Early health technology assessment of tongue swab for non-sputum based pulmonary tuberculosis diagnosis in Thailand

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Summary

Background Sputum-based diagnostic methods for pulmonary tuberculosis (PTB) are challenging for patients who cannot produce sputum. Non-sputum-based approaches, such as tongue swab (TS), can address this gap. This study conducts an early Health Technology Assessment (HTA) of TS for PTB diagnosis in Thailand.

Methods We conducted a landscape review, stakeholder consultation, early health economic modeling, and established a Target Product Profile (TPP). The landscape review included a comprehensive literature analysis to identify gaps and unmet needs in PTB diagnosis in Thailand. Stakeholder consultations gathered insights from TB experts to validate the information. An early health economic model evaluated the cost-effectiveness of two innovative strategies: tongue swab with Loop-Mediated Isothermal Amplification (LAMP) and tongue swab with real-time polymerase chain reaction (RTPCR). The TPP outlines three target levels to guide innovators in designing effective clinical studies.

Findings The landscape review identified the clinical workflow and reimbursement process of all PTB diagnostic tests in Thailand. The gap of tuberculosis management was around diagnosis and treatment. Stakeholders indicated that PTB detection remains inefficient due to issues such as low-test accuracy, costs, delays, drug-resistance testing, and the need for specialized laboratory techniques and personnel. TS RTPCR is the best-performing strategy, outperforming other strategies for the targeted population from the modelling analysis.

Interpretation TS may serve as a viable alternative worth further exploration and development. An ongoing collaboration between early HTA researchers and innovators has identified valuable information for innovation development.

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Keywords: Early health technology assessment; Early HTA; Tuberculosis; Tongue swab; Tuberculosis diagnosis; Economic evaluation; Economic model; Cost-effectiveness

Abbreviations: AFB, Acid-fast bacillus smear microscopy; AFB&Xpert, Acid-fast bacillus smear microscopy and sputum Xpert; CEA, Cost-effectiveness analysis; CET, Cost-effectiveness thresholds; CUA, Cost-utility analysis; EVPI, Expected value of perfect information; EVPPI, Expected value of partially perfect information; RIF, Rifampicin; HTA, Health technology assessment; ICER, Incremental cost-effectiveness ratio; IGRA, Interferon gamma release assay; LAMP, Loop-mediated isothermal amplification; LMICs, Low and middle-income countries; MORU, Mahidol-Oxford Tropical Medicine Research Unit; MTB, *Mycobacterium tuberculosis*; MTBc, *M. tuberculosis* complex; NHSO, National Health Security Office; NLEM, National List of Essential Medicines; NLEV, National List of Essential Vaccines; NMB, Net monetary benefit; PTB, Pulmonary tuberculosis; qPCR, Quantitative polymerase chain reaction; QALYs, Quality-adjusted life years; ROC, Receiver operating characteristic; RTPCR, Real-time polymerase chain reaction; TPP, Target Product Profile; TS, Tongue swab; TST, Tuberculin skin test; TSRI, Thailand Science Research and Innovation; UCS, Thai Universal Coverage Scheme; VOI, Value of information

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Research in context

Evidence before this study

Pulmonary tuberculosis (PTB) continues to be a major cause of death worldwide. Sputum-based diagnostic tests are not effective for individuals who have difficulty producing sputum, such as HIV patients and children. This has highlighted the need for alternative, non-sputum-based testing methods, with oral swab tests emerging as a promising solution. We conducted a search in January 2024 using the terms ("oral swab*" OR "tongue swab*" OR saliva OR "buccal swab*") AND (tuberculosis OR "pulmonary tuberculosis" OR "mycobacterium tuberculosis" OR TB OR "pulmonary TB"), covering publication in past two years, and repeated the search in September 2024 covering the publication from January 2024 to August 2024. Two systematic reviews published in 2024 were identified. One review examined the use of oral swabs with molecular tests for PTB detection. The other review focused on the diagnostic accuracy of oral swabs for PTB detection. The two systematic reviews examined feasibility of oral specimens, optimal swabbing location, sampling duration, the number of swabs needed, and the diagnostic accuracy for analysis. However, no evidence on the value for money of oral swab testing for PTB diagnosis was identified.

Added value of this study

We contributed to the literature by conducting an early Health Technology Assessment of tongue swab (TS), a type of oral swab, for the diagnosis of PTB, employing a comprehensive approach including a landscape review, stakeholder consultations, early health economic modelling, and development of a Target Product Profile (TPP). Relevant stakeholders including decision makers, innovators, and healthcare providers were engaged throughout the study to ensure the relevance of the recommendations. From the landscape review and stakeholder consultation, we identified the gaps in PTB management in Thailand and used the information to define the desired characteristics and use cases of the innovation. TS with real-time polymerase chain reaction (RTPCR) and TS with Loop-Mediated Isothermal Amplification (LAMP) were further explored in early health economic modelling. TS with RTPCR was the most cost-effective strategy, outperforming existing sputum-based tests and current practice. TPP characteristics including the sensitivity, specificity and cost of the innovation strategies, and the test and treatment non-compliance rate were identified to further inform the innovation development.

Implications of all the available evidence

The study demonstrated to innovators that TS could be a promising alternative method for PTB diagnosis, warranting further exploration and development. It recommended RTPCR as the preferred diagnostic method for TS. Compared to RTRCR, LAMP was not preferred as it incurred higher costs with lower number of patients diagnosed. Future research and development of the technology should focus on cost, sensitivity and specificity of tongue swab-based tests, as well as test-and-treatment non-compliance rate during follow-up visits.

Introduction

Early health technology assessment (HTA) is a relatively new multidisciplinary methodology for evaluating medical technology during its early stages of innovation development and clinical research. It utilizes all available evidence to inform the innovator and other relevant stakeholders about the value of emerging medical technology based on both qualitative and quantitative evidence.[1] Specifically, early HTA can provide innovators with information regarding priority setting, defining Target Product Profile (TPP) and clinical trial design by collecting all relevant data and structuring early economic models to perform the assessment.[2]

While early HTA is promising in guiding medical innovation development, its implementation is often challenging and complex. Usually, innovators are unaware of early HTA and reach out to researchers at a late stage of development, making early HTA efforts less relevant.[3] There is also a misconception that early HTA is solely about early health economic modelling, whereas it encompasses different methodologies to inform innovation development. Several studies have emphasised the significance of expert elicitation and literature review as crucial sources of evidence in early HTA.[4,5] Furthermore, the absence of stakeholder involvement and inadequate communication with innovators could lead to less robust and convincing results.

Another key challenge is the lack of guidelines for early HTA research, making it less visible and impactful. Some earlier early HTA literature primarily used modelling methods to inform innovators. Miller et al. (2005) introduced a series of methods such as clinical trial simulation, threshold analysis, and value of information(VOI) analysis.[6] Following these papers, there have been many articles discussing the methodology of early HTA,[3,7] but there is a lack of articles defining a framework and providing guidance for early HTA methodology. The confidentiality issues also hinder the development of early HTA. Early HTA is carried out in the early phases of research and development. The innovation team may not want the results to be publicly available. Early HTA case studies are important for raising awareness of early HTA and initiating discussion about early HTA guidelines.

Early HTA plays a vital role by facilitating effective communication among stakeholders, clinicians, and innovators to identify unmet medical needs and define desired solutions. Early health economic modelling assesses the potential cost-effectiveness of the innovation, supporting informed decision-making.[1] Early HTA identifies the TPP to outline the ideal characteristics of the technology under consideration.[2] Through headroom analysis, early HTA evaluates the potential value of the technology by estimating the price of intervention, providing insight into its market potential.[8] Threshold analysis identifies target values for specific technology characteristics to achieve a particular objective, guiding innovators in refining and further developing the technology. Furthermore, VOI measures the benefits of eliminating uncertainty by calculating the potential financial and opportunity costs of making wrong decisions under imperfect information. It enables innovators to assess the value of additional research or data collection to guide resource allocation and optimize outcomes.[6]

Since from 2008, the Thai government has utilized HTA to inform the coverage decisions on the Thai Universal Coverage Scheme (UCS) following three separate processes: (i) the National List of Essential Medicines (NLEM), (ii) the Universal Coverage Benefits Package (UCBP), and (iii) the National List of Essential Vaccines (NLEV). HTA plays a crucial role in the process of healthcare decision-making in Thailand. Topics are nominated annually by stakeholders for UCBP or experts for NLEM/NLEV. Working groups score topics based on criteria like disease burden, equity, and cost-effectiveness, selecting up to 35 annually. Assessments adhere to strict guidelines, incorporating cost-effectiveness analyses and stakeholder consultations.[9–11] Final decisions take into account factors such as cost, clinical guidelines, system readiness, and the current cost-effectiveness threshold of 160,000 Baht per Quality-Adjusted Life Year (QALY).[12] With over a decade of robust HTA implementation, stakeholders in Thailand are increasingly interested in early HTA to guide the development of health innovations.

In collaboration with a group of medical innovators from the Mahidol-Oxford Tropical Medicine Research Unit (MORU), we conducted an early HTA to evaluate the tongue swab (TS)-based assays, one of the non-sputum-based methods for diagnosis and treatment monitoring of pulmonary tuberculosis (PTB), the primary subtype of tuberculosis (TB). The innovator selected TS over other types of oral swabs based on existing evidence showing that TS produced significantly stronger signals compared to cheek swab and gum swab.[13]

The burden of PTB in Thailand has been on the top list reported by World Health Organization for over ten years.[14] Although the number of new cases per year has been decreasing, this corresponds to the END TB strategy, which is implemented in all government hospitals throughout the country.[15] The automated Cepheid Xpert MTB/RIF Ultra qPCR test (Xpert Ultra), which is commonly available in provincial hospitals, detects DNA of *M. tuberculosis* complex (MTBc) and rifampicin-resistant MTBc in expectorated patient sputum.[16] However, it is not the primary choice of test for patients with clinical symptoms suggesting PTB. According to the standard guideline, chest X-ray is prescribed to detect abnormality first. If abnormality is detected, acid-fast bacillus smear microscopy (AFB) is the next step. If abnormality of chest X-ray and negative AFB are found, a molecular detection method such as X-pert Ultra is prescribed. The AFB and chest X-ray have poor sensitivity and specificity for PTB diagnosis.[17] Another challenge for PTB diagnosis is that not every suspected PTB patient can expectorate or produce sputum, for example, in children's cases, people with HIV, or the elderly.[18,19] There are several specimen types reported as alternative samples for MTB detection, including urine, faeces, saliva, buccal swabs and TS. In the last five years, oral swabs (buccal or TS) have been reported as a promising alternative to sputum for molecular diagnosis of PTB.[20,21] Semi-quantitative real-time polymerase chain reaction (RTPCR) targeting IS*6110*, Loop-Mediated Isothermal Amplification (LAMP) and the Xpert Ultra have been developed and validated for detecting MTBc DNA in oral swabs.[22] The accuracy of PTB diagnosis using TS is variable because of several factors, including the specimen collection procedure, molecular-based method of choice, and patient characteristics.[23] Therefore, TS is of interest to be explored to improve sample collection methods. The translational project at MORU has attempted to test sensitivity and specificity of TS with LAMP and RTPCR in Thai settings and sought the guidance from early HTA to help develop the innovative strategy of PTB diagnosis.

This early HTA analysis aims to position the TS sampling collection tool for PTB detection within the Thai healthcare system by comparing it to existing detection strategies. It seeks to identify the TPP of TS-based method to make it preferred over the current practices and examine its potential cost-effectiveness. Additionally, the analysis aims to guide the innovator in refining the technology and planning further research to maximize the likelihood of the novel PTB screening technology being reimbursed.

Methods

This early HTA work consists of three main parts, a landscape review, stakeholder consultation and early health economic modelling. The early HTA researchers and medical innovators communicated throughout the collaboration to refine the research question and identify the additional information to obtain. A flow chart showing the timeline of the work is presented in Appendix 1.

Landscape review

A literature review was conducted to provide an overview the diagnosis, screening, care and management of TB in Thailand. Six English databases were searched including Medline (PubMed), EMBASE, Scopus, CINAHL (EBSCO), Cochrane Library, and Web of Knowledge in April 2024 for papers published between 2010 and 2024, as well as two Thai databases: Thai Journal of Public Health and Division of Tuberculosis, and Department of Disease Control. The search terms were presented in the Appendix 1. The inclusion criteria required papers to focus on TB in Thailand and be written in English or Thai. Various study types were included to address different research questions. For example, policy paper, programme evaluation studies, and Thai reports were reviewed to understand TB management in Thailand. Observational studies, randomized controlled trials, retrospective and prospective cohort studies, ecological studies, and cost-effectiveness analyses (CEAs) were analysed to evaluate the effectiveness, cost, and cost-effectiveness of different TB diagnostic strategies. The landscape review provided evidence to position the new non-sputum-based test. It aimed to comprehensively understand TB in Thailand, including epidemiology, disease burden, high-risk populations, policies, standard practices, and gaps in TB diagnosis. This information helped identify standard practices for screening, diagnosing, and treating PTB, the primary subtype of TB, forming the basis for the early HTA model. We defined target population groups, evaluated PTB diagnostic techniques, and confirmed standard and competitor strategies. A report summarizing the findings was generated and shared with the innovator. Additionally, we reviewed economic evaluations of PTB diagnosis in English and Thai to gather cost and outcome data for the model. The cost and outcome data were sourced from the 56 articles included in the landscape review and Thai reports. Of these, 19 papers and reports were included for deriving the cost and outcome data.

Stakeholder consultation

A focused group discussion was conducted in Thai with stakeholders, including TB clinicians, pediatric specialists, researchers, and policymakers from Thailand's Division of Tuberculosis, as well as innovators. Only stakeholders from Thailand were engaged, as the innovators aimed to focus on the Thai context at this stage. The discussion focused on PTB screening, diagnosis, and treatment procedures for adults and children in Thailand, stakeholders' perspectives on challenges in PTB care (including diagnosis, treatment, and monitoring), and opinions on the TS sampling tool. A guiding questionnaire, detailed in Appendix 2, was used. The discussion was audio recorded and transcribed by an external service provider. Stakeholders were later contacted via email for further consultation during the health economic modelling phase.

Modelling

Model structure and assumptions

A cost-utility analysis (CUA) was conducted using the input from literature and expert opinions. The analysis considered secondary and tertiary healthcare levels. Although TS can be used at the primary healthcare level, screening and diagnosing PTB in both children and adults cannot be performed at primary healthcare facilities in Thailand. Most primary healthcare facilities lack physicians, which limits the ability to confirm diagnoses and provide TB treatment according to Thai clinical guidelines. To account for variations in standard PTB testing by age, according to the elicited expert opinions, the population was divided into two groups: Group 1, individuals aged five years and older, and Group 2, children under five years, all exhibiting PTB-suspected symptoms. The standard test and potential competitors commonly used in Thailand were selected as comparators based on the landscape review and stakeholder consultations. In Group 1, AFB with sputum Xpert was the standard test, while sputum LAMP and sputum RTPCR served as competitors against tongue swab LAMP (TS LAMP) and tongue swab RTPCR (TS RTPCR). In Group 2, the standard test was the tuberculin skin test (TST) with no competitors; TS LAMP and TS RTPCR were considered innovative approaches. Details of these strategies and populations are outlined in Table 1.

The primary outcome of the CUA is the incremental cost-effectiveness ratio (ICER), calculated by dividing the cost difference between two strategies by the difference in QALYs over a one-year time horizon from a societal perspective.[24] Based on a landscape review and stakeholder input, a conceptual decision tree model was constructed based on Thailand's PTB patient pathway (Figs. 1 and 2). The early HTA model encompasses three stages: screening (chest X-ray for suspected cases), diagnosis (molecular tests such as LAMP, RTPCR, AFB, Xpert, and follow-up), and treatment. The treatment phase involves two months of intensive therapy with HRZE (isoniazid, rifampin, pyrazinamide, ethambutol)

Strategy	Group 1 (≥5 years old)	Group 2 (<5 years old)
Standard test	AFB&Xpert	TST
Innovation 1	TS LAMP	TS LAMP
Innovation 2	TS RTPCR	TS RTPCR
Competitor 1	Sputum LAMP	
Competitor 2	Sputum RTPCR	

Abbreviations: TS LAMP, tongue swab Loop-Mediated Isothermal Amplification; TS RTPCR, tongue swab real-time polymerase chain reaction; AFB&Xpert, acid-fast bacillus smear microscopy and sputum Xpert; TST, tuberculin skin test. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years.

Table 1: **Strategies for Group 1 and Group 2.**

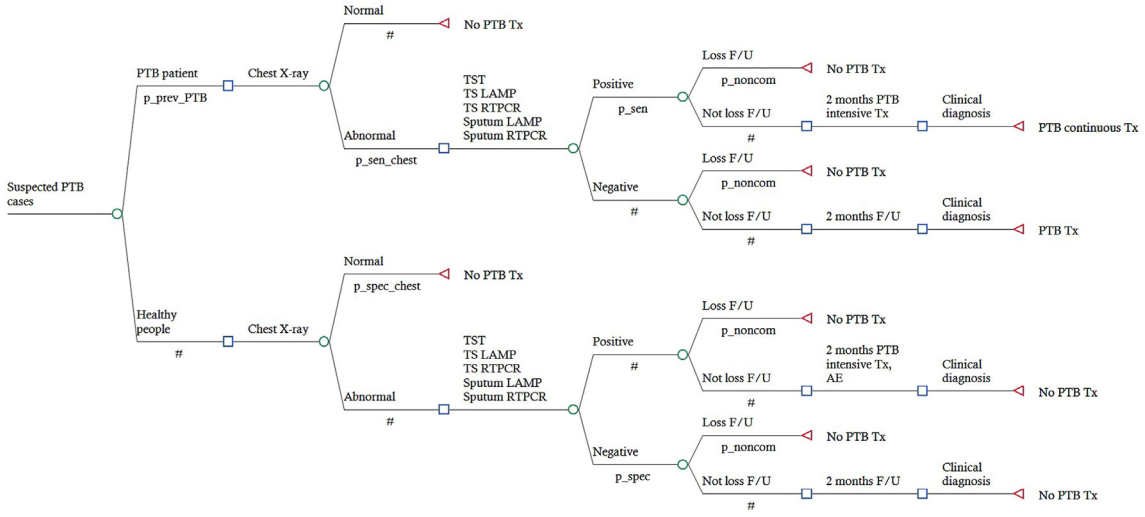

***Fig. 1:* Structure of decision tree model for TST, TS LAMP, TS RTPCR, sputum LAMP, sputum RTPCR strategies**. Abbreviation: TST: tuberculin skin test; TS LAMP: tongue swab Loop-Mediated Isothermal Amplification; TS RTPCR: tongue swab real-time polymerase chain reaction; F/U: follow up. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years. Suspected PTB cases involve the person who exhibits at least one of the following symptoms: a persistent cough lasting more than 2 weeks, hemoptysis, an unexplained cough without a specific disease, fever, weight loss, or night sweats. Diagnostic tests for Group 1 include TS LAMP, TS RTPCR, sputum LAMP, and sputum RTPCR. For Group 2, the diagnostic tests used are TS LAMP, TS RTPCR, and TST.

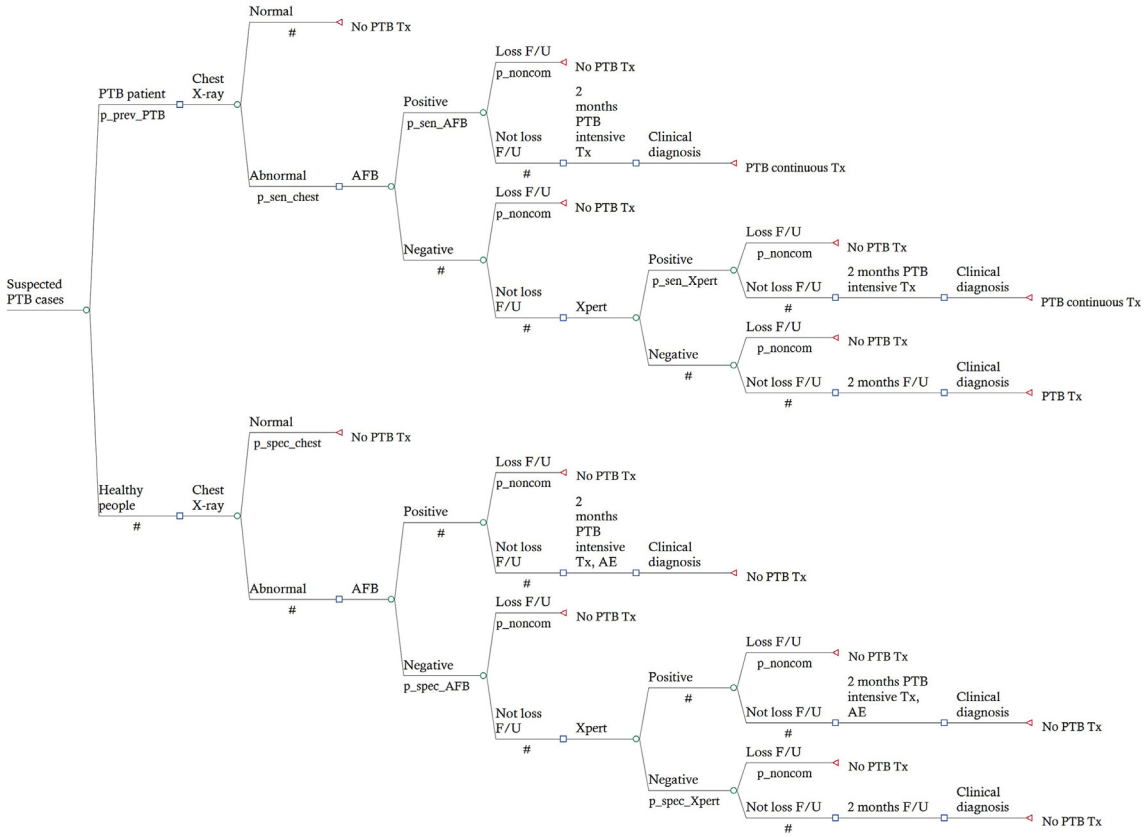

***Fig. 2:* Structure of decision tree model for AFB and sputum Xpert strategy**. Abbreviation: AFB: Acid-fast bacillus smear microscopy. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years. The AFB&Xpert strategy only involves Group 1.

followed by 4.6 months of continuous therapy with HR (isoniazid, rifampicin).[25]

Model input parameters

The values, distributions, sources and references of all the input parameters are shown in the Appendix 1. Cost data occurred within one year, from a societal perspective, were obtained from the innovator's input, Thai studies, the Comptroller General's price list, and the National Health Security Office (NHSO), and inflated to 2023 in Thai Baht. Most utility data were gathered from published studies. Since the time horizon in the model was one year, no discount rate was applied to costs and QALYs. Transition probabilities were collected from existing literature, expert opinions, and the innovator.

Model analysis

a. CUA: Base-case analysis

Under the base-case analysis, ICER was generated comparing the innovations with the standard care, and with the competitors. The base case assumed that suspected cases provided one sample (e.g. one sputum sample or one tongue-swab sample) for a diagnostic test. Cost-effectiveness threshold(CET) in Thailand (160,000 Thai Baht), was used as benchmark in the analysis.[26]

b. Sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed in the modelling analysis. The cost-effectiveness acceptability curve (CEAC) was drawn up in the PSA to present the overall uncertainty of results. For Group 1, the CEAC incorporated TS LAMP, TS RTPCR, sputum LAMP, sputum RTPCR, and AFB&Xpert. In Group 2, the CEAC was generated considering TS LAMP, TS RTPCR, and TST. The CEAC compared the probability of being cost-effective at different CET.

c. TPP

A significant role of early HTA is to utilize quantitative methods to define innovation parameters, aiding innovators in clinical trial design. The tool for this is the TPP which outlines desired innovation characteristics at three levels: minimal, acceptable, and ideal targets.[2] In this study, given multiple current practices and innovation technologies were available, we defined the three targets as follows: the minimal target requires that an innovation outperforms the standard practice (AFB&Xpert or TST in Group 1 and Group 2, respectively); the acceptable target requires that the innovation exceeds the current best practice including standard practice and sputum-based test; and the ideal target requires that the innovation surpasses all the remaining available strategies, including standard practice, sputum-based test, and TS test. The innovation outperforms a comparator if the ICER is lower than the CET in Thailand. The targeted values were obtained by achieving an ICER equal to the CET in Thailand.

The process of selecting key parameters was shown in Appendix 1. After identifying the key parameters, each key parameter was then varied individually, with others held constantly, to determine the values that made the innovation superior at three target levels, guiding innovation design.

d. Scenarios analysis

We proposed two scenarios to assess parameters not included in the model that could impact the changes in outcomes. The two scenarios affected only Group 1. Scenario 1 assumed that 10% of individuals generate low-quality sputum which cannot be used for analysis, leading to negative sputum-based test results for these individuals, regardless of their actual PTB status. The 10% was considered conservative because the smaller percentage of individuals not being able to produce high-quality sputum, the better situation for sputum-based assays and the less favorable for the innovations of TS. Some evidence shows that one-third of suspected cases in Indonesia or two-third of HIV-infected population could not produce sputum.[27,28]

Scenario 2 represents the situation where an AFB test requires three sputum samples collected over three days based on the practice in Thai settings, with a positive result indicated if at least one sample is positive. This scenario impacted the cost, sensitivity, and specificity of the AFB test. Each scenario was compared to the base-case model and presented the outcomes including total cost, total QALYs, and ICER values across the three strategies: sputum LAMP, sputum RTPCR, and AFB&Xpert.

e. VOI

VOI is a computational approach to estimate the expected benefit derived from obtaining additional information to reduce uncertainty in decision-making. VOI analysis evaluates if additional research is worth the investment by comparing the costs of additional research with the benefits that the research brings. This aids researchers in determining whether to make their decisions based on existing evidence or if further evidence is needed to reduce decision uncertainty.[29] The population expected value of perfect information (population EVPI) at various CET was used in this study to derive the expected VOI for all parameters in the early HTA model. The expected value of partial perfect information (EVPPI) was calculated to determine the expected value of single parameter in reducing uncertainty. The calculation details of population EVPI and EVPPI are attached in the Appendix 1.

Role of funders
The funders had no role in the study design, data collection, data analysis, interpretation, writing of this report or in the decision to submit this manuscript for publication.

Results

Landscape review
From the six databases, 1182 papers were identified, of which 231 were duplicates, leaving 951 unique papers. Two researchers assessed the titles and abstracts, identifying 102 papers relevant to TB diagnosis and screening in Thailand, with 56 contributing to the understanding of the TB landscape. Additionally, the review included five supplementary Thai papers and reports. The PRISMA flow diagram is attached to the Appendix 1.

The landscape review indicated that most TB cases are found in Asia and South Africa, making it a leading global cause of death. By 2022, over 10 million new TB cases had been reported, with a mortality rate of 16% among those infected. Thailand is among the top 30 high-burden TB countries.[14] In 2011, Thailand reported 143 cases of TB per 100,000 individuals, contributing to a total of approximately 103,000 diagnosed TB patients in the country. Among all TB cases, 84%–91% are PTB.[30]

In Thailand, common PTB screening methods include chest X-ray, AFB smear microscopy, sputum culture, interferon gamma release assay (IGRA), Xpert MTB/RIF, RTPCR, and LAMP.[31] Chest X-rays are typically the initial mass screening test for PTB, with additional tests performed if abnormalities are detected.[32] For these cases, AFB combined with Xpert was the standard diagnostic test for PTB. Molecular diagnostics like Xpert MTB/RIF, RTPCR, and LAMP were intended to identify MTB genetic material in specimens. Literature and reports revealed a gap in PTB diagnosis, particularly for patients who struggled to provide sputum, such as young children and those with comorbidities like HIV.[14] A new sampling technique, such as the TS, could address this unmet need, highlighting its potential market value for PTB screening.

Stakeholder consultation
The stakeholders discussed PTB care in Thailand, outlining the current processes for diagnosis, treatment, and follow-up. Adults typically begin with chest X-rays for screening, followed by sputum-smear microscopy (AFB test) and the sputum Xpert molecular test. In contrast, children start with a TST and follow age-specific diagnostic pathways. Experts favored sputum Xpert for its automation and accuracy, while RTPCR was commonly used; LAMP was less preferred due to its complexity and technician exposure risks due to pre-treatment process namely DNA extraction. Adult treatment generally followed established guidelines, whereas pediatric treatment often began with isoniazid without confirmatory tests. Tailored treatments are provided for special populations, including pregnant women and HIV patients.

Key challenges include the high costs of diagnostic tests like TST and IGRA, along with risks from current methods. Follow-ups generally involve bimonthly appointments for one to two years, extending to two years for multidrug-resistant PTB cases. Stakeholders stressed the need for more accessible, cost-effective diagnostic tools to improve PTB care, address regional disparities, and enhance patient compliance and outcomes in Thailand.

Early health economic modelling
1. Base-case analysis

The base-case results of the CUA results for two groups are shown in Table 2. In Group 1, TS RTPCR was the most cost-effective strategy among all five strategies, with an ICER in comparison with AFB&Xpert of 10,401.33 Baht/QALY, which was lower than Thailand's CET of 160,000 Baht/QALY. The most cost-effective current practice was sputum RTPCR. Compared to the standard test AFB&Xpert, TS LAMP was cost-effective, while sputum LAMP was not, with an ICER of 160,070.49 Baht/QALY, exceeding Thailand's CET threshold. In Group 2, both TS LAMP and TS RTPCR were cost-effective in comparison to the standard test TST. TS RTPCR was more valuable compared to TS LAMP in both categories due to its lower cost and higher QALY.

2. Sensitivity analysis

The PSA results for Groups 1 and 2 are shown in the CEAC (Fig. 3). In Group 1, as the CET increased, TS LAMP and sputum LAMP remained not cost-effective. TS RTPCR's cost-effectiveness initially increased with the CET but then declined compared to other strategies. The probability of sputum RTPCR being cost-effective rose from 0% to 60%, making it the most likely to be cost-effective. In Group 2, TS RTPCR dominated the other strategies, with its cost-effective probability approaching 100% as the CET increased, while TS LAMP maintained a low likelihood of becoming cost-effective.

3. Target product profile

The detailed TPP for TS LAMP and TS RTPCR varied in different groups (Table 3). The sensitivity for all input parameters was illustrated in pie chart in Appendix 1. The modifiable factors that were used in the three options of TPP include sensitivity, specificity, price of the innovation, and test and treatment non-

Group 1	Total cost (Baht)	Total QALY	Incremental cost to AFB&Xpert (Baht)	Incremental QLAY to AFB&Xpert	ICER to AFB&Xpert (Baht/QALY Gained)
AFB&Xpert	1747.79	0.8211	0	0	0
TS LAMP	1919.40	0.8224	171.61	0.0013	134,242.25
Sputum LAMP	2000.84	0.8227	253.05	0.0016	160,070.49
TS RTPCR	1790.48	0.8252	42.69	0.0041	10,401.33
Sputum RTPCR	1881.50	0.8247	133.71	0.0037	36,418.39
TS LAMP vs Sputum RTPCR			37.90	−0.0024	−15,837.61
TS RTPCR vs Sputum RTPCR			−91.02	0.0004	−210,402.87
Group 2	**Total cost (Baht)**	**Total QALY**	**Incremental cost to TST (Baht)**	**Incremental QLAY to TST**	**ICER to TST (Baht/QALY Gained)**
TST	1571.97	0.8208	0	0	0
TS RTPCR	1838.22	0.8362	266.24	0.0155	17,217.02
TS LAMP	1967.80	0.8332	395.83	0.0125	31,714.54
TS LAMP vs TS RTPCR			129.58	−0.0030	−43,444.11

Abbreviations: TST, tuberculin skin test; TS LAMP, tongue swab Loop-Mediated Isothermal Amplification; TS RTPCR, tongue swab real-time polymerase chain reaction; AFB, acid-fast bacillus smear microscopy. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years. AFB&Xpert as the standard test in Group 1, TST as the standard test in Group 2. Sputum LAMP and sputum RTPCR as the competitor tests in Group 1. Total costs included the costs of the strategy spent on the model.

Table 2: **Base-case result for Group 1 and 2.**

compliance rate. The test and treatment non-compliance rate referred to the probability of lost follow-up at each visit within the model.

When calculating the target value for each key parameter to enable the two innovative strategies, TS LAMP and TS RTPCR, to achieve different targets, only one parameter was adjusted at a time while the other parameters were fixed at their base-case values. In Group 1, for TS LAMP to surpass AFB&Xpert, the minimal target required at least one of the following criteria to be satisfied at a time: 81.6% sensitivity, 93.7% specificity, a price of 913.45 Baht, or a 10.2% test and treatment noncompliance rate. In Group 2, as only one strategy is available on the ground, the minimum target and the acceptable target are the same. TS LAMP could outperform TST in achieving the minimum target and the acceptable target, by having at least one of the following criteria to be satisfied at a time: 37.1% sensitivity, 58.2% specificity, price of 3458.56 THB, or a noncompliance rate of 16.2%. It is not possible to achieve ideal target for TS LAMP by changing specificity or price alone as the target values were out of reasonable ranges.

In Group 1, for TS RTPCR, to achieve the minimal target, at least one of the following criteria needs to be satisfied at a time: 72.6% sensitivity, 84.2% specificity, a cost of 1666.41 Baht, or the test and treatment non-compliance rate of 14.1%. The acceptable target and the ideal target are the same as Sputum RTPCR was the best strategy among all the current available strategies on the ground and among all the available strategies including innovation. In Group 2, minimal target and acceptable target require 28.3% sensitivity, 48.8% specificity, cost of 4253.37 Baht, or a non-compliance rate of 19.9%, respectively.

4. Scenario analysis

The results of the scenario analysis shown in Fig. 4 indicate that both scenarios only affect Group 1. In Scenario 1, where a portion of the population was unable to produce sputum, the ICER for sputum LAMP compared to AFB&Xpert significantly increased. In contrast, the changes in ICER values for sputum RTPCR were minimal. Additionally, the total QALYs for all three strategies decreased compared to the base-case analysis.

In Scenario 2, where the AFB test required collecting three sputum samples and conducting three tests, the ICER values for sputum LAMP compared to AFB&Xpert shifted from positive to negative, as the incremental QALY changed from positive in the base-case analysis to negative in scenario 2. Additionally, in Scenario 2, AFB&Xpert showed higher overall costs and total QALY compared to the base-case analysis.

5. Value of information

The VOI results are shown as population EVPI and EVPPI in Figs. 5 and 6. The innovator estimated a target population of 2194 tests for Group 1 and 22 tests for Group 2 in one year in Thailand. As the CET increases from 0 to 300,000 Baht, the population EVPI for Group 1 rises, reaching 236,713.39 Baht at the current Thai CET of 160,000 Baht per QALY, indicating the maximum investment to reduce uncertainty. In contrast, Group 2's population EVPI was nearly 0, which suggests the best strategies dominating the other strategies at the CET of 160,000 Baht. Fig. 5 illustrates the EVPPI of the top four parameters in Group 1, including specificity of sputum RTPCR, sensitivity of TS RTPCR, specificity of TS RTPCR, and hazard ration of death

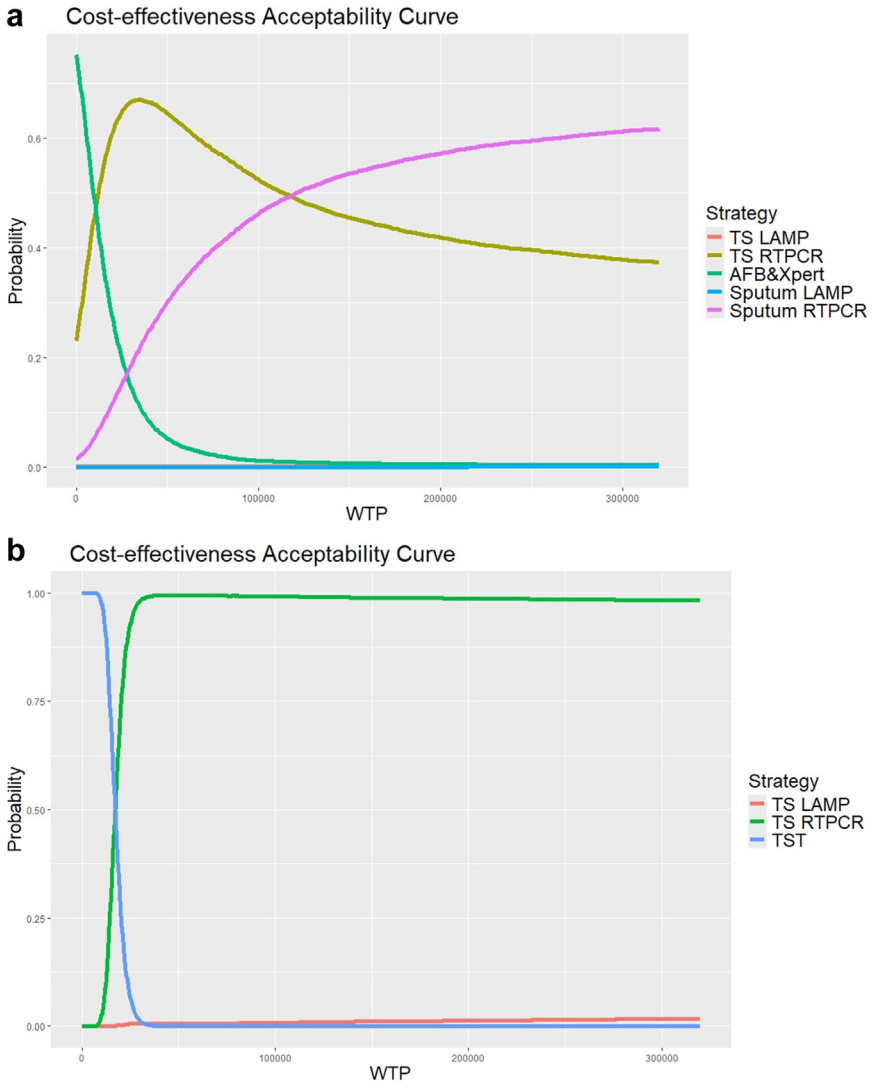

Fig. 3: **Cost-effectiveness Acceptability Curve for a and b**. Abbreviation: TST, tuberculin skin test; TS LAMP, tongue swab Loop-Mediated Isothermal Amplification; TS RTPCR, tongue swab real-time polymerase chain reaction; AFB, acid-fast bacillus smear microscopy. **a** shows the Cost-effectiveness Acceptability Curve for Group 1; As the CET increases, AFB&Xpert initially show the highest cost-effectiveness. Then, TS RTPCR takes the lead, at the highest CET Sputum RTPCR becomes the most likely to be cost-effective. TS LAMP and Sputum LAMP consistently have zero probability. **b** presents the Cost-effectiveness Acceptability Curve for Group 2. As the CET increases, the probability of TS RTPCR being cost-effective rises, while TST decreases. Meanwhile, probability of TS LAMP remains consistently at zero.

comparing PTB with early treatment and without early treatment, highlighting the parameters that worth researching to reduce uncertainty and improve outcomes. Group 2 showed zero EVPPI for all parameters, which means reducing uncertainty of one individual parameter at a time cannot change the optimal strategy.

Discussion

We conducted an early HTA to evaluate the use of TS as a new sampling method for PTB diagnosis. This comprehensive study assessed the TS combined with LAMP and RTPCR molecular tests for PTB detection, incorporating a landscape review, stakeholder consultation, and early HTA modeling. Our study contributes to both literature on innovative PTB diagnosis test and literature on early HTA.

The study findings indicate that TS RTPCR is the most cost-effective PTB diagnostic strategy for all population. With an ICER of 10,401.33 Baht/QALY compared to the standard method of AFB&Xpert in Group 1, and an ICER of 17,217.02 Baht/QALY compared to TST in Group 2, which are both below the Thailand's CET of 160,000 Baht/QALY. TS RTPCR

Characteristic	Base case values	Minimal target	Acceptable target	Ideal target
TS LAMP				
Group 1: age ≥5		Superior to AFB&Xpert	Superior to Sputum RTPCR	Superior to TS RTPCR
Sensitivity of TS LAMP	0.826	0.816	0.952	1.000
Specificity of TS LAMP	0.945	0.937	Above 1	Above 1
Price of TS LAMP (Baht)	860	913.45	177.08	Below 0
Test and treatment non-compliance rate for Group 1	0.1	0.102	0.071	0.060
Group 2: age <5		Superior to TST (Minimal and Acceptable Target)		Superior to TS RTPCR
Sensitivity of TS LAMP	0.826	0.371		0.998
Specificity of TS LAMP	0.945	0.582		Above 1
Price of TS LAMP (Baht)	860	3458.56		Below 0
Test and treatment non-compliance rate for Group 2	0.05	0.162		0.008
TS RTPCR				
Group 1: age ≥5		Superior to AFB&Xpert	Superior to Sputum RTPCR (Acceptable and Ideal Target)	
Sensitivity of TS RTPCR	0.910	0.726	0.862	
Specificity of TS RTPCR	0.989	0.842	0.951	
Price of TS RTPCR (Baht)	670	1666.41	930.05	
Test and treatment non-compliance rate for Group 1	0.1	0.141	0.111	
Group 2: age <5		Superior to TST (Minimal and Acceptable Target)		Superior to TS LAMP
Sensitivity of TS RTPCR	0.910	0.283		0.738
Specificity of TS RTPCR	0.989	0.488		0.851
Price of TS RTPCR (Baht)	670	4253.37		1654.81
Test and treatment non-compliance rate for Group 2	0.05	0.199		0.091

Abbreviations: TST, tuberculin skin test; TS LAMP, tongue swab Loop-Mediated Isothermal Amplification; TS RTPCR, tongue swab real-time polymerase chain reaction; AFB, acid-fast bacillus smear microscopy. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years.

Table 3: **Target product profile for TS LAMP and TS RTPCR in Group 1 and Group 2.**

outperforms TS LAMP in both groups, suggesting its greater potential value in PTB detection. The modelling results align with PTB expert opinions derived from the stakeholder elicitation, supporting RTPCR as a more reasonable method for TS sample. TS LAMP is cost-effective compared to AFB&Xpert and TST. This indicates its benefit for all the population, especially children under five, which currently have limited detection tests available. In real-world scenarios, if RTPCR machines are accessible, TS RTPCR can be the optimal choice, especially in rural areas, due to the ease and convenience of TS sampling. If RTPCR machines are unavailable, TS LAMP is the preferred option for PTB diagnosis. In circumstances where RTPCR and LAMP are inaccessible, AFB&Xpert can be an alternative. If the innovator is willing to enhance the performance of TS LAMP, improving sensitivity, price, and the non-compliance rate can make it superior to sputum RTPCR in Group 1 (aged five or older). Achieving the acceptable target would position TS LAMP as a better option than sputum RTPCR. In Thailand, sputum RTPCR and sputum LAMP are commonly used, with sputum RTPCR being cost-effective compared to AFB&Xpert, showing an ICER of 36,418.39 Baht/QALY. However, sputum LAMP is not cost-effective compared to AFB&Xpert in Group 1. This study confirmed the cost-effectiveness of TS-based diagnostic tests for PTB. However, the result may not be generalizable to settings where TS is used as a screening tool. Given the convenience and rapid processing of TS-based tests, they hold potential as a screening tool. Further research is required to assess the feasibility of TS-based testing as a screening tool.

During the stakeholder consultation, the stakeholders highlighted the availability of GeneXpert machine in Thailand and its benefit including automated process and detecting rifampicin (RIF) resistance. In fact, GeneXpert machine is available globally, including low-resource settings. In 2022, Thailand has 172 labs qualified for Xpert MTB/RIF (ultra) TB test.[33] However, many hospitals in Thailand, equipped with GeneXpert MTB/RIF machines that are limited to four modules and a maximum capacity of 12 tests per day, often experience delays in processing due to high specimen volumes. This results in challenges with specimen quality and extended turnaround time for results.[34] In terms of detecting drug resistance, the stakeholders highlighted the limitation of the TS-based tests not able

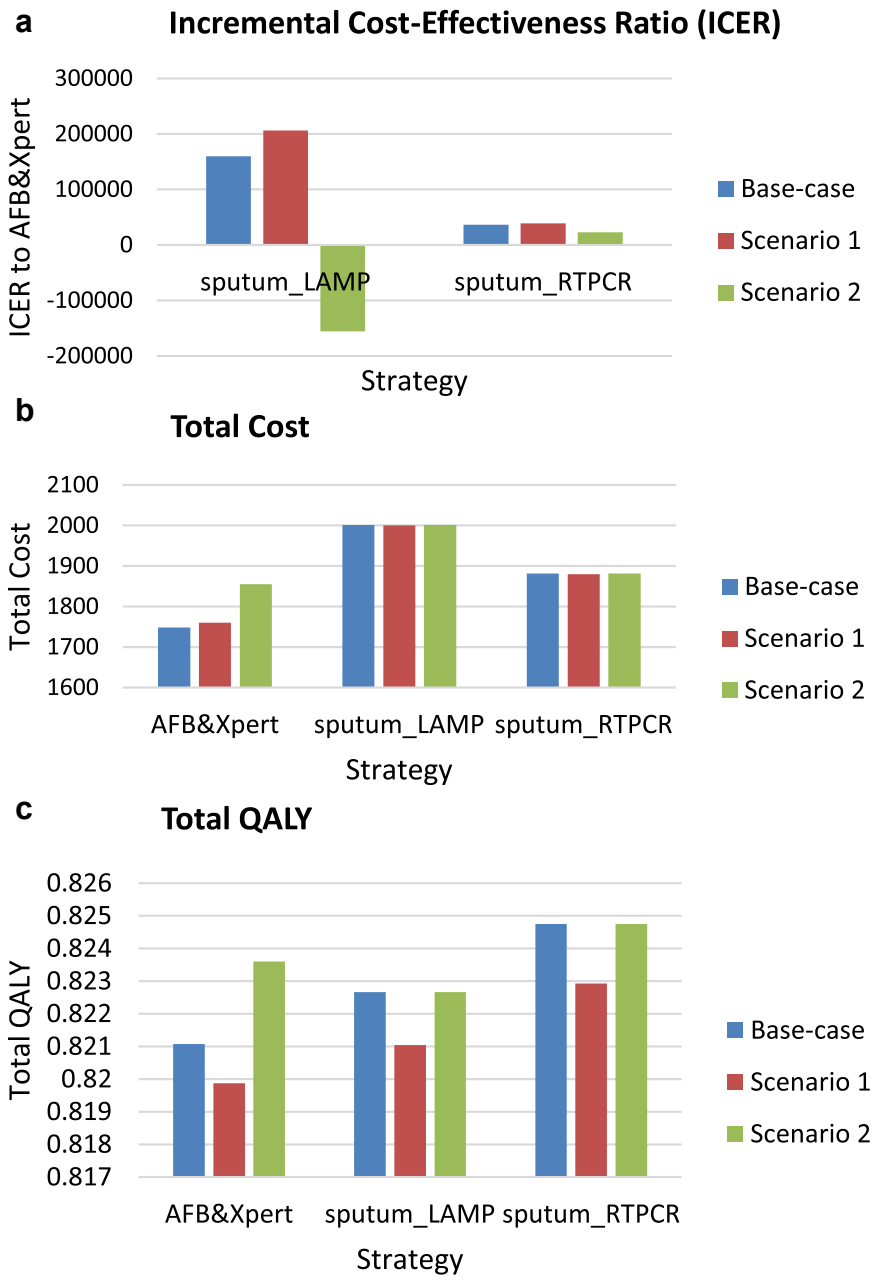

Fig. 4: **Scenario 1 and 2 analyses**. Comparing Incremental Cost-Effectiveness Ratio (ICER) (**a.**) of sputum LAMP and sputum RTPCR to AFB&Xpert, Total Cost (**b.**) and Total QALY (**c.**) of the three strategies—AFB&Xpert, sputum LAMP and sputum RTPCR. Abbreviation: LAMP, Loop-Mediated Isothermal Amplification; RTPCR, real-time polymerase chain reaction; AFB, acid-fast bacillus smear microscopy; ICER, Incremental Cost-Effectiveness Ratio. Scenario 1: a portion of the population are unable to produce sputum for sputum-based tests. Scenario 2: AFB test requires collecting three sputum samples and conducting three tests.

to detect drug resistance and expressed a desire for this feature to be incorporated in the future. We further conducted a scenario analysis considering that a proportion of patients are with drug-resistant PTB.[35,36] The results, presented in Appendix 1, indicate that the conclusion on cost-effectiveness of the strategies under examination remains unchanged.

For early HTA literature, our study showcased the collaboration between innovators and early HTA researchers. Through landscape review, stakeholder consultation, and early health economic modelling, the innovators and early HTA researchers collectively identified the useful information for technology positioning and further developed. During the early

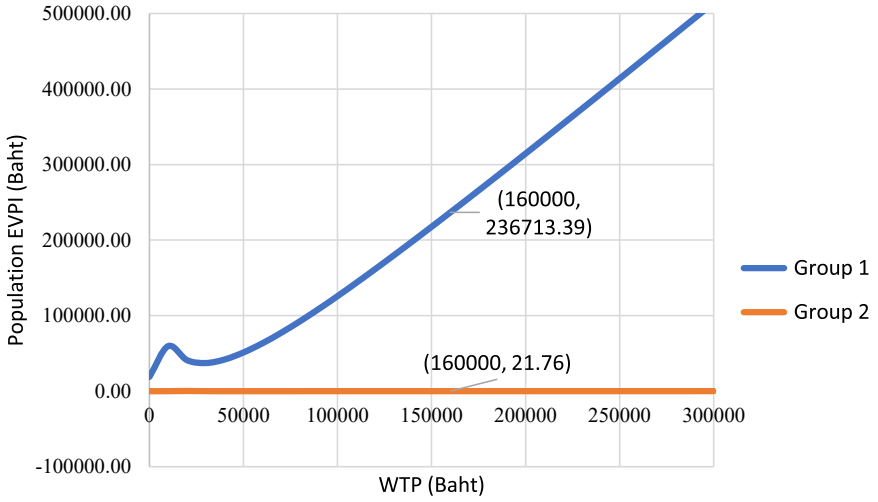

Fig. 5: **Expected value of perfect information (EVPI) for Group 1 and Group 2**. Group 1: suspected PTB cases aged five years and older, Group 2: suspected PTB cases younger than five years. The population EVPI compared the NMB of TS LAMP, TS RTPCR, sputum LAMP, sputum RTPCR, AFB&Xpert in Group 1, and NMB of TS LAMP, TS RTPCR, TST in Group 2.

health economic modelling stage, we focused on explorative analysis including identifying TPP, scenario analysis, and VOI analysis. More case studies like this are needed to help early HTA researchers develop guidelines and standard practices for early HTA work.

The World Health Organization recently published TPP for TB diagnosis and drug resistance detection. The document highlights the use of non-sputum tests to increase access to testing for individuals unable to produce sputum. It defined the minimum targets for non-sputum test for different healthcare settings, for instance, diagnostic sensitivity requirement ranges from 65% for point-of-care tests to 80% for low-complexity assay.[37] Our work further refined the required targets for selected characteristics to align with the Thai context, considering factors such as inclusion criteria and reimbursement policies. In our base-case analysis, TS RTPCR is the most valuable strategy in both groups; even by reducing its sensitivity, specificity, or increasing

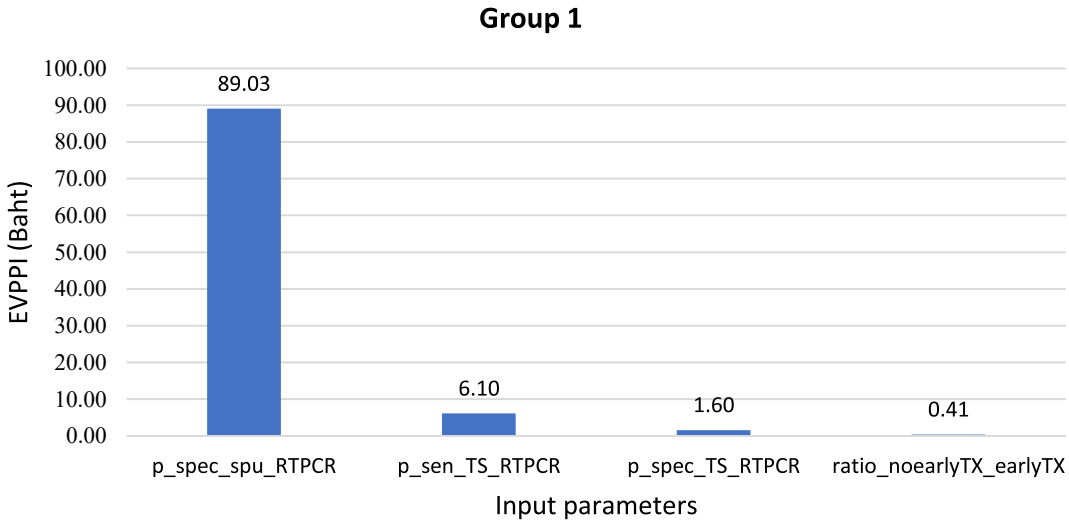

Fig. 6: **The Expected Value of Perfect Parameter Information (EVPPI) for the top four parameters for Group 1**. Abbreviation: TS, tongue swab; Tx, treatment; LAMP, Loop-Mediated Isothermal Amplification; AE, adverse event; TS RTPCR, tongue swab real-time polymerase chain reaction; p_spec_spu_RTPCR, specificity of sputum RTPCR; p_sen_TS_RTPCR, sensitivity of TS RTPCR; p_spec_TS_RTPCR, specificity of TS RTPCR; ratio_noearlyTX_earlyTX, hazard ratio of mortality for active PTB case without early PTB treatment during initial assessment compared with early PTB treatment. Group 1: suspected PTB cases aged five years and older.

price, it can still meet the acceptable target. For TS LAMP, adjusting its sensitivity to 99.8% or test to treatment non-compliance to 0.8% in Group 2 allows it to meet the ideal target, while other parameters remain out of limit. In Group 1, modifying specificity and price fail to make TS LAMP as cost-effective as TS RTPCR, though it can reach the minimal target by separately adjusting them. For TS LAMP to achieve the acceptable target in Group 1, the price needs to be reduced to 177.08 Baht which is much lower than the base-case value.

For the two scenarios in our study, in Scenario 1, a portion of the target population is unable to produce sputum, addressing a key unmet need. Studies show that young children and HIV patients often struggle to generate quality sputum, rendering sputum-based PTB tests ineffective for them.[38] We assumed 10% of the population cannot produce sputum, reducing the sensitivity and specificity of sputum-based tests. This impacts the total cost, QALY, and ICER of TS LAMP, TS RTPCR, sputum LAMP, and sputum RTPCR compared to AFB&Xpert. It is crucial for the innovators to collect data on the proportion of those who cannot produce sputum in future clinical research. Scenario 2 also impacts Group 1 only. Experts noted that in some areas, the AFB test requires three sputum samples, raising costs due to an extra visit and additional containers. The sensitivity and specificity of the AFB test were calculated based on the combined results of the three tests. The findings from Scenario 2 show that this scenario significantly affects outcomes for Group 1. In this scenario, AFB&Xpert incur higher costs and provide greater utilities than the base-case, causing the ICER of sputum LAMP to shift from positive in the base-case to negative in Scenario 2. Reducing the number of sputum samples required can enhance the outcomes by reducing loss-to-follow up and decreasing cost. However, this also requires good quality sputum sample and better PTB test.

The results of population EVPI across the CET variations differ between Group 1 and Group 2. Group 1 includes five strategies for comparison, whereas Group 2 has only three strategies (Table 1). More choices lead to higher uncertainty in selecting the best practice, making perfect information highly valuable and worth additional resources to obtain. This indicates the high value of the study for Group 1. However, in Group 2, due to the limited number of options, the value of additional research is not as high. Furthermore, the best strategy dominated the other strategies even in PSA using the CET in Thailand, making it extremely low chance of wrong decision. Additionally, the targeted population in Group 1 is significantly larger than in Group 2, contributing to the substantial difference in population EVPI between the two groups. However, TS LAMP and TS RTPCR remain essential for Group 2, as children under five have limited PTB testing options, making the development of new non-sputum-based sampling methods crucial.

The study has several limitations, the primary one being the inability to obtain the correlation between the sensitivity and specificity of TS LAMP and TS RTPCR. In diagnostic tests, clinical diagnostic sensitivity and diagnostic specificity are inversely related, typically represented by a receiver operating characteristic (ROC) curve that plots sensitivity against 1-specificity.[39] This relation is present for our intervention strategies, TS LAMP and TS RTPCR; however, we were unable to obtain the ROC curves for these assays. Consequently, in the TPP analysis, we calculated sensitivity and specificity separately to reach various targets. This limitation affects the precision of the TPP for TS LAMP and TS RTPCR regarding their sensitivity and specificity. The second limitation is the model's one-year time horizon, which may not fully capture long-term impacts. Extending the time frame would require additional data, increasing uncertainty. However, since the innovation focuses on accurate PTB detection and timely treatment, a one-year horizon is deemed reasonable. Nevertheless, we conducted an analysis using lifetime time horizon, and the result is presented in Appendix 1. A similar conclusion was obtained for the lifetime time horizon scenario, where the rank of the value for money of different test strategies remained same with the rank observed from analysis using one-year horizon. Future improvement could involve collecting more long-term cost and utility data. Lastly, assumptions must be made regarding the performance of non-sputum-based TS tests. The innovation team is currently conducting clinical trials to evaluate the new technology in Thai settings. Once data from these trials become available, the results from the early health economic modelling will be updated accordingly.

The strengths of this article are notable. The comprehensive early HTA study integrated a landscape review from literature and government reports, stakeholder elicitation, and economic modelling. The landscape review outlined the Thailand's PTB situation and highlighted the value of the TS for PTB diagnosis. Stakeholder elicitation involved gathering insights from TB clinicians, researchers, and policymakers about the real-world PTB scenario. Given that early HTA is typically conducted at the initial stage of innovation development, the primary challenge is the lack of data. Some data, such as test and treatment non-compliance rates, are not available in publications and must be collected from experts, making expert elicitation a crucial source of information. The early HTA model was constructed based on the current workflow of PTB screening, diagnosis, and treatment in Thailand, aligning closely with actual practices. In addition, all input data in this study were sourced from papers on Thailand and Thai government reports, and all experts consulted were from Thailand, making the early HTA analysis highly relevant to Thailand's context.

Contributors

Y.W., Y.T., P.K., J.T., and T.W. conceptualized the study.
L.M., and A.P. contributed to the literature search.
L.M., Y.W., T.W., A.P., and P.C. designed the questionnaire.
T.W., A.P., and P.C. conducted the stakeholder consultation.
L.M., and Y.W. cleaned the data and conducted formal analysis.
L.M., A.P., and P.K. wrote the original draft.
Y.W., Y.T., T.W., P.K., and J.T. reviewed and edited the manuscript.
Y.W., T.W., and Y.T. obtained funding support.
All authors read and approved the final manuscript.

Data sharing statement

The model and data supporting this analysis are available from the corresponding author upon reasonable request.

Declaration of interests

All authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2025.100533.

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