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Cost-effectiveness analysis comparing QuantiFERON test and tuberculin skin test for the diagnosis of latent tuberculosis infection in immunocompetent children under 15 years of age in Colombia

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ABSTRACT

Objective To determine the cost-effectiveness of the QuantiFERON (QFT) test versus the tuberculin skin test (TST) in diagnosing latent tuberculosis infection (LTBI) in immunocompetent children under 15 years of age who are in contact with active tuberculosis (TB) patients in the context of the Colombian healthcare system.

Design Health economic evaluation. Decision tree over a horizon of <1 year.

Setting From the perspective of the Colombian healthcare system, the direct healthcare costs related to tests were considered, and diagnostic performance was used as a measure of effectiveness. The currency was the US dollar (US$) for the year 2022, with a cost-effectiveness threshold of US$6666.

Participants A simulated hypothetical cohort of 2000 immunocompetent children under 15 years of age who are in contact with active TB patients and were vaccinated with BCG at birth.

Interventions QFT test and TST to detect LTBI.

Primary outcome measure The incremental cost-effectiveness ratio (ICER) was estimated, and univariate deterministic and probabilistic sensitivity analyses were conducted using 5000 simulations.

Results QFT was found to be cost-effective with an ICER of US$705 for each correctly diagnosed case. In the one-way deterministic sensitivity analysis, QFT remained cost-effective across nearly all proposed scenarios; however, the QFT was considered 'potentially cost-effective' when TST specificity reached its highest value. The ICER was unaffected by variations in LTBI prevalence. In the probabilistic sensitivity analysis, QFT was cost-effective in 85.06% of the simulated scenarios, while TST was dominant in 11.8%.

Conclusions This study provides evidence of the cost-effectiveness of QFT compared with TST in diagnosing LTBI among immunocompetent children under 15 years who have been in contact with active TB patients in the Colombian context.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The decision model was developed based on recommendations for Colombia provided by the Instituto de Evaluación Tecnológica en Salud.
⇒ The model's results were replicated across various scenarios in the sensitivity analyses to confirm its robustness.
⇒ The decision model considered only the diagnostic performance of the tests in immunocompetent children under 15 years of age who were vaccinated with BCG at birth, as performance varies in adults and immunosuppressed patients.
⇒ The prevalence of latent tuberculosis infection and the intrinsic characteristics of diagnostic tests are estimated indirectly, as real values cannot be obtained due to the absence of a gold standard for diagnosis.
⇒ The cost of treating multidrug-resistant tuberculosis, and the cost associated with a case of reactivated tuberculosis were not considered.

BACKGROUND

Latent tuberculosis infection (LTBI) is defined as an infection with *Mycobacterium tuberculosis* in which the bacteria remain viable, but immunological control prevents clinical disease manifestation.[1] To diagnose LTBI, indirect tests are used to stimulate memory T cells with *M. tuberculosis* antigens through the interferon-gamma release assay (IGRA) and the tuberculin skin test (TST).[2] These tests vary in diagnostic performance and have low concordance.[3–6] All four generations of QuantiFERON (QFT) are available in Colombia and have been funded since 2021, meaning that both QFT and TST are covered by the healthcare system (*Plan de Beneficios en Salud*). According to Colombia's current diagnostic algorithm for managing patients in contact with tuberculosis (TB), the use of the TST is preferred (based on expert opinion).[7]

In 2019, there were 237 506 new cases of TB reported in the Americas, with just over 50%

originating from three countries: Brazil (33.1%), Peru (13.4%) and Mexico (10.3%). Colombia ranked fourth, with 19 000 cases, accounting for 6.6% of the region's total. In 2022, 380 Colombian children under 15 years of age were reported with TB (2.7% of total cases),[8] and the mortality rate in this age group was 0.32 per million inhabitants.[8 9] Efforts should focus on making LTBI screening as effective and efficient as possible. In the Colombian context, the TST may be suboptimal due to reduced specificity in vaccinated populations,[2 10] as Colombia has a high national coverage of BCG vaccination (89.9%).[9] Unlike the TST, IGRA's diagnostic performance is unaffected by BCG vaccination status or prior TST application.[11 12]

It is crucial to avoid inappropriate interventions based on false positive results from tests with poor diagnostic performance, while also addressing the risks associated with false negatives, which carry a high risk of LTBI reactivation and an increased likelihood of fatal outcomes due to delayed treatment. If this situation is not improved, healthcare system costs for managing complications, along with patients' out-of-pocket expenses, will continue to increase significantly.[13] To our knowledge, the cost-effectiveness of these diagnostic tests for LTBI has only been evaluated in Colombia for adult patients, not for children.[14]

This study aimed to determine the cost-effectiveness of QFT compared with TST for diagnosing LTBI in immunocompetent children under 15 years of age, who have been in contact with active TB patients in the context of the Colombian healthcare system.

METHODS

Model structure and assumptions

Given that the intervention was a diagnostic test and the time horizon was less than 1 year, a decision tree model (figure 1) was developed based on recommendations for Colombia provided by the Institute for Health Technology Assessment (*Instituto de Evaluación Tecnológica en Salud* (IETS)).[15 16] The model and the overall methods were constructed from the payer's perspective within Colombia's General System of Social Security in Health.

The possible outcomes in immunocompetent children for each diagnostic test were as follows: QFT (negative, positive) and TST (negative (<5 mm), positive (≥5 mm)). As shown in figure 1, regardless of the QFT or TST result, a chest X-ray is performed to detect any pulmonary abnormalities indicative of active TB. If the chest X-ray is abnormal, a case of active pulmonary TB is considered. If the QFT or TST result is a true positive and the chest X-ray is normal, a case of LTBI is diagnosed. If the QFT or TST result is a false positive and the chest X-ray is normal, a case of LTBI is incorrectly established. If the QFT or TST result is a true negative and the chest X-ray is normal, a case of no TB infection is considered. If the QFT or TST result is a false negative and the chest X-ray is normal, this would be a case of potential TB infection that is not detected.

The model assumes that any child under 15 with a false negative result from QFT or TST is at potential risk for TB reactivation. To simplify the model and given that the QFT test is reported to have a 0% likelihood of indeterminate results,[17 18] such outcomes or the need to repeat the test were not considered.[7]

Target population

The model included a hypothetical cohort of 2000 immunocompetent children under 15 years of age (1000 in each branch) who were vaccinated with BCG at birth and had close contact with active TB patients. Immunocompetence was defined as the absence of primary or secondary immunodeficiency syndrome.[19] A QFT or TST was performed independently to diagnose LTBI; the

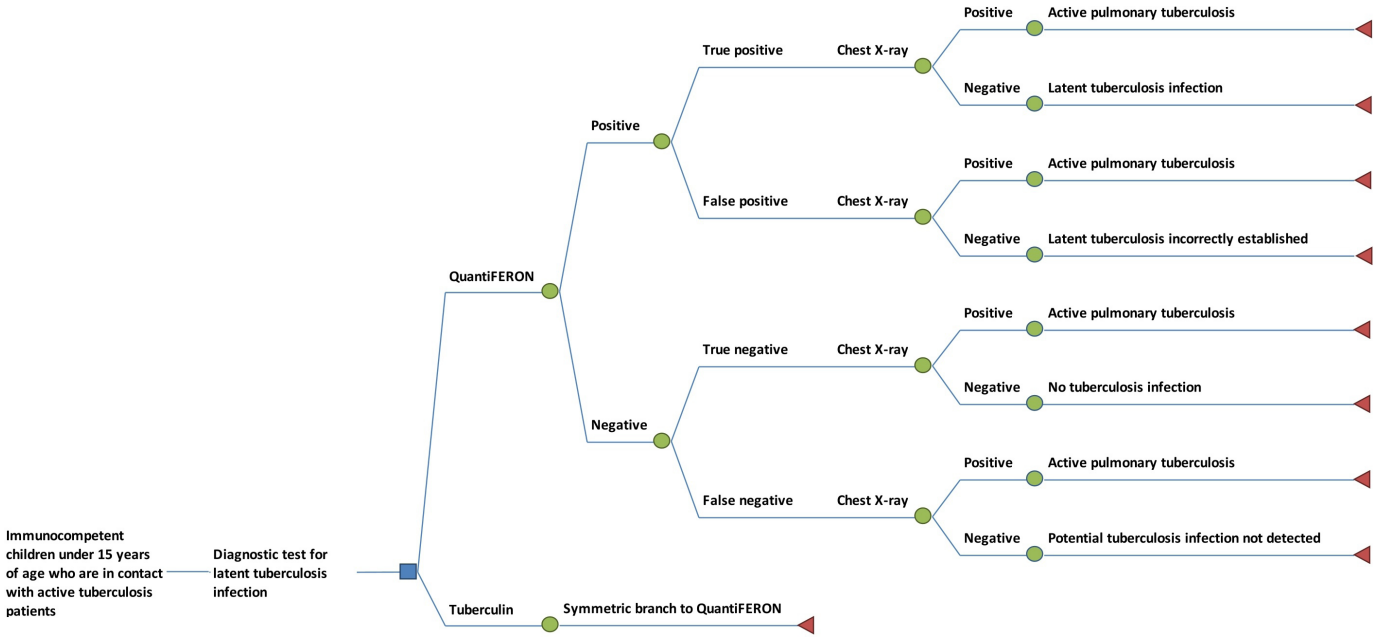

Figure 1 Structure of the decision tree comparing QuantiFERON and tuberculin skin test.

Table 1 Summary of the input parameters of the cost-effectiveness analysis comparing QuantiFERON and tuberculin skin test

Variable	Cost	Cost range	Estimator	95% CI	Distribution	Source
QuantiFERON cost	$93	$61–165			Triangular	Ministry of Health and Social Protection's 2019 resolution on maximum budgets[21] Price list of reference laboratories
Tuberculin skin test cost	$13				Not applicable (unique price)	Ministry of Health and Social Protection[20]
Chest X-ray cost	$9				Not applicable (unique price)	Ministry of Health and Social Protection[20]
Average cost of first medical consultation	$15				Not applicable (unique price)	Ministry of Health and Social Protection[20]
Average cost of medical follow-up visits	$16				Not applicable (unique price)	Ministry of Health and Social Protection[20]
Latent tuberculosis infection prevalence (Year 2019)			0.0831	0.0829 to 0.0833	Beta	Institute for Health Metrics and Evaluation[25]
QuantiFERON sensitivity			0.81	0.56 to 0.94	Beta	Estupiñán-Bohorquez *et al*[24]
QuantiFERON specificity			0.84	0.75 to 0.9	Beta	Estupiñán-Bohorquez *et al*[24]
Tuberculin skin test sensitivity			0.76	0.6 to 0.86	Beta	Estupiñán-Bohorquez *et al*[24]
Tuberculin skin test specificity			0.72	0.55 to 0.84	Beta	Estupiñán-Bohorquez *et al*[24]
Chest X-ray sensitivity			0.919	0.627 to 0.987	Beta	Vonasek *et al*[54]
Chest X-ray specificity			0.96	0.833 to 0.991	Beta	Vonasek *et al*[54]

Market exchange rate for 2022: US$1 = COP$4255.
COP, Colombian pesos; US$, US dollar.

scenario of conducting ≥2 tests simultaneously was not considered.

Time horizon and discount rate

The time horizon was set at 6 months, accounting for the time required for patients to complete the tests and return to the clinic with results. No discount rate was applied where costs and outcomes might vary.

Costs

The direct healthcare costs considered included the cost per diagnostic test (QFT, TST and chest X-ray), as well as the costs of the initial consultation and follow-up visits with a paediatrician. Costs associated with the administration and interpretation of diagnostic tests, sample transportation, laboratory personnel and laboratory supplies are included in the cost of each procedure, as outlined in the pricing manual.

Monetary values for the procedures were estimated using official prices from: the 2021 Capitation Payment Unit sufficiency database (*base de datos de suficiencia de la Unidad de Pago por Capitación);*[20] the Colombian Ministry of Health and Social Protection's 2019 resolution on maximum budgets[21]; and the Drug Price Information System website.[22] Additionally, the average cost of QFT was calculated by consulting various reference laboratories with locations across multiple cities in Colombia, considering the costs of all four generations of QFT available. Currency was converted to US dollars (US$) at the 2022 market exchange rate of US$1 = COP$4255 (Colombian pesos). The values were adjusted to 2022 prices based on the annual increase in the Consumer Price Index.[23]

Effects

Sensitivity and specificity data for each test were derived from a systematic review and meta-analysis conducted to inform the Colombian Clinical Practice Guideline for children who have had contact with pulmonary TB patients.[24] This meta-analysis combined data from eight studies evaluating the performance of all four generations of QFT. The prevalence of LTBI was obtained from the 2019 Global Burden of Disease study.[25]

Decision rule and sensitivity analysis

The decision rule was based on the quotient between the difference in diagnostic test costs and the difference in correctly diagnosed cases, which included true positive and true negative subjects. The cost-effectiveness

Table 2 Summary of cost-effectiveness analysis comparing QuantiFERON and tuberculin skin test

Variable	QuantiFERON	Tuberculin skin test	Difference
Cost (US$)	$132 807	$52 314	$80 493
Correctly diagnosed cases	838	723	114
Incremental cost-effectiveness ratio	Not applicable	Not applicable	$705

Cost-effectiveness threshold=US$6666.
Market exchange rate for 2022: US$1 = COP$4255.
COP, Colombian pesos; US$, US dollar.

threshold applied was set at 1 GDP (gross domestic product) per capita for Colombia in 2022, equivalent to US$6666.[26]

The sensitivity analysis included a univariate deterministic analysis, evaluating parameters such as the costs of QFT (minimum and maximum) and TST (±30%), the sensitivity and specificity of QFT and TST (according to 95% CI) and the prevalence of LTBI, using data from the countries with the lowest (Jordan) and highest (Vietnam) number of recorded cases.[27] An additional analysis was conducted with a threshold of 3 GDP per capita (US$19 998). The results are presented using a tornado diagram. The second type of sensitivity analysis was probabilistic, involving 5000 Monte Carlo simulations that used a triangular distribution for QFT costs and a beta distribution for probabilities (sensitivity, specificity and LTBI prevalence). A probability distribution for the cost of tuberculin was not assumed, as a single value was derived in the costing process. Results are displayed on a cost-effectiveness plane scatter plot and on an acceptability curve, which considers various willingness-to-pay thresholds, showing the strategy most likely to be cost-effective as the one plotted higher at each threshold.[28]

All information obtained was stored and modelled in multiple spreadsheets using Microsoft Excel - Office 365 (Microsoft Corporation, Redmond, Washington, USA). A summary of the model's input parameters is shown in table 1.

Bias type and control

Bias mitigation followed the recommendation of Evers *et al*.[29] Narrow perspective bias could not be avoided, as the IETS recommendation for Colombia is to conduct studies from a narrow payer perspective, excluding other cost types. Inefficient comparator bias was avoided by comparing two diagnostic tests. Cost measurement omission bias was minimised by including all costs that could negatively impact the cost-effectiveness of the test. Intermittent data collection bias did not apply to the decision tree model. Invalid valuation bias was mitigated by assigning accurate monetary values to each measurement. Ordinal incremental cost-effectiveness ratio (ICER) bias was irrelevant, as ordinal scales were not used in the ICER calculations. Double-counting bias was avoided by ensuring costs were not considered more than once. Inappropriate discounting bias did not apply, as no discount rate was used. Limited sensitivity analysis bias was controlled by following IETS recommendations for Colombia. Sponsor bias was not an issue, because the study was sponsored by a national government entity. Finally, the reporting and dissemination bias was controlled, as the study will be published regardless of the results.

Ethics approval was not required for this health economic assessment at our institution.

Patient and Public Involvement: None.

RESULTS

Base case scenario

This model, developed in the context of the Colombian healthcare system, showed that QFT had an ICER of US$705 per correctly diagnosed case compared with TST, using a threshold of US$6666. This result indicates that QFT is a cost-effective diagnostic test (see table 2).

The total expected cost of administering QFT to 1000 children was US$132 807, while the total expected cost of the TST was US$52 314, amounting to 39% of the cost of QFT. In terms of correctly diagnosed cases (true positives and true negatives) per 1000 children in each branch of the model, QFT accurately identified 838 cases, compared with 723 cases for TST. QFT produced 147 false positives, while TST resulted in 257 false positives—a relative increase of 75%. The number of false negatives was 16 for QFT and 20 for TST.

Univariate deterministic sensitivity analysis

With a threshold of 1 GDP per capita (US$6666), QFT was found to be cost-effective in nearly all proposed scenarios for accurately diagnosing children under 15 suspected of having LTBI. When TST specificity was at its highest value, QFT was considered 'potentially cost-effective' (figure 2). In no scenario was QFT dominated by TST. The model's input parameters are detailed in online supplemental table S1, and results for each scenario are provided in online supplemental table S2.

The variable that most significantly impacted the ICER was TST specificity. When TST specificity was set at 84%, the ICER increased from US$705 to US$19 375. Since this ICER falls between 1 and 3 GDP per capita, QFT should be considered 'potentially cost-effective' in this scenario. The second most influential variable was QFT specificity; at 75% specificity, the ICER increased from US$705 to US$2542, while at 90% specificity, the ICER dropped from US$705 to US$476. The third most impactful variable was

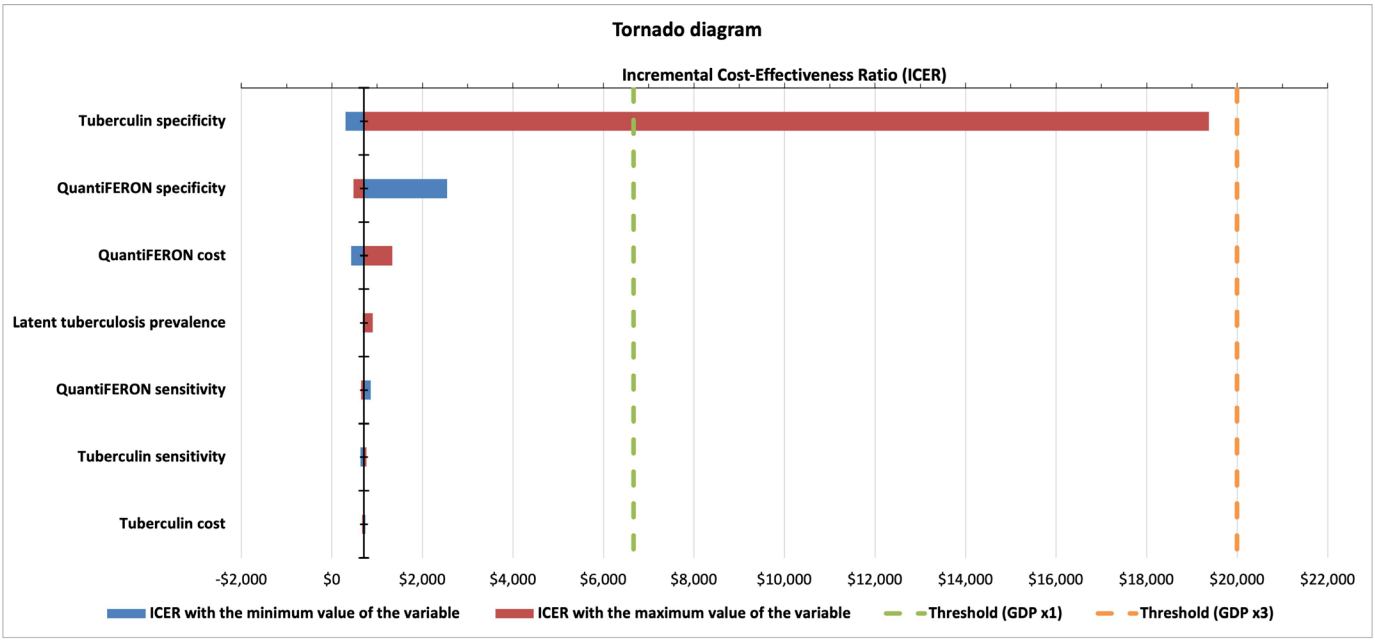

Figure 2 Tornado diagram of the one-way deterministic sensitivity analysis comparing QuantiFERON and Tuberculin skin test. GDP, gross domestic product; ICER, incremental cost-effectiveness ratio.

QFT cost; with a QFT cost of US$61, the ICER decreased from US$705 to US$423, whereas with a cost of US$165, the ICER increased from US$705 to US$1333. The variable with the least influence on ICER was TST cost; at a TST cost of US$9, the ICER increased from US$705 to US$739, and at a TST cost of US$17, the ICER decreased from US$705 to US$671. In a scenario of perfect diagnostic performance for QFT (100% sensitivity and 100% specificity), the ICER would only decrease to US$291.

Probabilistic sensitivity analysis

In the Monte Carlo simulation (5000 iterations) with a threshold of 1 GDP per capita (US$6666), QFT was cost-effective in 85.06% of simulated scenarios (4253 out of 5000). TST was found to be a dominant alternative in 11.8% of scenarios (590 out of 5000), and QFT had an ICER higher than the threshold in 3.14% of cases (157 out of 5000) (figure 3). At a higher threshold of 3 GDP per capita (US$19 998), QFT was cost-effective in 87.28% of scenarios (4364 out of 5000), with TST remaining dominant in 11.8% of scenarios (590 out of 5000) and the ICER for QFT exceeding the threshold in 0.92% of cases (46 out of 5000) (figure 3).

The acceptability curve shows that QFT has a 50% probability of being cost-effective at a willingness-to-pay threshold of US$819. With a willingness-to-pay of US$10 000, the probability rises to 86.3%, with minimal increase beyond this threshold (online supplemental figure S1).

DISCUSSION

This study shows that QFT is a cost-effective test for diagnosing LTBI in immunocompetent children under 15 years of age who have been in contact with active TB patients, compared with TST in the context of the Colombian healthcare system. Given Colombia's 2022 threshold of 1 GDP per capita for (US$6666), the use of QFT raises the cost for each correctly diagnosed case to US$705.

The univariate sensitivity analysis indicated that TST specificity is the variable with the greatest influence on the ICER, potentially impacting decision-making; with high TST specificity, the ICER falls between 1 and 3 GDP per capita (US$19 375). The cost of QFT ranked as the third most influential variable on the ICER, and a price reduction of >86.2% would make QFT a dominant test over TST. These findings may vary considerably depending on the sensitivity and specificity values used, as the diagnostic performance of each test may differ for specific populations, such as adults, compared with the values applied in this study.[14]

In the probabilistic sensitivity analysis, TST dominated QFT in 11.8% of the 5000 simulated scenarios due to its lower cost and occasional superior results. This finding is significant in regions where QFT is not readily available, as establishing the infrastructure and technology needed to implement this test for population-wide screening would be costly. Increasing the price of QFT from US$93 to US$165 raises the ICER from US$705 to US$1333 (a difference of US$628), resulting in substantial additional financial burden—especially in resource-limited areas. In these scenarios, TST would be the preferred intervention, as recommended by the WHO.[30 31]

The decision tree analysis showed that the number of false negatives was similar for both tests, with 16 cases for QFT and 20 cases for TST per 1000 subjects modelled. This similarity is due to the relatively close sensitivity values used in the model (81% for QFT and 76% for the TST),[24] resulting in comparable negative predictive values

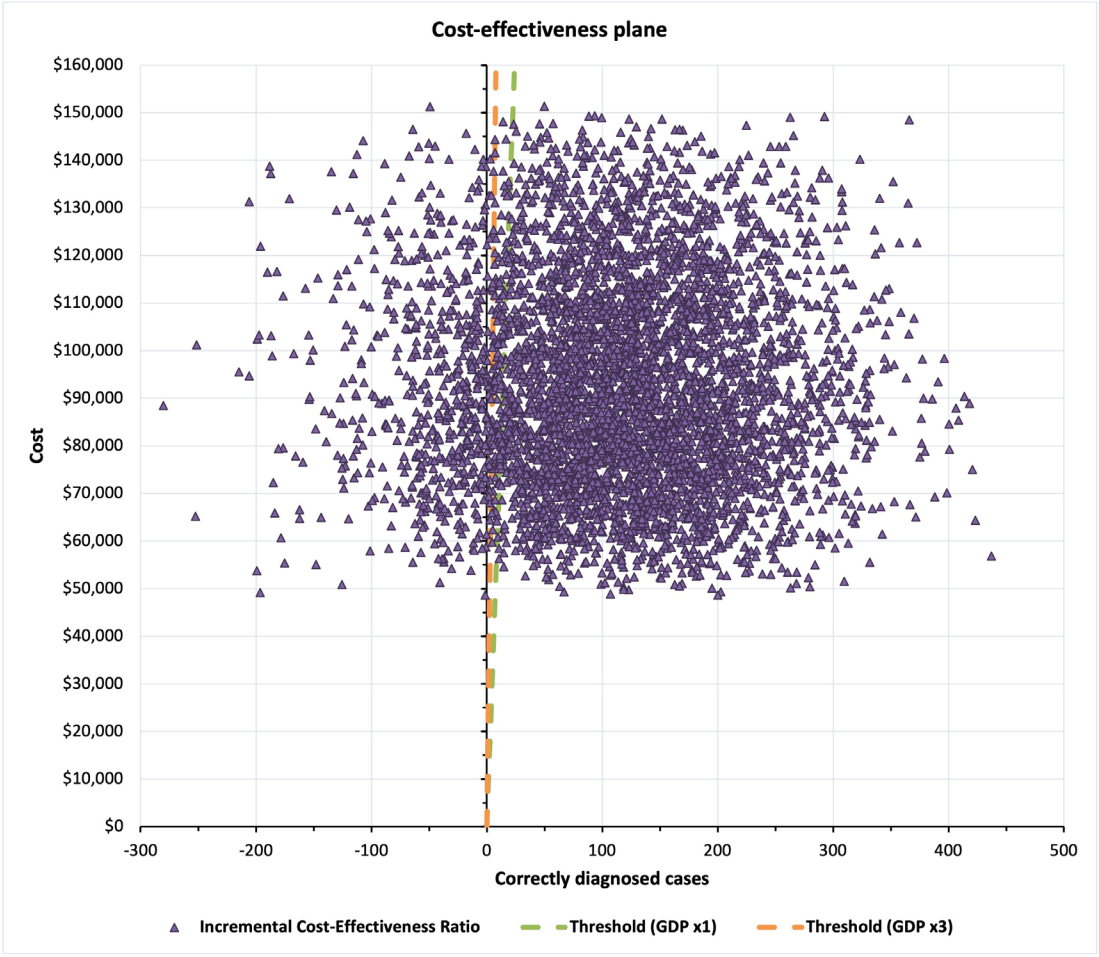

Figure 3 Cost-effectiveness plane scatter plot of QuantiFERON versus tuberculin skin test. The green and orange dotted lines represent the thresholds of US$6666 and US$19 998, respectively. GDP, gross domestic product.

for both tests. However, a marked difference in false positives was observed; QFT yielded 147 false positives, while TST produced 257 false positives per 1000 children, indicating that TST generates 75% more false positive cases than QFT. This difference is attributable to the specificity values of both tests, which were 84% for QFT and 72% for TST,[24] impacting each test's positive predictive value.

Although no studies have assessed the diagnostic performance of TST in Colombia, at national level based on the sensitivity (0.76 (95% CI 0.6 to 0.86)) and specificity (0.72 (5% CI 0.55–0.84)) values used in this study,[24] and considering that it is the preferred test for diagnosing LTBI (according to the Colombian diagnostic algorithm),[7] a significant increase in false positives is expected to occur annually. The high number of false positives is concerning, as these individuals may be unnecessarily exposed to anti-TB treatment regimens (for active or latent TB) and additional diagnostic tests. This not only increases public expenditure on medications but also places children at risk of adverse drug reactions, potentially compromising their health and quality of life.[32]

Several studies have evaluated the cost-effectiveness of TST and IGRA as screening strategies for immunocompetent children who have had close contact with an infectious TB case, though with varying methodologies and outcomes. Mandalakas *et al* used a decision tree model to estimate the ICER based on the cost per life-year saved in two age groups (0–2 years and 3–5 years).[33] They modelled five diagnostic strategies: no test, TST alone, IGRA alone, TST positive followed by IGRA and TST negative followed by IGRA. The decision tree, combined with Markov modelling, considered the effectiveness of isoniazid therapy for LTBI. The results showed that the non-testing strategy followed by isoniazid therapy was the dominant approach in both age groups. In 2016, the National Institute for Health Research published a decision tree model for children under 5 years of age, comparing TST alone, IGRA alone, TST positive followed by IGRA and simultaneous testing.[34] The outcomes were that the ICER for cost per QALY (quality-adjusted life-year) and cost per diagnostic error avoided. For diagnostic accuracy, the TST (≥10 mm) alone was the dominant strategy over others, except in comparison to T-SPOT.TB (an IGRA test), where the ICER was £2711 (threshold unspecified). With a willingness-to-pay of £20 000 per QALY gained, the TST (≥5 mm) negative followed by QFT-gold in-tube test (an IGRA test) was the most cost-effective strategy, with an ICER of £18 871

per QALY. Other studies in the literature have focused on high-risk populations, such as immunosuppressed adults,[35–38] migrants,[39–41] healthcare workers[42–48] and adults who have had close contact with TB.[49–53] In most cases, IGRA was confirmed to be cost-effective in these populations.

Based on the evidence published to date, this study is, to our knowledge, the first to evaluate the cost-effectiveness of QFT compared with TST in children under 15 using a critical outcome measure directly related to test performance—correctly diagnosed cases—without the influence of additional variables, such as utilities estimations for QALYs.

This study has several limitations. First, age restrictions were applied, and the model only considered the diagnostic performance of the tests in immunocompetent children under 15 years of age who were vaccinated with BCG at birth, as test performance differs in adults and immunosuppressed patients; therefore, these findings cannot be extrapolated to those populations.[14] Second, the prevalence of LTBI and the intrinsic characteristics of diagnostic tests are estimated indirectly, as real values cannot be obtained due to the absence of a gold standard for diagnosis. Third, the model did not include costs associated with treating reactivated TB in patients with false negative results, mortality rates, deterioration of their quality of life, adverse effects of anti-TB treatment regimens or related costs, as these exceed the study's objectives and warrant a separate detailed model. Fourth, the cost of treating multidrug-resistant TB was not considered, as this lies beyond the study's scope; diagnosing and treating multidrug-resistant bacillus does not depend on the diagnostic tests evaluated here. Fifth, indeterminate QFT results, which would require repeating the test or applying TST as a sequential strategy, were not considered, as the test has a 0% likelihood of indeterminate results when properly administered, as reported by the national laboratories consulted during the costing process.[17 18] Finally, a serial testing strategy using both QFT and TST to confirm positive or negative results, as seen in other studies,[33 34] was excluded because it is not recommended by the Colombian Ministry of Health and the WHO.[7 31] Such a strategy would likely increase costs and would not be feasible in remote regions lacking the infrastructure for IGRA administration. A strength of this study is the model's robustness, demonstrated by the sensitivity analyses, in which the results were consistently replicated across different scenarios.

We hope this model may be used and adapted in other contexts, allowing for cost-effectiveness analyses to evaluate the feasibility of financing and implementing this diagnostic test in other countries. These results contributed to the development of a Colombian clinical practice guideline aimed at improving clinical decision-making for physicians and health policymakers. By promoting the rational and appropriate use of public resources, which are increasingly limited, this guideline seeks to positively impact public health in Colombia.

In conclusion, this study provides evidence supporting the QFT test as a cost-effective intervention compared with TST for diagnosing LTBI in immunocompetent children under 15 years of age who have been in contact with active TB patients in the context of the Colombian healthcare system, using a threshold of US$6666. The results are robust, showing low sensitivity to variations in QFT cost, LTBI prevalence and the intrinsic characteristics of diagnostic tests.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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