1.1 Equipment required

a. Stool or sputum container, wide-mouthed and able to hold 3-5 gram of stool
b. Sealable plastic bag
c. Plastic sheeting
d. Label
e. Pen or permanent marker



Figure 1. Example of a stool container

Source: Practical manual of processing stool samples for diagnosis of childhood TB, WHO, 2022

1.2 Stool collection process

Stool collection is usually done by the caregivers or the patients themselves, depending on the age of the child. In ideal practice, stool collection can be done in Puskesmas. However, to obtain a specimen on demand may challenging; therefore, stool also can be collected at home. Research team will provide a delivery service to help caregivers or the patients to return and submit the sample to Puskesmas.

The caregivers and patients will be provided with a stool container. If applicable, sputum container is also allowed. The container must be provided in a plastic bag to keep the container clean during the transport to and from the home.

The caregivers and patients will be provided with a flyer to provide the information or steps on how to collect the stool sample, and health worker or the responsible research team contacts who collect the stool. The flyer will contain the instructions as following steps:

1. Collect the stool sample during the first daily bowel movement. If possible, first, empty the bladder to avoid mixing urine with the stool sample.
2. Put some clean plastic sheeting on the spot where the stool will be dropped, to ensure the collection of a clean sample. Avoid contamination of the plastic with soil, detergent or disinfectant from the toilet.



Figure 2. Plastic sheet position for toilet and diaper to prevent contamination during stool collection

Source: Practical manual of processing stool samples for diagnosis of childhood TB, WHO, 2022

3. In children under-5 who use diaper, either collect the stool directly from the diaper as soon as the defecation process or put a plastic sheet on the surface of the diaper before to avoid contamination of substances in diaper.
4. Fill the stool container with stool sample up to half full, using the spoon provided. **Do not fill the container to the bring.** Only a small amount of stool (8 gr or thumbnail size) is required for testing.
5. Close the container tightly, place the container in the sealable plastic bag provided.
6. As soon as the stool sample has been collected, store the plastic bag containing the stool container in a clean and cool place until the sample being picked up by the responsible research team, avoiding exposure to direct sunlight.
7. **Do not freeze the sample.**

1.3 Stool delivery and storage process

Research team will provide a delivery service to help caregivers or the patients to return and submit the sample to Puskesmas. Caregivers and patients will be provided by the health worker or responsible research team contacts to help the patients return the stool sample to Puskesmas, maximum 1-day after children with tuberculosis household contact being screened in Puskesmas.

For transport and storage of stool sample, the same conditions apply as for transport and storage of sputum sample for Xpert testing. Thus, between collection and testing, stool sample can be kept at a maximum of 35 °C for up to 3 days, followed by a maximum of 7 days at 2–8 °C. Ideally, stool sample containers should be kept at 2–8 °C while being sent to the laboratory and should then be stored in the refrigerator (at 2–8 °C) until testing can be performed. Sample preparation and testing should be started as soon as possible. Before processing the stool with GeneXpert MTB/RIF, allow the stool sample to warm up to room temperature.

2. Stool-Xpert processing method

2.1 Equipment required

a. Sample reagent (SR)
b. Conical tube
c. Wooden stick
d. Balloon pipettes
e. GeneXpert MTB/RIF kit, including machine and cartridge
f. Medical gloves
g. Stool sample

2.2 Stool processing procedure

The stool processing will be done my laboratory staff by the Simple One-Step (SOS) method. This method uses one step to release *Mycobacterium tuberculosis* from stool. Particulate matter is sedimented by gravity, and it is assumed that this allows TB bacilli to float to the top of the watery solution after the lipid-containing cell wall.

The laboratory staff will do the SOS method by following steps below:

a. Before stool processing, the laboratory staff will assess the stool sample as two types of samples, formed stool or liquid stool.
b. For formed stool, 0.8 g or a thumb size amount of stool is directly transferred from the stool container into the SR bottle using a wooden stick.
c. For liquid stool, SR as much as 2 ml will be removed from the SR bottle then 2 ml of stool is transferred to the SR bottle using a balloon pipette.
d. After step (b) and (c), the SR bottle is shaken vigorously in 30 seconds until both buffer and stool become homogeny.
e. The homogeny sample will be warmed up in incubator machine for 10-15 minutes. This step is repeated once.
f. If the solid particles and debris have settled, transfer 2 ml of the supernatant sample inside the SR bottle to the Xpert MTB/RIF cartridge with pipette carefully to avoid any bubbles during the transfer process.
g. Insert the cartridge into the Xpert MTB/RIF machine.

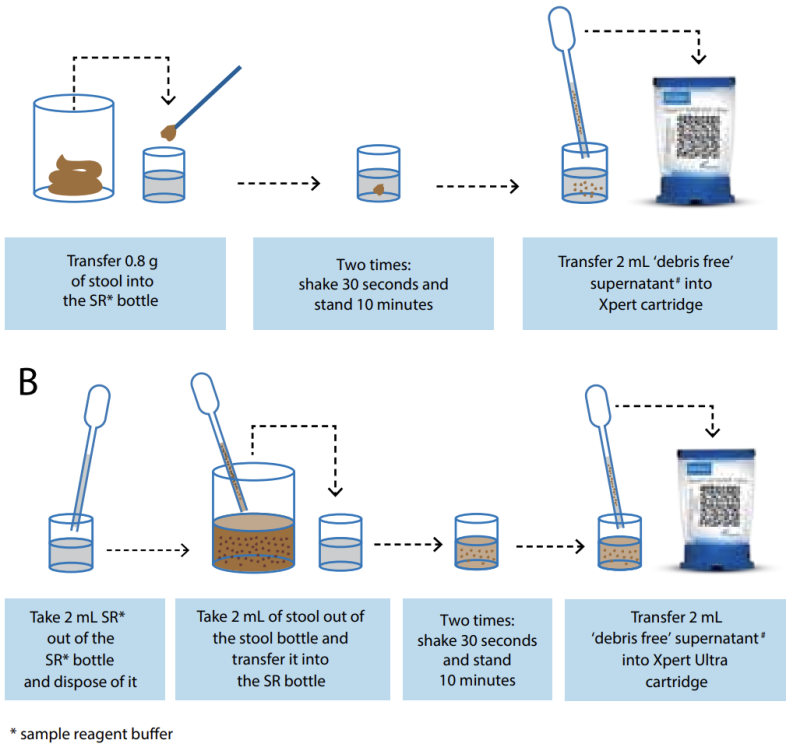


Figure 3. Schematic overview of the SOS stool processing method for GeneXpert MTB/RIF machine

Source: Practical manual of processing stool samples for diagnosis of childhood TB, WHO, 2022

3. Stool analysis and interpretating process

3.1 Starting the analysis process

Stool sample must be put into analysis system maximum 4 hours after the cartridge is inserted to the GeneXpert machine. There are several steps to run the sample analysis process as listed below:

a. Ensure the computer and the GeneXpert machine already turned on and run the diagnosis process as written in the GeneXpert machine guideline book.

b. In the main page of GeneXpert Diagnosis System, choose "Create test" and scan the cartridge barcode request will show up.

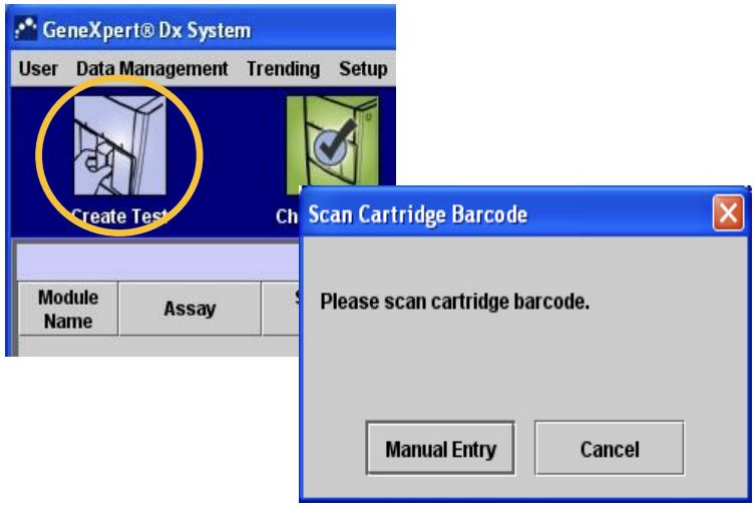


Figure 4. The window of Create test menu

Source: Petunjuk Teknis Pemeriksaan TB menggunakan Tes Cepat Molekuler, Ministry of Health of Indonesia, 2017

c. Scan the cartridge barcode with a barcode scanner, or click "manual entry" and type the cartridge series number manually.



Figure 5. Barcode scanning and series number of cartridge

Source: Petunjuk Teknis Pemeriksaan TB menggunakan Tes Cepat Molekuler, Ministry of Health of Indonesia, 2017

d. After the cartridge series number is inserted, type the citizenship registry number of the patient and e-TB system registry number. Then, the "Select module" notification will be automatically showed up and filled. Click the "start test" option.
e. The green light in GeneXpert MTB/RIF machine will be on in the selected module. Open the module and insert the cartridge.



Figure 6. GeneXpert MTB/RIF with green light

Source: Petunjuk Teknis Pemeriksaan TB menggunakan Tes Cepat Molekuler, Ministry of Health of Indonesia, 2017

f. There will be a *"click"* sound if you already close the module perfectly. The analysis process will run for 2 hours. After the analysis process is finished, the green light will automatically off and the module will open.

3.2 Monitoring the analysis process

a. The laboratory staff can monitor the analysis process and the indicator process by click the "Check status" in the main page.

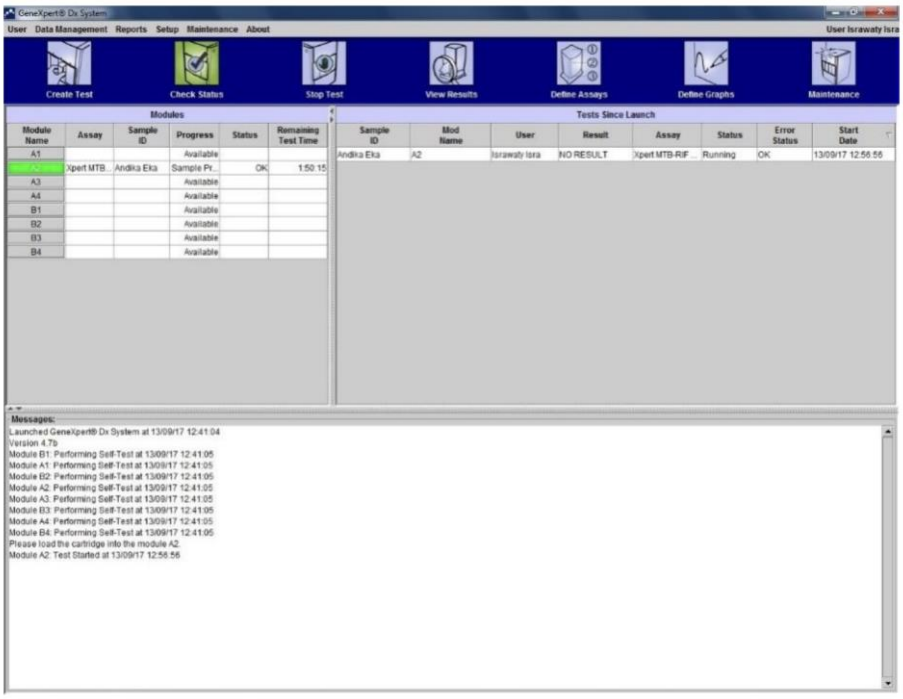


Figure 7. The window of Check status menu

Source: Petunjuk Teknis Pemeriksaan TB menggunakan Tes Cepat Molekuler, Ministry of Health of Indonesia, 2017

The "Module" column will show the current step of assay test and how many times left to finish the test. While the "Messages" column will show the date and time of laboratory staff start the analysis process. If the analysis process is still running, then the result of the "Result" column will show "NO RESULT".

b. If the laboratory staff want to stop the test due to several conditions such as electricity off, staff can use "Stop test" option to stop individual or all tests in program. Consequently, the sample and cartridge which already used cannot be use anymore.

3.3 Interpreting the analysis result

To read the result, the laboratory staff can follow the steps as listed below:

a. Click the "View result" option in the main page of GeneXpert Diagnosis System. Click the "View test" option after result window show up.

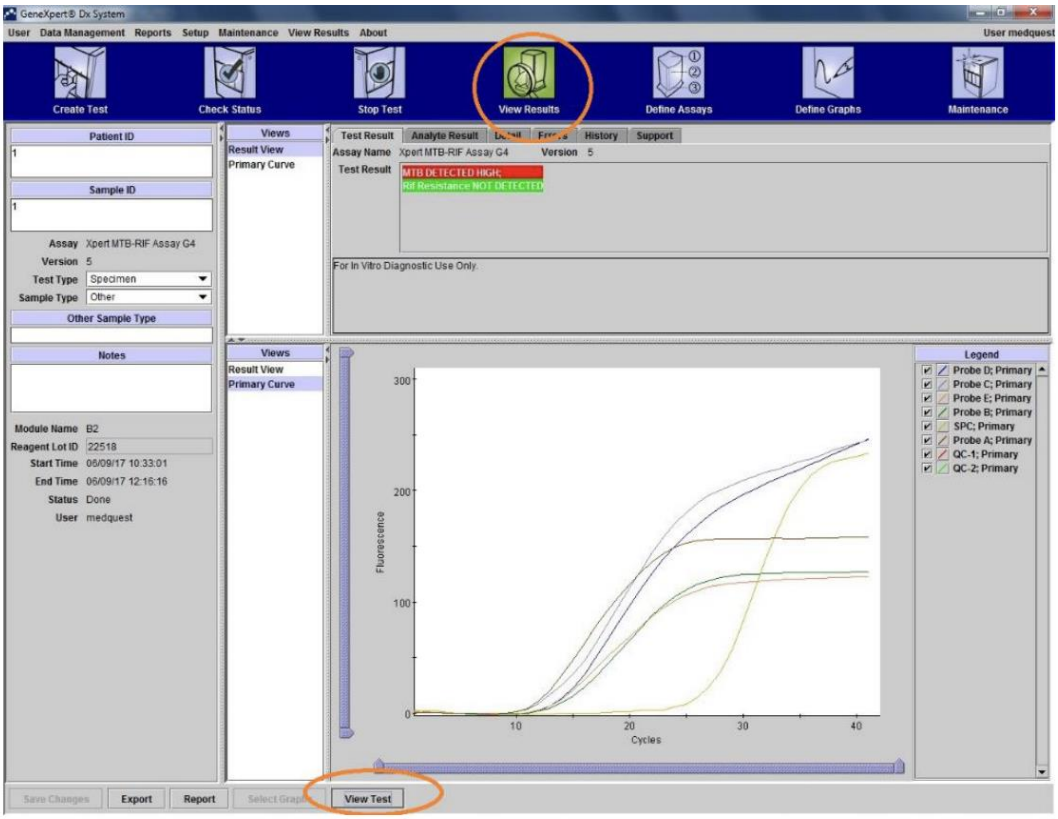


Figure 7. The window of View Result menu

Source: Petunjuk Teknis Pemeriksaan TB menggunakan Tes Cepat Molekuler, Ministry of Health of Indonesia, 2017

b. The "Select test to be viewed" window will open and choose the testing result to be showed. Click "Ok" and the result will be viewed.

c. The "Result" window will also provide information of the patients and the diagnosis result, category of error which happen during the analysis is run, and detailed of equipment is used for the test. There is also an advance view of

"Result" window with comprehensive result of the test such as curve and limitation of the test.

d. The result will follow the information listed below:

Table 1. The result and interpretation of GeneXpert MTB/RIF diagnosis system

No	Result	Interpretation	Suggested follow-up method
1.	MTB detected; Rif Resistance detected	• DNA MTB detected • Mutation on rpoB gene detected, high possibility of TB rifampicin resistance (RR-TB)	Follow the diagnosis flow and treatment rules of RR-TB
2.	MTB detected; Rif Resistance not detected	• DNA MTB detected • None of mutation on rpoB gene detected, high possibility of drug susceptible TB (DS-TB)	Follow the diagnosis flow and treatment rules of DS-TB
3.	MTB detected; Rif Resistance indeterminate	• DNA MTB detected • Mutation on rpoB gene or RR cannot be decided since there is no enough signal of resistance detected	Do re-test as soon as possible with a good quality sample
4.	MTB trace	• DNA MTB detected in lower levels • RR is not detected	Follow the diagnosis flow and treatment rules od DS-TB
5.	MTB not detected	DNA MTB are not detected	Follow the diagnosis flow and treatment rules of TB
6.	Invalid	The existence of DNA MTB cannot be decided due to the curve not showing the growth of amplicon, unstandardized sample processing, or PCR reaction	Do re-test with new cartridge and new sample, ensure that there is no contamination during the sample processing method
7.	Error	The existence of DNA MTB cannot be decided, the internal quality control is failed or there is system failure	Do re-test with new cartridge, ensure the

			standard of sample processing method
8.	No result	The existence of DNA MTB cannot be decided due to underperformed of PCR reaction	Do re-test with new cartridge

To be noted, the result of “indeterminate”, “invalid”, “error”, and “no result” only can be re-tested for one more time. For research purpose, the result of stool-Xpert MTB/RIF also will be recorded on the medical sheet of the child patient by the research team. However, the anonymity and confidentiality will be strictly maintained throughout the study.

Appendix 9. Certificate as presenter in conference



Appendix 10. Manuscript

28th National Graduate Conference (2/2024) [1]
17-18 May 2024 @ Bangkok, Thailand (Online Conference)

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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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

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[2]

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).

[4]

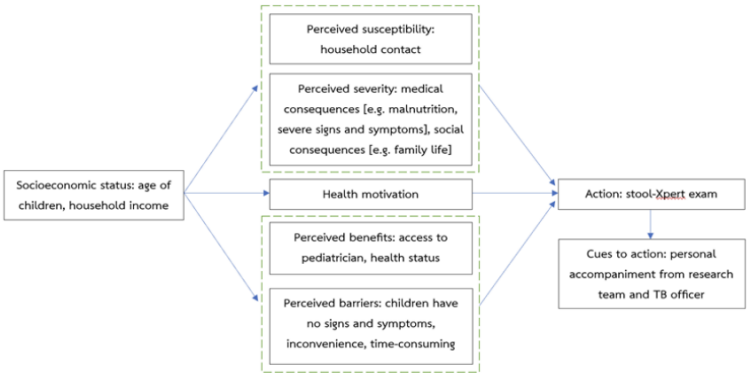

Figure 1 The proposed health belief model for stool-Xpert screening for childhood tuberculosis

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

[5]

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.

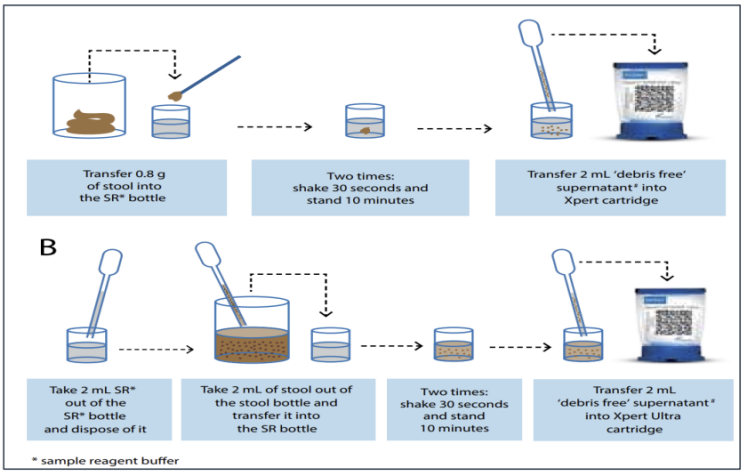

Figure 2 The stool procedures Source: (World Health Organization, 2020)

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.

[6]

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

[7]

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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List of Publication and Proceeding

1. 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. Paper presented at: The National Graduates Conference 2/2024; 2024 May 17-18; Bangkok, Thailand.
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