A costing framework to compare tuberculosis infection tests

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ABSTRACT

Objective To develop a framework to estimate the practical costs incurred from, and programmatic impact related to, tuberculosis (TB) infection testing—tuberculin skin tests (TST) versus interferon gamma release assay (IGRA)—in a densely populated high-burden TB area.

Methods We developed a seven-step framework that can be tailored to individual TB programmes seeking to compare TB infection (TBI) diagnostics to inform decision-making. We present methodology to estimate (1) the prevalence of TBI, (2) true and false positives and negatives for each test, (3) the cost of test administration, (4) the cost of false negatives, (5) the cost of treating all that test positive, (6) the per-test cost incurred due to treatment and misdiagnosis and (7) the threshold at which laboratory infrastructure investments for IGRA are outweighed by system-wide savings incurred due to IGRA utilisation. We then applied this framework in a densely populated, peri-urban district in Lima, Peru with high rates of Bacillus Calmette–Guérin (BCG) vaccination.

Findings The lower sensitivity of TST compared with IGRA is a major cost driver, leading to health system and societal costs due to misdiagnosis. Additionally, patient and staff productivity costs were greater for TST because it requires two patient visits compared with only one for IGRA testing. When the framework was applied to the Lima setting, we estimate that IGRA-associated benefits outweigh infrastructural costs after performing 672 tests.

Conclusions Given global shortages of TST and concerns about costs of IGRA testing and laboratory capacity building, this costing framework can provide public health officials and TB programmes guidance for decision-making about TBI testing locally. This framework was designed to be adaptable for use in different settings with available data. Diagnostics that increase accuracy or mitigate time to treatment should be thought of as an investment instead of an expenditure.

INTRODUCTION

Tuberculosis (TB) is the greatest infectious cause of death globally behind COVID-19. Roughly one quarter of the world’s population is estimated to be infected with TB, and 5%–10% of these individuals are anticipated to progress to TB disease in their lifetime. In recent years, prior to the COVID-19 pandemic, global TB burden has stagnated at a decrease of 1.5% annually, a rate that already fails to meet international targets for TB elimination.

This stagnated progress necessitates comprehensive approaches that prioritise rapid and risk-based case-finding for TB; appropriate treatment for the disease alongside patient-centred approaches to ensure treatment completion; prevention of TB infection (TBI) and, should infection be identified or suspected, rapid initiation of tolerable regimens of TB preventive therapy (TPT)
In many settings where there is a high burden of TB and poorly quantified prevalence of TBI, a risk-based strategy is recommended for initiating TPT; that is, individuals at high risk of TB and those identified to be infected with TB where active disease is ruled out should be initiated on TPT. However, in many high burden settings, both TPT and risk-based strategies for preventing TB are not prioritised. Without efforts to identify logistically and economically feasible strategies to address TBI, including efficient approaches to TBI testing, high-burden settings will remain behind global targets to eliminate TB.

Tuberculin skin test (TST) is commonly used for identifying TBI in high-TB burden settings. This requires two patient-provider interactions; one for the intradermal injection of the product and a second for interpreting the results. Barriers to TST implementation include specialised training for staff administering the test, inter-reader and intra-reader variability, the need for cold-chain storage, and that a single vial of tuberculin once opened must be used prior to its expiry, presenting the risk of wastage. Newer technologies, including whole-blood tests like interferon-gamma release assays (IGRA), can also aid in the diagnosis of TBI. IGRA requires a single patient-provider interaction where 4 mL blood is drawn. Barriers to IGRA implementation include requiring staff trained in phlebotomy and ELISA, laboratory infrastructure capable of ELISA, time-sensitive processing constraints for fresh and/or whole blood samples including incubation time and considerations around analysing multiple samples to maximise test kit yields.

While IGRA has superior sensitivity and specificity compared with TST, TST is generally considered less expensive to use at a population level due to the laboratory infrastructure necessary to run ELISA. However, a test with lower accuracy may miss individuals with TB and, therefore, not identify individuals who may benefit from TPT. Paradoxically, TST is commonly used in low- and middle-income settings with high TB burdens and with high rates of Bacillus Calmette–Guérin (BCG) vaccination, which reduces the risk of TB disease in children while also reducing the accuracy of TST. Should these individuals missed from TBI to active disease, they would incur higher treatment costs, as care for TB is generally more expensive than care for TBI. At a societal level, reliance on TST may be more expensive than initial investments necessary to introduce and implement IGRA diagnostic tools. However, few practical tools exist for TB programmes to evaluate the cost of using TST as the standard-of-care diagnostic compared with IGRA.

To our knowledge, most costing studies comparing TB diagnostics ignore the opportunity cost—the cost of opportunity forgone, or the potential benefit that would have been incurred should the alternative been chosen—in their calculations, particularly in high-burden, low-income settings. For example, cost analyses of TB diagnostics measure patients’ lost income due to diagnosis but do not incorporate benefit to society in the form of reduced transmission. If new tests improve a diagnostic algorithm’s accuracy, treatment is also more quickly available to a patient, and further disease transmission is averted. Therefore, in calculating the economic and social impact to society, one should include these benefits accruing to stakeholders.

Here, we estimate the practical costs incurred from, and programmatic impact related to, TBI testing—TST versus IGRA in the context of a densely populated high-burden setting. This costing framework, therefore, is intended to evaluate the comparative costs from the societal perspective, including those costs incurred due to sustained transmission, resulting from testing inaccuracies.

**METHODS**

**Framework development & overview of costing inputs**

We identified all potential costing inputs—including time, physical resources and personnel—which are used to test for TBI and provide TB care (table 1). This includes 15 inputs: average hourly wages per patient, transportation costs, TST consumables, technical staff salary for TST, IGRA consumables, technical staff salary for IGRA, laboratory personnel salary for IGRA, lost productivity for sick patients, healthcare staff salary, tests and consumables to rule out active TB disease, miscellaneous treatment, TB disease treatment, support staff stipend, TB treatment, and fixed laboratory equipment. These inputs are detailed in table 1.

The 15 costing inputs are then applied to a seven-step framework, which we describe below. In some settings, costs including infrastructure, utilities and additional transportation may need to be accounted for. In our setting, we did not include these infrastructure and utility costs because they could not be precisely measured per-testing unit, as infrastructure and operations were already established prior to the introduction of IGRA. We did not include transportation costs in calculations for treatment as we anticipated significant variability in the frequency and modes of travel to clinics to receive care for disease diagnosis, TB disease treatment and TPT. This resulted in a more conservative estimate in the difference in costs. However, if infrastructure, utilities and transportation must be included, they must be calculated on a per-patient basis and incorporated into Calculations x and xiii. Per-patient infrastructure and utilities may also be incorporated into Calculation vii.

**Step 1. Estimate the underlying prevalence of TBI**

The underlying prevalence of TBI in a population is necessary in order to calculate the rates of expected positive and negative results from the two infection tests being compared. As the prevalence of TBI is not available in many settings, it may be estimated with a weighted prevalence by using published estimates for TBI prevalence in demographically similar populations and weighting these estimates according to the demographic makeup of the target population.
### Table 1: Costing inputs for consideration along TB infection pathway

<table>
<thead>
<tr>
<th>Input</th>
<th>Input title</th>
<th>Definition</th>
<th>Input details</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Average hourly wages per patient</td>
<td>Lost opportunity cost per patient per hour</td>
<td>Average monthly wage, average time spent travelling roundtrip to a health facility, average time spent in the health facility, number of clinic visits necessary.</td>
</tr>
<tr>
<td>B</td>
<td>Transportation costs</td>
<td>Roundtrip to a health facility</td>
<td>Average miles travelled roundtrip, average cost per mile for transportation services, number of clinic visits necessary</td>
</tr>
<tr>
<td>C</td>
<td>TST consumables</td>
<td>Commodities required for administering TST, per manufacturer instructions</td>
<td>Vial of tuberculin, syringe, number of TSTs that can be completed per vial</td>
</tr>
<tr>
<td>D</td>
<td>Technical staff salary for TST</td>
<td>Salary of personnel administering and interpreting TST</td>
<td>Salary per month of personnel administering the tuberculin injection and interpreting the induration size, number of tests conducted in a day, number of working days per month</td>
</tr>
<tr>
<td>E</td>
<td>IGRA consumables</td>
<td>Commodities required for administering IGRA, per manufacturer instructions</td>
<td>Costs of a specific type of IGRA test kit ELISA, blood collection tubes for IGRA test, and micropipette tips, with assumptions on the number of tests that can be analysed per test kit</td>
</tr>
<tr>
<td>F</td>
<td>Technical staff salary for IGRA</td>
<td>Salary of personnel administering IGRA</td>
<td>Salary for individual completing phlebotomy</td>
</tr>
<tr>
<td>G</td>
<td>Laboratory personnel salary for IGRA</td>
<td>Salary of laboratory staff who process/analyse IGRA</td>
<td>Salaries of: laboratory director, supervisor, coordinator, technician, data entry clerk, maintenance personnel. Percent effort devoted to IGRA processing. We make assumptions about the quantity of IGRAs analysed daily and the number of working days per month</td>
</tr>
<tr>
<td>H</td>
<td>Lost productivity for sick patient</td>
<td>Lost productivity cost when an individual is sick with TB</td>
<td>Local average hourly wage, number of hours worked per month, average length of TB treatment, per cent of lost productivity</td>
</tr>
<tr>
<td>I</td>
<td>Healthcare staff salary</td>
<td>Salary of staff contributing to the diagnosis of, and providing care for, TB disease,</td>
<td>Salaries of: physicians, radiologists, non-clinician medical professionals, nursing technicians. We make assumptions about the time each spends with a patient with TB.</td>
</tr>
<tr>
<td>J</td>
<td>Tests and consumables to rule out active TB</td>
<td>Consumables to complete TB diagnostic tests, per local diagnostic algorithms, to rule out active TB disease</td>
<td>Sampling for bacteriologic staining and smear microscopy, Gene Xpert, samples for MGIT and LJ cultures, first/second line drug sensitivity testing, chest radiography, clinical evaluation, number of patients evaluated using each test</td>
</tr>
<tr>
<td>K</td>
<td>Miscellaneous treatment</td>
<td>Other care/treatment for patients prior to a TBI or disease diagnosis</td>
<td>Average time spent per patient-provider visit, average patient-time lost by attending visits, transportation, average cost of alternative treatments, average cost of physicians’ time, cost of lost patient productivity, average number of patient visits, proportion of patients to whom this miscellaneous treatment applies</td>
</tr>
<tr>
<td>L</td>
<td>TB disease treatment</td>
<td>Cost of TB disease treatment</td>
<td>Cost of treatment for drug-susceptible and drug-resistant TB, proportion of patients in whom this applies</td>
</tr>
<tr>
<td>M</td>
<td>Support staff stipend</td>
<td>Remuneration for support staff for routine follow-up of patients on treatment</td>
<td>Amount received monthly, number of patients they support monthly</td>
</tr>
<tr>
<td>N</td>
<td>TB infection treatment/TPT</td>
<td>Cost of TB infection treatment/TPT</td>
<td>Cost of the standard-of-care provided in the local setting</td>
</tr>
<tr>
<td>O</td>
<td>Fixed laboratory equipment</td>
<td>Cost of equipping a laboratory with infrastructure capable of processing/analysing IGRA</td>
<td>ELISA reader and washer, refrigerator and incubator, micropipettes, centrifuge and computer</td>
</tr>
</tbody>
</table>

IGRA, interferon gamma release assay; TB, tuberculosis; TPT, TB preventive therapy; TST, tuberculin skin tests.
Prevalence = \(\frac{\text{Prevalence}_{\text{subpopulation 1} \times \text{Prevalence}_{\text{subpopulation 2}} \times \text{Prevalence}_{\text{subpopulation 3}} \times \ldots \times \text{Prevalence}_{\text{subpopulation n}}}}{\text{Target population}}\) (i)

where \(n_{\text{target population}} = n_1 + n_2 + n_3 + \ldots + n_{i-1} + n_i\)

Step 2. Estimate the number of true and false positives and negatives that would be observed if the diagnostic test was used in the target population

The number of true positive and negative results that would be identified by a given test are necessary to estimate the cost of care for people with TBI. The number of true positives can be estimated with the test’s sensitivity and the weighted prevalence estimate (Calculation i).

\[
\text{True positives}_{\text{TST}} = \text{Sensitivity}_{\text{TST}} \times \left(\frac{\text{Prevalence \_Calculation \_i \times \text{Target population size}}}{\text{Target population}}\right) \quad (\text{ii. a})
\]

\[
\text{True positives}_{\text{IGRA}} = \text{Sensitivity}_{\text{IGRA}} \times \left(\frac{\text{Prevalence \_Calculation \_i \times \text{Target population size}}}{\text{Target population}}\right) \quad (\text{ii. b})
\]

The true negatives can be estimated with the test’s specificity and weighted prevalence estimate.

\[
\text{True negatives}_{\text{TST}} = \text{Specificity}_{\text{TST}} \times \left(\frac{\text{Prevalence \_Calculation \_i \times \text{Target population size}}}{\text{Target population}}\right) \quad (\text{iii. a})
\]

\[
\text{True negatives}_{\text{IGRA}} = \text{Specificity}_{\text{IGRA}} \times \left(\frac{\text{Prevalence \_Calculation \_i \times \text{Target population size}}}{\text{Target population}}\right) \quad (\text{iii. b})
\]

People who are falsely positive for TBI may be prescribed TPT unnecessarily or otherwise receive unnecessary healthcare services. The number of false-positive results to be expected can be calculated using the test specificity and the number of true negatives expected for a given test’s utilisation (Calculation iii).

\[
\text{False positives}_{\text{TST}} = \frac{\text{True positives}_{\text{TST} \_\text{Calculation \_iii \_a}} \times \text{Target population size}}{\text{Target population size}} \quad (\text{iv. a})
\]

\[
\text{False positives}_{\text{IGRA}} = \text{True positives}_{\text{IGRA} \_\text{Calculation \_iii \_a}} \times \frac{\text{Target population size}}{\text{Target population size}} \quad (\text{iv. b})
\]

The number of false-negative test results can be used to estimate the cost of healthcare for people who go undiagnosed and whose infection progresses to active disease. The number of expected false-negative results can be calculated by using the test sensitivity and the number of true positives expected for a given test’s utilisation (Calculation ii).

\[
\text{False negatives}_{\text{TST}} = \frac{\text{True positives}_{\text{TST} \_\text{Calculation \_ii \_a}} \times \text{Target population size}}{\text{Target population size}} \quad (\text{v. a})
\]

\[
\text{False negatives}_{\text{IGRA}} = \text{True positives}_{\text{IGRA} \_\text{Calculation \_ii \_a}} \times \frac{\text{Target population size}}{\text{Target population size}} \quad (\text{v. b})
\]

Step 3. Estimate the cost of test administration

We incorporate average hourly wages per patient (A), transportation costs (B), the per-test cost of consumables for TST (C) and IGRA (D) and salary for the technical staff administering TST (E) and IGRA (F). Each of the costing inputs are converted into cost per-test unit.

Cost of per-test utilisation (vi) must be calculated two times, once for testing using IGRA and once for testing using TST. Lost patient productivity during IGRA and TST administration is estimated using inputs (A) and (B) and may vary with the number of required health facility visits. Inputs (C) and (D) are used to calculate per-test TST and IGRA consumables costs, respectively. Inputs (E) and (F) are used to calculate per-test cost of staff for TST and IGRA utilisation, respectively. Input (G) is used to calculate per-test cost of laboratory staff for IGRA utilisation only. For estimating input (F), it is important to consider the full time effort (FTE) required per staff member to analyse IGRA in a laboratory where ELISA is rarely used, or IGRA is infrequently used, compared with the FTE necessary in a setting where IGRA is routinely used, and whether this affects the staff members’ efficiency.

The per-test cost of test utilisation can then be calculated by summing the per-test costing inputs:

\[
\begin{align*}
\text{Per test cost of test utilisation}_{\text{IGRA}} &= \text{per test costs incurred by patient} [\text{Inputs A and B}] + \text{per test consumable cost [Input C]} + \text{per test cost of technical staff [Input F]} + \text{per test cost of laboratory staff [Input G]} \\
\text{Per test cost of test utilisation}_{\text{TST}} &= \text{per test costs incurred by patient} [\text{Inputs A and B}] + \text{per test consumable cost [Input C]} + \text{per test cost of technical staff [Input E]}
\end{align*}
\]

The difference in the cost of testing between the selected tests (vii) can be calculated from the difference in the costs of testing specifically for TST and IGRA from Calculation vi:

\[
\text{Difference in per test cost of test utilisation} = \left| \frac{\text{IGRA per test cost of test utilisation [Calculation vi a]}}{\text{TST per test cost of test utilisation [Calculation vi b]}} \right| \quad (\text{vii})
\]

Step 4. Estimate the cost of false negatives

Patients who receive false-negative results from the TBI test may not appropriately be provided TPT; a proportion of which will progress to active TB disease and, in turn, contribute to further disease transmission. This leads to additional costs related to clinical evaluations, diagnostic testing, disease treatment and treatment support. Discounting and inflation were not applied to these costs, as the majority of progression to disease occurs within 2 years of infection.20

Potential costs of additional diagnostic tests for active disease include those for smear microscopy, Gene Xpert MTB/RIF, culture, first-line and second-line drug sensitivity testing, chest radiography and clinical evaluation (Input J). Often, a combination of nurses, non-physician medical experts and physicians are necessary to diagnose active disease (Input I). Given the concerns of poor treatment adherence or loss to follow-up during treatment, supportive staff such as community health...
workers (CHW) often work in parallel to the medical care provided in clinical settings (Input M).

Treatment for drug-resistant (DR) TB is longer and more expensive compared with treatment for drug-susceptible TB. The proportion of TB patients sick with DR TB must be informed by local epidemiologic observations. This proportion is incorporated into the per-patient cost of TB treatment, including drugs (Input L) and duration of treatment (Inputs H and M Multiplier).

For some patients, TB disease is not immediately suspected by a care provider, and costs are incurred by additional clinical visits, alternative therapies such as antibiotic courses and lost patient productivity (Input K).

Cost of treating one missed patient =
\[
\text{[lost patient productivity } [H] \times \text{number of months of treatment}] +
\text{[per patient cost of caregiving medical staff salaries } [I]] +
\text{[per patient cost of tests for diagnosing active TB } [J]] +
\text{[average per patient cost of miscellaneous treatment } [K]] +
\text{[per patient cost of one regimen of active TB therapy } [L]] +
\text{[per lost productivity of support staff } [M] \times \text{number of months of treatment]}
\]

While the transmission rate of TB varies widely and is highly dependent on the context, we assumed conservatively that one case of active TB would lead to one additional case of active TB disease.\(^2\) As most disease is the result of recent transmission, discounting was not applied.\(^2\) Therefore, the impact of each falsely diagnosed individual who become sick is double:

Cost of treating one missed patient and sick contact =
\[
\text{Cost of treating one missed patient } \times (1 + \text{Additional contacts becoming sick due to contagion})
\]

The cost of false negatives must be calculated two times, once for using IGRA and once for using TST. To calculate the cost of false negatives, we multiply the cost of treating and diagnosing false-positive individuals and one additional sick contact (Calculation xi) by the number of false negatives expected through use of IGRA (Calculation viii) and through use of TST (Calculation ix).

Total cost of treating false negative patients diagnosed
\[
\text{with IGRA who progress to disease } = \text{Cost of treating and diagnosing missed patient and sick contact } \times \text{False Negatives}_{\text{IGRA}}
\]

(x.a)

Total cost of treating false negative patients diagnosed
\[
\text{with TST who progress to disease } = \text{Cost of treating and diagnosing missed patient and sick contact } \times \text{False Negatives}_{\text{TST}}
\]

(x.b)

Step 5. Estimate the cost of treating all individuals who test positive
We assumed that every individual receiving a positive result for TBI, including those receiving false-positive results, is initiated on TPT promptly and will not progress to TB disease. Six months of isoniazid is most commonly prescribed for treating TBI despite the development of shorter regimens. We optimistically assume no occurrences of adverse reactions under this treatment regimen. We assume that follow-up through auxiliary or supportive caregivers, such as CHW, is provided to patients for the duration of their treatment. It is important to consider the cost of routine care and monitoring based on national guidelines and local programmes.

Cost of treating one TBI-positive patients = (Cost of TPT \([\text{Input N}]\) + \text{Cost of lost productivity among support staff } [\text{Input M}] \times \text{Number of months that support staff cares for patient})

(xi)

The cost of treating all TBI-positive patients including both true positives and false positives will be calculated two times, once based on the number of true and false positives expected through use of IGRA (Calculations ii a and iv a), and once based on the number of true and false positives expected through TST (Calculations ii b and iv b).

Cost of treating all TBI-positive patients given positive IGRA =
\[
\text{Cost of treating one TBI-positive patients } \times (\text{True Positives}_{\text{IGRA}} \times \text{Cost of treating positive patients given positive IGRA})
\]

(xii. a)

Cost of treating all TBI-positive patients given positive TST =
\[
\times (\text{True Positives}_{\text{TST}} \times \text{Cost of treating positive patients given positive TST})
\]

(xii. b)

The cost of treating all individuals misdiagnosed with TBI can be calculated using the number of expected false positives through IGRA use (Calculation iv a) and TST use (Calculation iv b).

Cost of treating IGRA misdiagnosed TBI-positive patients = \text{Cost of treating one TBI-positive patients } \times (\text{False Positives}_{\text{IGRA}} \times \text{Cost of treating TBI-positive patients given positive IGRA})

(xiii. a)

Cost of treating TST misdiagnosed TBI-positive patients = \text{Cost of treating one TBI-positive patients } \times (\text{False Positives}_{\text{TST}} \times \text{Cost of treating TBI-positive patients given positive TST})

(xiii. b)

Step 6. Calculate the per-test cost incurred due to diagnosis, misdiagnosis and treatment
The cost of care incurred for all patients tested with either IGRA or TST is calculated by summing the cost of treating false-negative patients who progress to active disease and their contacts (Calculation x) with the cost of treating all TBI-positive patients (Calculation xii). This is calculated twice, one each given IGRA testing results and TST testing results.

Cost of care for all patients tested for TBI with IGRA = \text{Cost of care for all patients missed through IGRA and their contacts } \times \text{Cost of treating all IGRA diagnosed TBI-positive patients}

(xiv. a)
IGRA compared with TST

It is possible to estimate the cost of unnecessary TPT provided to individuals with false-positive test results and the cost of avoidable TB disease care for individuals with false-negative results who do not receive TPT and progress to active disease. However, in many high TB-burden settings, TPT provision is recommended based on exposure rather than on the results of a diagnostic test, meaning TPT may be an expected cost for programmes for individuals, regardless of diagnostic test results. The cost of care for tested individuals must be calculated two times, once each for TST and IGRA testing, to account for the differences in the expected number of false-positives and negatives.

We can then approximate the comparative per-test cost of care by finding the difference in cost due to treatment for an IGRA-diagnosed population (Calculation xiv a) and cost due to treatment for a TST-diagnosed population (xiv b). This is divided by the number of individuals (ie, the target population) for whom testing data are available.

Per test savings due to unnecessary TPT treatment and

necessary treatment and diagnosis = 
\[
\left( \frac{\text{Cost of care for all patients tested for TBI using IGRA (Calculation xiv a) - Cost of care for all patients tested for TBI using TST (Calculation xiv b)}}{\text{Target population}} \right)
\]

(xv)

We can then calculate the cost-savings realised by using IGRA compared with TST.

Total difference in cost savings from test utilization and resulting care =

\[
\text{Per test cost or benefit due to treatment and diagnosis (Calculation xv) + Difference in per test cost of testing (Calculation xvi) }
\]

(xvi)

Step 7. Identify the testing threshold at which laboratory infrastructure investment costs are less than the benefits accrued by benefits of more sensitive tests

Laboratory capacity to process IGRA requires that equipment capable of performing ELISA, including ELISA plate readers and washers, an incubator, a refrigerator, a centrifuge, micropipettes and a computer per the QFT-Plus package insert. Investment in this infrastructure can be cost-prohibitive to policymakers. Existing infrastructure may vary from fully set up laboratories, to established laboratory infrastructures, which lack ELISA capacity, to lack of basic laboratory infrastructure. Thus, necessary investment may vary by setting and may even need to account for costs of construction or capacity-building alongside the cost of equipment (Input O).

Framework application

We demonstrate the application of this framework to three high-TB risk subpopulations in the urban and peri-urban areas of Lima, Peru: household contacts of TB patients, military personnel and healthcare workers based in facilities in Lima Norte. TST is the standard of care locally for diagnosing TBI in Lima. Although all contacts of TB patients should be screened for TB per national guidelines, in practice, individuals under 19 years of age most frequently receive screening. While all contacts with a positive TST are eligible for TPT, in most cases, TPT is only administered to under-5 contacts.

Between December 2018 and October 2020, 10 000 units of the IGRA test, QFT-Plus, were donated from QIAGEN Sciences (Germantown, Maryland) to the non-governmental organisation Socios En Salud Sucursal Peru (SES), which works with the Ministerio de Salud (MINSA) to provide TB care. The tests were then administered in the three districts where SES has a long history of providing TB support services. IGRA testing was prioritised for individuals at high risk of TB disease, including household contacts of individuals diagnosed with TB, healthcare workers and military members residing in barracks. Three of the tests were unable to be processed due to normal processing errors; the remaining IGRA tests (n=9997) were processed locally at the SES laboratory, which interfaces routinely with the TB programme and lacked ELISA capacity prior to the introduction of IGRA. Care was provided jointly by MINSA and SES as part of ongoing programmatic collaboration.

Information regarding financial inputs for administering both diagnostic tests was gathered from SES who routinely support these tests, including laboratory personnel, and from publicly available sources. Costing data were collected in Peruvian soles and converted into USD at a rate of 1 USD: 3.2 PEN per the exchange rate at the time of data collection.

We leveraged this existing data in order to demonstrate the use of this framework. To apply this framework to the local setting, we assumed an established laboratory infrastructure and existing equipment capable of performing ELISA to process 100 IGRA per day; there was minimal loss-to-follow-up for individuals returning to have their TST interpreted due to the extensive network of CHW in the area; and individuals eligible for TPT were appropriately treated and said treatment was effective. This represents an idealised programme and not the reality in many settings; however, policies in Lima and elsewhere are moving towards more effective and accessible treatment for TBI. Adjustments to these assumptions can easily be made based on differences in other settings/populations.
RESULTS
The overall framework demonstrating the costing inputs, calculations and seven steps is depicted in figure 1. Costing inputs are reported in table 2.

Step 1. Underlying prevalence of TBI
Our target population comprised 45.2% HCW, 46.5% military personnel and 8.3% HHC. We assumed the prevalence of TBI to be 56.0% among HCW, based on the burden of TBI estimated in a similar population in Lima and 24.8% among both military personnel and HHC per IGRA diagnosis based on global burden estimates. We estimated that the weighted prevalence of TBI as indicated by testing with IGRA was 38.9%.

Step 2. The number of true and false positives and negatives that would be observed if the diagnostic test was used in the target population
Estimates of true and false positives and negatives expected through the use of 10 000 IGRA and TST testing units are summarised in table 3. We expect that 3658 true positives, 5987 true negatives, 122 false positives and 233 false negatives would be observed using IGRA. We estimate that 2802 true positives, 3604 true negatives, 2505 false positives and 1090 false negatives would be observed.

Step 3. Cost of test administration
Costing outputs are described in table 4. The total cost of IGRA use (Calculation vi a) is $26.26 per test. The total cost of TST use is $31.41 per test. Use of IGRA, therefore, incurred cost-savings of $5.15 per test compared with TST.

Step 4. Cost of false negatives
We estimate that 10% of falsely negative individuals will progress to active disease and that each case will lead to one additional sick contact. The estimated cost for each falsely negative individual and sick contact was $4574 for medical staff time, diagnostics, treatment and lost productivity. Per 10 000 TSTs performed, this contagion cost amounted to $498 339 in unnecessary expenses among an estimated 10% of the 1090 false-negative individuals (Calculation v b) who progress to active disease plus their one sick contact. Per 10 000 IGRAs performed, this furthered contagion cost amounted to $106 787 in unnecessary expenses among 23 individuals with false-negative tests who progress to active disease plus one sick contact.

Step 5. Cost of treating all TBI-positive patients
Individuals with positive test results should receive IPT, which includes the cost of 6 months of isoniazid ($15) and cost of support staff for 6 months ($62). Per 10 000 TSTs performed, this would lead to $410 708 in TPT costs for all individuals testing positive, including $193 854 for unnecessary treatment of individuals with false-positive test results. Per 10 000 IGRAs performed, this translated to $292 571 in TPT costs for all individuals testing positive, including $9456 in treatment of individuals with false-positive results.

Step 6. Total difference in cost-savings from test use and care
The cost of providing IPT to all patients testing positive for TBI and providing active TB treatment to patients with false-negative results who eventually progress to TB...
disease is estimated to be $909 046 per 10 000 TST and $399 358 per 10 000 IGRA. Thus, there is a cost saving of $50.97 for every IGRA administered in the place of TST. The total cost saving from using IGRA compared with TST, inclusive of the savings incurred during test administration, is $56.12 per test.

**Step 7. Testing threshold at which laboratory infrastructure investment costs are less than the benefits accrued by benefits of more sensitive tests**

We estimated that once 673 IGRA tests can be analysed by the programme, enough savings are amassed through avoiding unnecessary care delivery and lost patient/provider productivity to overcome the cost of the laboratory investment required to process the IGRA tests.

**DISCUSSION**

When applied to a multisectoral programme in Lima, Peru, the costing framework identified that TST costs $56.12 more per test performed compared with IGRA. Due to the better discriminatory properties of IGRA compared with TST, programmatic utilisation of IGRA would save $509 689 per 10 000 in this setting. We found that once 673 IGRA tests are performed, IGRA-associated cost-savings overcome the costs necessary for establishing laboratory infrastructure required to process IGRA. In a
medium to high-burden setting, like the catchment area of the study programme in Lima, this likely represents a fraction of the number of tests that a laboratory would perform in 1 year time.

The comparative cost of TST and IGRA can vary widely by setting and population.25–27 Our findings from the application of our analytical model substantiated existing evidence that IGRA can be an economically feasible option for identifying TBI in BCG-vaccinated populations compared with TST.28–30 To the best of our knowledge, this is the first time IGRA has been shown to be cheaper and more efficient compared with TST in a high TB burden setting within a middle or upper middle-income country (MIC/UMIC).

Compared with previous research, our methodology and findings differ in several important ways. Most costing and cost-effectiveness studies have been conducted in high-income settings with a low TB burden among the general population, or among high-burden subpopulations in a low-TB burden, high-income setting.26 In contrast, through an analysis set in a similarly UMIC, high TB burden setting, TST was found to be more cost effective than IGRA, but IGRA would be more cost effective should TST’s specificity be <59% and IGRA cost <$USD27.30 Such parameters are reflected in this study. Also, to the best of our knowledge, this study is the first comparison of the newest generation IGRA, QFT-Plus, to TST.

This costing framework allows the user to conduct a direct comparison of two diagnostic tools and determine the threshold at which investment in a TB diagnostic technology is overcome by cost-savings incurred by that technology. Our framework incorporates lost opportunity costs and the effects of diagnostic sensitivity and specificity on the effect of contagion, two important drivers of TB-related costs that are infrequently incorporated in the existing literature. The findings of this framework’s application suggest that costs to individual patients, health systems and society can be reduced if more sensitive diagnostics are made available to people at risk of TBI, and if the time required for diagnosis can be reduced.11 25 31

Optimising test utilisation presents an opportunity to further decrease the cost of testing. In our application, increasing the number of IGRA tests performed would mean the threshold calculated with this model would be more quickly reached. Our example analysis did not account for instances where the ELISA is not processed at full capacity, and we similarly did not account for instances wherein tuberculin goes unused, because this model was applied in a high burden setting. In both cases, respective per-test cost would increase considerably. Therefore, areas that are most likely to realise the highest cost-savings are those with a high burden of TB and where high-risk populations are routinely tested for infection.

Among this study’s strengths is the flexibility with which the costing framework can be applied. This analytical framework may be adapted to leverage existing data to arrive at a threshold beyond which the cost of investment in infrastructure is outweighed by the benefit incurred by a more sensitive test. Additionally, this study incorporates estimators for patients’ lost wages. While imperfect, this enables users to consider the economic consequences of a diagnostic tool’s broad application.

Among its limitations, this model’s example application makes several assumptions that must be considered prior to its application to other settings. For example, this model assumed that all patients receiving TST return for their TST interpretation. More than 95% of patients in SES’s catchment area return for their second visit, but this rate is uncommonly high and may be due to the high levels of patient support provided by SES. In other settings, loss to follow-up for TST can be upwards of 55%.32 Thus, the rate per 10 000 people diagnosed with TBI using TST would likely be lower than estimated in this analysis, and cost of care for people missed and developing TB disease would be higher.

Similarly, this model assumed that all diagnosed patients are linked to care and adhere to TPT and active TB therapy. In real-world settings, especially those which are resource constrained, treatment enrolment and adherence can vary.33 Shorter and more tolerable regimens may promote adherence, thereby reducing progression to active TB and preventing TB transmission.34 Therefore, additional costs from treatment uptake, adherence and subsequent lost productivity from illness must be considered.

This analysis did not include some costing inputs that may be relevant to other settings. These included overhead and infrastructure costs, which could not be calculated as a per-testing unit cost because operations and infrastructure were extant prior to the implementation of IGRA. We also did not include transportation costs in steps 4–6 as we expect significant variability in our

Table 3 Calculating estimated TB infection prevalence and test positivity and negativity using TST and IGRA (n=10 000)

<table>
<thead>
<tr>
<th>Analysis level</th>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72%*</td>
<td>94%†</td>
</tr>
<tr>
<td>Specificity</td>
<td>56%*</td>
<td>98%†</td>
</tr>
<tr>
<td>Expected positives</td>
<td>5306</td>
<td>3780</td>
</tr>
<tr>
<td>True positives</td>
<td>2802</td>
<td>3658</td>
</tr>
<tr>
<td>False positives</td>
<td>2505</td>
<td>122</td>
</tr>
<tr>
<td>Expected negatives</td>
<td>4694</td>
<td>6220</td>
</tr>
<tr>
<td>True negatives</td>
<td>3604</td>
<td>5987</td>
</tr>
<tr>
<td>False negatives</td>
<td>1090</td>
<td>233</td>
</tr>
</tbody>
</table>

*Menziez et al.36
†QIAGEN GmbH.37
IGRA, interferon gamma release assay; TB, tuberculosis; TST, tuberculin skin tests.
setting’s population and how they access health services for TB and TBI, but this resulted in a more conservative estimate. Applications of this framework to other settings might consider whether including these inputs would increase or decrease estimation accuracy.

As a final limitation, we chose not to conduct a sensitivity analysis. Many assumptions were informed by real-world information from site-based colleagues, which provided more accuracy than might otherwise be achieved. As this was a conservatively designed analysis, the outputs of this framework may be considered the lower bound of possible savings achievable. Finally, this study is intended to report the development of a costing framework for flexible use in other settings, and the application to Peru is intended to demonstrate its use to programme decision-makers.

Table 4 Outputs of costing analysis for use of IGRA and TST in a peri-urban, high TB burden area of Lima, Peru

<table>
<thead>
<tr>
<th>Costing analysis step</th>
<th>Costing analysis calculation</th>
<th>Results of analysis for TST</th>
<th>Results of analysis for IGRA</th>
<th>Assumptions made for Lima application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>(i) Weighted prevalence of TBI in the target population</td>
<td>0.3891</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>(ii) Number of true positive results expected in the target population</td>
<td>2802</td>
<td>3658</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(iii) Number of true negative results expected in the target population</td>
<td>3604</td>
<td>5987</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(iv) Number of false positive results expected in the target population</td>
<td>2505</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(v) Number of false negative results expected in the target population</td>
<td>1090</td>
<td>233</td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>(vi) Per-test cost of test utilisation</td>
<td>$31.41</td>
<td>$26.26</td>
<td>Per clinic visit, 40 min of patient time spent commuting routine to clinical setting and 20 min of patient time spent in clinic.</td>
</tr>
<tr>
<td></td>
<td>(vii) Difference in cost of testing</td>
<td>$5.15 in savings by using IGRA compared with using TST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>(viii) Cost of treating one ‘missed’ patient</td>
<td>$2287</td>
<td>$2287</td>
<td>For 5% of patients, TB disease is not suspected and Input K is applied. In those instances, we assume two additional clinical visits are required, demanding 30 min of physician time and 1.5 hours of lost patient productivity per visit.</td>
</tr>
<tr>
<td></td>
<td>(ix) Cost of care per ‘missed’ patient and contacts becoming sick through effect of contagion</td>
<td>$4574</td>
<td>$4574</td>
<td>One additional person becomes sick per individual who progresses to active disease.</td>
</tr>
<tr>
<td></td>
<td>(x) Cost of false negatives</td>
<td>$498 339</td>
<td>$106 787</td>
<td>10% of people with TBI who are falsely negative (Calculation viii) will progress to active disease.</td>
</tr>
<tr>
<td>Step 5</td>
<td>(xi) Cost of treating one TBI-positive patient</td>
<td>$77.4</td>
<td>$77.4</td>
<td>TBI treatment is 6 months of isoniazid.</td>
</tr>
<tr>
<td></td>
<td>(xii) Cost of treatment for all positives given positive test</td>
<td>$410 708</td>
<td>$292 571</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(xiii) Cost of treating misdiagnosed TBI-positive patients (ie, false positive patients)</td>
<td>$193 854</td>
<td>$9456</td>
<td></td>
</tr>
<tr>
<td>Step 6</td>
<td>(xiv) Cost of care for all patients tested for TBI</td>
<td>$909 046</td>
<td>$399 358</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(xv) Per-test savings due to treatment and diagnosis</td>
<td>$50.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(xvi) Total difference in cost savings from test use and care</td>
<td>$56.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 7</td>
<td>(xvii) Infrastructure investment threshold</td>
<td></td>
<td>673 IGRA tests</td>
<td></td>
</tr>
</tbody>
</table>

Equations and referenced roman numerals correspond to equations listed in methods section. IGRA, interferon gamma release assay; TB, tuberculosis; TBI, TB infection; TST, tuberculin skin tests.
Policymakers seeking to reduce the costs incurred by TB should consider the factors described in the present model when deciding which test is the best screening tool for their TB programme. If a laboratory is already established, IGRA may present an economic advantage compared with TST. If an investment in equipment must be made to implement IGRA, a laboratory should operate in a catchment area where a greater number of tests can be performed to achieve cost-savings greater than the cost of investment. This may be difficult to achieve in rural settings, whereas urban areas are more likely to meet the conditions of having an established laboratory and having a high burden of TB. Therefore, conditions in rural and low-resource settings necessitate alternate strategies for improving TBI diagnosis, such as point of care diagnostics.

CONCLUSION
Diagnosing and treating TBI remains underprioritised in many high TB burden settings. Although delayed diagnosis and inaccurate diagnostic tools ultimately increase costs for individuals and for society, the cost of investment in laboratory infrastructure and equipment necessary for processing IGRA often disincentivises changes in the status quo where programmes rely on TST for diagnosing TBI. However, the benefits of a more sensitive test can be difficult to quantify in comparison to upfront costs of equipment and ongoing consumable and personnel expenses.

This costing framework is adaptable and practical for guiding decision-making related to optimising programmatic use of TBI diagnostics. Users may input existing and literature-published data related to costs and epidemiologic burden in their own setting, and it is practical such that it requires less time to apply to real-world settings compared with other methods such as a total costing analysis. This tool may assist decision-makers with understanding drivers of cost in their TB programmes and estimating the cost of the consequences of care standards that rely on less-sensitive diagnostics.

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