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Methods Used in Economic Evaluations of Tuberculin Skin Tests and Interferon Gamma Release Assays for the Screening of Latent Tuberculosis Infection: A Systematic Review

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ABSTRACT

Background: Latent tuberculosis infection (LTBI) provides a constant pool of new active tuberculosis cases; a third of the earth's population is estimated to be infected with LTBI. **Objective:** The objective of this systematic review was to assess the quality and summarize the available evidence from published economic evaluations reporting on the cost-effectiveness of tuberculin skin tests (TSTs) compared with interferon gamma release assays (IGRAs) for the screening of LTBI. **Methods:** An extensive systematic review of the published literature was conducted. A two-step process was adopted to identify relevant articles: information was extracted into evidence tables and then analyzed. The quality of the publications was assessed using a 10-item checklist specific for economic evaluations. **Results:** Twenty-eight studies were identified for inclusion in this review. Most of the studies found IGRAs to be more cost-effective than TSTs; however, the conclusions from the studies varied significantly. Most studies scored highly on the checklist although only one fulfilled all the stipulated criteria. A wide variety of methodological approaches were documented; identified differences included the type of economic evaluation and model, time horizon, perspective, and outcomes measures. **Conclusions:** The lack of consistent methods across studies makes it difficult to draw any firm conclusions about the most cost-effective option between TSTs and IGRAs. This problem can be solved by improving the quality of economic evaluation studies in the field of LTBI screening, through adherence to quality checklists.

Keywords: economic evaluations, interferon gamma release assays, screening, systematic review, tuberculin skin tests, tuberculosis.

Introduction

Tuberculosis (TB) is an infectious disease that can be attributed to a single bacillus, *Mycobacterium tuberculosis*. It most commonly affects the lungs (pulmonary TB), although it can affect practically any other site of the human body (extrapulmonary TB) [1]. TB pathogens are released in the air, usually when an infected person with pulmonary TB coughs, spits, or sneezes, and only a few inhaled bacteria are enough to infect a healthy individual [1]. Once infected, a person might develop active disease from exposure to TB bacteria. In most of the infected individuals, however, the disease remains latent [2]. These individuals carry a 10% lifetime risk of TB reactivation. It is possible for progression (reactivation) to occur many years later, when the immune system is more vulnerable; for instance, individuals with comorbidities, especially those needing immunosuppressive medication, are at a higher risk of presenting with active TB [3]. Other high-risk groups include close contacts of active pulmonary TB cases, HIV-positive individuals, individuals with radiographic findings consistent with prior untreated or not adequately treated TB, recent immigrants from high TB-burden countries, cigarette smokers, and drug or alcohol abusers [4]. Patients with latent tuberculosis infection (LTBI) do not have any symptoms and cannot spread the disease.

Two classes of tests used to identify LTBI are currently available: tuberculin skin tests (TSTs) and interferon gamma release assays (IGRAs). Mantoux test, Heaf test, and the Tine test represent some of the TSTs; and T-SPOT.TB, QuantiFERON-TB (QFT), QuantiFERON-TB Gold (QFT-G), and QuantiFERON-TB Gold In-Tube (QFT-GIT) represent the IGRAs. Of these, only T-SPOT.TB and QFT-GIT tests are the currently commercially available IGRA tests.

One of the main differences between the two sets of tests is the way they are conducted; IGRAs are blood-based immunological tests that measure the release of interferon gamma in response to a given antigen, whereas TSTs involve injecting a standardized killed extract of cultured TB into the skin. The type of antigens used to measure the response differs between these tests; some assays measure response to the killed extract of cultured TB, which is called purified protein derivative (TSTs and QFT), whereas other assays measure reaction to antigens such as early secretory antigen target 6 and culture filtrate protein 10 (QFT-G, QFT-GIT, and T-SPOT.TB). The results of screening can be

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positive, negative, or indeterminate. A negative test result after testing with TSTs or IGRAs does not mean that the individual is not infected with TB; further examination is suggested for people at high risk of infection [5]. A positive result should also be further investigated; TSTs and IGRAs cannot differentiate between active and latent TB [6]; therefore, a chest X-ray should be used to exclude active disease before choosing a treatment regimen [7].

For many years, TSTs have been the "criterion standard" in LTBI screening, but there are a few disadvantages associated with this type of tests that led to the development of IGRAs with the aim of replacing TSTs. For example, it has been reported that the specificity and sensitivity of TSTs is affected by a number of factors; false-positive results could be a result of prior Bacillus Calmette-Guerin (BCG) vaccination or a "booster" phenomenon of repeated testing with TSTs (e.g., in health care workers) [8]. Another major disadvantage of TSTs is that the test results are subjectively interpreted (using cutoff points), and thus can lead to incorrect diagnoses. IGRAs, however, are more expensive tests, but are not subject to reader bias in the interpretation of results, results are ready within 24 hours, and the testing requires only one patient visit to draw blood [9]. Most importantly, the results of IGRAs are not affected by prior BCG vaccination and frequent testing.

An economic evaluation seeks to evaluate the differences in costs and effects between two or more interventions [10]. The main types of economic evaluation are the cost-benefit analysis, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-minimization analysis, with the difference between them being the outcome measures used in the analyses. In cost-benefit analysis, both costs and benefits are quantified in monetary terms; in CEA, outcomes are measured in natural or physical units such as lives saved and cases prevented. CUA uses quality-adjusted life-years, whereas in a cost-minimization analysis, the outcomes are assumed to be same and so only differences in costs are considered. Economic evaluations that are CEA or CUA typically adopt an incremental approach in which differences in costs and outcomes between two or more interventions are expressed using an incremental cost-effectiveness ratio.

The validity of the results of an economic evaluation depends on the methodological quality of the analysis, so economic evaluations should be conducted with rigor. A well-defined research question (objectives) and comprehensive description of the interventions under evaluation are required to guide the scope of the analysis, alongside the viewpoint under which the analysis is performed. This can be narrow (insurer/patient perspective) or quite broad (societal perspective) according to whether costs related to society in general (patient/family costs, costs imposed from losses in productivity) are included in the analysis. Sources of inputs (both costs and consequences) should be cited to show their quality and relevance to the topic. For costs, it is preferable if resource use is given separately from the unit prices of resources. In cases in which inputs are calculated, calculations should be provided. Economic evaluations with a time horizon longer than 1 year should allow for the differential timing of costs and consequences with discounting applied as appropriate [11]. Results of economic evaluations are subject to uncertainty, which can be taken into consideration by conducting sensitivity analyses that can focus on the model parameters, assumptions, and structure [11].

Mathematical modeling has become a popular way to evaluate the cost and consequences of health programs. The two main types of models are static models and dynamic models. Dynamic models account for interactions between individuals such as when modeling the disease transmission between susceptible and infected individuals [12]. Static models assume that the probability of disease exposure is constant over time, irrespective of any interventions that target that disease [13]. Given the infectious nature of TB, dynamic models are more appropriate for modeling TB screening strategies [12]. Decision trees and static Markov models cannot account for active disease transmission between individuals.

The objective of this systematic review was to examine economic evaluations focused on testing for LTBI, and specifically those that compare the cost-effectiveness of IGRAs with that of TSTs. This study sought to assess the quality and examine the validity of the methods used in the economic evaluations in this setting, to gain a greater understanding of the parameters used to model the nature of the disease, as well as to examine how the infectious nature of TB has been modeled in economic evaluations where appropriate.

Methods

Inclusion Criteria

Focusing on economic evaluations that consider the cost-effectiveness testing for LTBI, the inclusion/exclusion criteria for the studies considered in this review are described in Table 1.

Search Strategy

Searches were conducted on August 7, 2015, of the following databases: PubMed, EMBASE, Cochrane Library, EconLit, CINAHL,

Table 1 – Inclusion/exclusion criteria.

Population	Inclusion criteria	Target population: individuals screened for LTBI
	Exclusion criteria	Any other population
Intervention/comparators	Inclusion criteria	IGRAs (QFT, QFT-G, QFT-GIT, T-SPOT.TB) compared with TST ± additional strategies (e.g., chest X-ray, no screening)
	Exclusion criteria	Any study that does not compare TSTs with IGRAs
Outcomes	Inclusion criteria	Studies that report an incremental cost-effectiveness ratio (ICER), net benefit, or difference in costs
	Exclusion criteria	Any study that does not report an ICER, net benefit, or difference in costs
Study design and language	Inclusion criteria	Economic evaluations (e.g., CEA, CUA, CBA, and CMA) published in English language with a full-text available
	Exclusion criteria	Any study other than economic evaluations and studies in a non-English language, available in abstract form only, conference abstracts, systematic and narrative reviews

CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis; IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; QFT, QuantiFERON-TB; QFT-G, QuantiFERON-TB Gold; QFT-GIT, QuantiFERON-TB Gold In-Tube; TST, tuberculin skin test.

Table 2 – Abstract screening coding of studies.

Group	Criteria	Action	Notes
A	Economic evaluations focused on IGRAs vs. TST for LTBI screening	Retrieve full text	
B	Economic evaluations focused on the cost-effectiveness of strategies for LTBI screening but unsure whether both IGRAs and TST were evaluated	Retrieve full text	Unsure about intervention/comparator
C	Discussed costs or economic impacts of IGRAs and TSTs for LTBI screening but unsure if economic evaluation	Retrieve full text	Unsure if economic evaluation
D	Systematic review of economic evaluations that report data on the cost-effectiveness of IGRAs and TSTs for LTBI screening	Retrieve full text	Manually search the reference list and then exclude as irrelevant study design
E	Economic evaluation but did not evaluate screening strategies for patients with suspected LTBI	Exclude	Not a population of interest
F	Economic evaluation that evaluates LTBI screening strategies, but does not compare TSTs with IGRAs	Exclude	No intervention/comparator of interest
G	No economic data are reported (costs, cost-effectiveness, and/or cost-utility ratios)	Exclude	No outcomes of interest
H	Not an economic evaluation, or is a narrative review, abstract-only publication, non-English study	Exclude	Not a design of interest/language of interest

IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

and CRD (including NHS-EED, DARE, and HTA) (for search strategies, see Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.11.006). No date limits were used for the search. In addition, the reference lists of systematic reviews identified during abstract screening were manually searched for any further potentially relevant studies that were not identified through database searching.

Selection of Studies

Initial screening by title and abstract against predefined eligibility criteria based on the population, intervention, comparator, outcome, and study design (PICOS) criteria [14] was conducted to exclude references that were irrelevant to the research topic (Table 1). Based on the title and abstract, the references were then categorized into groups listed in Table 2.

Excluded articles and the reasons for their exclusion were documented. After the initial abstract screening, the full text of the articles in groups A to D was retrieved for further scrutiny. Only those that met the inclusion criteria were included in the final review. A data collection spreadsheet was then used to extract relevant information from eligible articles (see Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.11.006).

Assessment of Study Quality

The quality of the included studies was assessed against a list of questions from an adaptation of the Drummond's checklist [15] (see Appendix). A score was assigned to each study on the basis of answers to 10 questions. For each question, M.K. assigned scores of 1.00, 0.50, and 0 to "yes," "cannot tell," and "no," respectively, with an aggregate score obtained for each study [16]. Any uncertainties were resolved through discussions with A. S. and L.D. Thus, each study was scored from a minimum score of 0 (bad quality) to a maximum score of 10 (good quality).

Research Questions

For each article in this systematic review, data extraction was conducted to answer the following research questions:

1. Which patient populations were considered in the analysis?
2. Which screening strategies were evaluated?
3. Modeling approach—What type of model was used? Was the infectious nature of the disease modeled appropriately? Were the consequences of test inaccuracies (i.e., sensitivity and specificity) considered in the analyses? Were uncertainties in data considered (sensitivity analyses)?
4. Model inputs—Which cost categories were used as inputs to the economic evaluation and were they in accordance with the perspective adopted? Was the sensitivity and specificity of tests assumed, calculated, or taken from existing studies? Was prior BCG vaccination included in the analyses?
5. Model outputs—How was the effectiveness of the interventions measured?
6. Conclusion of the studies—Which class of test was found to be more cost-effective?

Results

The indexed database search yielded a total of 276 publications. After filtering (see Fig. 1), 28 eligible articles were identified for this review. A summary of the studies is given in Table 3, with the key characteristics of the studies described in Table 4. Most of the studies focused on screening, with CEA and CUA being equally used as a type of economic evaluation.

Quality Assessment Scores

The score assigned to the studies after the quality assessment phase ranged from 6.5 to 10 (Table 3 and Appendix). Most of the studies had a score above 8 (n = 25), and only one study had a perfect score of 10 (22). The mean quality score was 8.6 across all studies, and standard deviation was 0.77. All but four studies [22–25] did not report resource use and unit costs separately. Only four of the studies did not specify a perspective of the analysis [18,24,25,35].

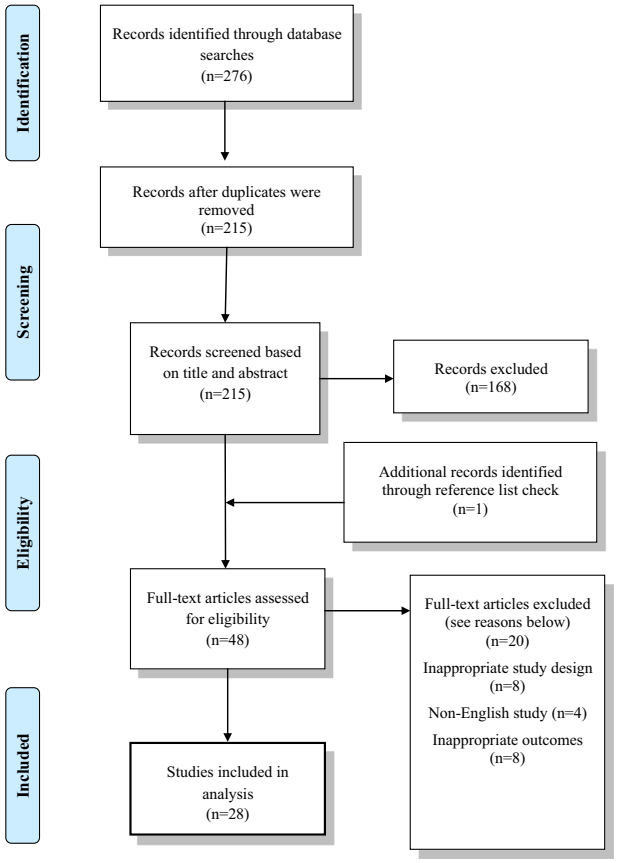

Fig. 1 – Flow diagram of search results.

Modeling Approach

Most of the economic evaluations were model-based studies (n = 26), with the remainder being economic evaluations undertaken alongside observational studies [18,24,25,40]. A combination of a decision tree and a Markov model was used in most of the studies (n = 18), with the testing pathway being modeled using a set of branches on a decision tree, and the outcomes described by Markov cycles at the end of the screening pathway branches. Only a few analyses used decision trees alone (n = 8).

The time horizons of the studies varied significantly; only 10 studies used a lifetime horizon, with the remaining studies using horizons that ranged from 1 year to 30 years. Four did not report a time period over which the costs and benefits were measured [18,25,32,37].

Almost all the studies that used a time horizon longer than 20 years discounted both costs and benefits. In contrast, some studies that used a shorter time horizon of 2 years justified the lack of discounting as being unnecessary due to the short horizon, but then did not vary the discount rate in any subsequent sensitivity analysis [20,21,41,43]. One study discounted costs but did not discount benefits [36]. Two studies that did not report a time horizon for the analysis did not include information about discounting [24,25], and one study did not report information regarding the model's time horizon but discounted both costs and benefits at an annual rate of 3% [32].

Four studies modeled the secondary transmission of TB from infected to susceptible individuals [21,35,38,40]. Marra et al. [38] modeled the costs and effects associated with the secondary spread of TB from patients infected with active TB to healthy individuals. Linas et al. [35] and Pareek et al. [40] only mentioned the probability of secondary transmission of TB without mentioning the costs associated with this scenario. Diel et al. [21] used a dynamic model approach to describe the number of subsequent infections and future TB cases averted by LTBI treatment within the time horizon of the analysis (20 years). Even though the authors called this a dynamic approach, all four articles used a combination of static models, namely, a decision tree and a static Markov model. A number of studies explicitly stated that the secondary transmission of TB was outside the scope of their analyses [17,19,22,36,41].

Model Inputs and Outputs

All the studies included the cost of screening with TST and IGRAs; however, there was heterogeneity in the breakdown of total testing costs. Almost one-third of the studies just mentioned the total cost of the tests, whereas other studies provided a detailed breakdown of cost components (such as the cost of placement/administration and the cost of reading the results for the TST strategy, laboratory costs, screening kit costs, costs of drawing blood, and labor costs of laboratory technicians and phlebotomists for IGRAs). Three studies gave details for the costs of the TST, but no details on the costs of IGRAs were reported [34–36]. Ten studies did not include labor costs in their analyses [19,22–24,36,37,40,41,43,44]. More than half the studies (n = 16) included costs of chest X-ray to rule out active TB [18,19,21–23,27–34,37,42,43].

All but one of the studies [24] included treatment costs of LTBI; another study included only the indirect costs of treatment related to the time lost because of a course of therapy [36]. Drug-related adverse event costs were reported in 21 of these studies, and 3 of the studies explicitly stated that adverse event costs were not included in the analysis [21,22,37]. A variation in the costs regarding treatment for LTBI was observed across the studies. Even though all the studies that reported specific regimen included costs of treatment with isoniazid, the length of therapy varied significantly and ranged from 2-month partial treatment to the full 9-month regimen.

The vast majority of the studies that used a societal perspective included costs related to loss of productivity because of illness/time off work. Transportation costs paid by the patients were included as an indirect cost category in two studies [37,39]. One study stated that both indirect and direct costs were included in the analysis; however, no indirect cost calculations were provided [18].

Seventeen studies considered different sensitivities and specificities of TSTs according to prior BCG vaccination, whereas the remaining studies did not mention details about BCG vaccination and how this might have an impact on the results of the analysis. Five of these studies took into account costs associated with test inaccuracies (costs resulting from false positives and false negatives) [18,21,25,41,44]. The numbers of false-positive and false-negative cases were estimated in all these studies, and in one study it was assumed that false-negative patients had a higher risk of reactivation due to not getting treated for LTBI [44].

Most of the studies used sensitivity and specificity estimates from published meta-analyses, systematic reviews, and prospective clinical studies (n = 22). The meta-analysis of Pai et al. [45] was used in 12 of these studies, whereas several other meta-analyses were used in the remainder [6,32,33,37,46–48]. Meta-analyses from Mandalakas et al. [37] and Santin et al. [47] were used in only one study each. Eight of the studies included estimates from more than one meta-analysis [19,28,30–33,40,42].

Thirteen studies adopted a CUA, whereas for the CEA studies a wide variety of outcome measures were used. Active TB cases prevented and life-years gained were the most commonly used

Table 3 – Summary of included studies.

Author and year	Interventions under examination	Outcome measures	Quality score	Author and year	Interventions under examination	Outcome measures	Quality score
de Perio et al. 2009 [17]	TST alone; QFT-G alone; QFT-GIT alone	QALY	9	del Campo et al. 2012 [18]	TST alone; QFT-G alone; TST followed by QFT-G	Active TB cases prevented, NNT	7
Deuffic-Burban et al. 2010 [19]	TST alone; QFT alone; TST followed by QFT	Life-years gained	9	Diel et al. 2006 [20]	TST alone; QFT alone; TST followed by QFT-G (for close contacts and BCG-vaccinated contacts with a positive TST)	NA	5/7*
Diel et al. 2007 [21]	TST alone using the standard induration cutoff size (>5 mm); QFT-G alone; TST alone with a higher cutoff induration size of >10 mm; TST with a cutoff induration size of >5 mm, followed by a QFT-G assay in all TST-positive individuals	Life- years gained and cases prevented	9	Diel et al. 2007 [22]	TST alone using the Swiss-standard induration cutoff size (≥10 mm); TST alone using an induration cutoff size (≥5 mm); TST alone using an induration cutoff size (≥15 mm); T-SPOT.TB alone; TST with a cutoff induration size of ≥10 mm, followed by a T-SPOT. TB assay in all TST-positive individuals	Life- years gained	10
Diel et al. 2009 [23]	TST alone; QFT alone; TST followed by QFT	Cost per 1000 close contacts	9	Hardy et al. 2010 [24]	CXR followed by TST if CXR is normal, followed by QFT if TST result was positive; QFT followed by CXR if QFT result was positive; Different cutoffs for TST were used	LTBI cases identified	8.5
Iqbal et al. 2014 [25]	TST alone; QFT-G alone	Cost savings	6.5	Kowada et al. 2008 [26]	TST alone; QFT alone; TST followed by QFT in all TST-positive individuals	QALY	9
Kowada 2010 [27]	TST alone; QFT alone	QALY	9	Kowada 2012 [28]	TST followed by CXR; QFT followed by CXR; CXR alone	QALY	9
Kowada 2013 [29]	TST alone; QFT alone; TST followed by QFT; CXR	QALY	9	Kowada 2013 [30]	TST followed by CXR; QFT followed by CXR; CXR alone	QALY	9
Kowada 2014 [31]	TST followed by CXR; TST followed by QFT; TST followed by T-SPOT; QFT followed by CXR; T-SPOT followed by CXR	QALY	9	Kowada et al. 2015 [32]	QFT-GIT alone; T-SPOT alone; TST alone; TST followed by QFT-GIT; TST followed by T-SPOT; CXR	QALY	8.5
Kowada 2015 [33]	QFT alone; T-SPOT alone; QFT + NRT; T-SPOT + NRT; TST alone; TST + NRT	QALY	8	Laskin et al. 2013 [34]	No screening; Questionnaire followed by TST if questionnaire is positive; TST alone; IGRA alone (model did not differentiate between QFT and T-SPOT.TB); Questionnaire followed by IGRA if questionnaire is positive; TST followed by IGRA if TST result is positive	QALY	9
Linas et al. 2011 [35]	IGRAs alone; TST alone; no screening	QALY	9	Mancuso et al. 2011 [36]	No screening; Questionnaire followed by TST if questionnaire is positive; TST alone; IGRA alone (model did not differentiate between QFT and T-SPOT.TB); Questionnaire followed by IGRA if questionnaire is positive; TST followed by IGRA if TST result is positive	Cases of active TB prevented	9
Mandalakas et al. 2013 [37]	TST alone; QFT alone; TST followed by QFT in all TST-positive individuals; TST followed by QFT in all TST-negative individuals; No screening	Life-years saved	8.5	Marra et al. 2008 [38]	TST alone; QFT alone; TST followed by QFT in all TST-positive individuals	QALY	9

continued on next page

Table 3 – *continued*

Author and year	Interventions under examination	Outcome measures	Quality score	Author and year	Interventions under examination	Outcome measures	Quality score
Oxlade et al. 2007 [39]	Immigration entry screening: No screening; CXR; TST followed by CXR; QFT followed by CXR; TST followed by QFT in all TST-positive individuals; Close contact screening: No screening; TST followed by CXR; QFT followed by CXR	Cases prevented	9	Pareek et al. 2013 [40]	CXR followed by: – QFT-GIT – T-SPOT.TB – TST – TST→ QFT-GIT if TST result is positive – TST→ T-SPOT.TB if TST result is positive – CXR alone – Or – No CXR: – QFT-GIT – T-SPOT.TB – TST – TST→ QFT-GIT if TST result is positive – TST→T-SPOT.TB if TST result is positive	Number of active TB cases averted, NNT to prevent one case of active TB	9.5
Pooran et al. 2010 [41]	TST alone; T-SPOT.TB assay alone; QFT-GIT alone; TST followed by T-SPOT.TB assay when TST result was positive; TST followed by QFT-GIT when TST result was positive	Active TB cases prevented, NNT	8	Shah et al. 2012 [42]	TST alone; TST followed by QFT-GIT when TST result was positive; CXR was used to rule out active TB	QALY and expected active TB cases per referral	9
Steffen et al. 2013 [43]	TST followed by CXR if TST result was positive; QFT followed by CXR if QFT result was positive; TST followed by QFT in all TST-positive individuals	Averted new TB cases in 2 y, NNT	8	Swaminath et al. 2013 [44]	TST alone; QFT alone	Reactivation of TB; death from TB reactivation; false-positive test results	8

BCG, Bacillus Calmette-Guerin; CMA, cost-minimization analysis; CXR, chest X-ray; IGRA, interferon gamma release assay; NA, not available/applicable; NNT, number needed to treat; NRT, nicotine replacement therapy; QALY, quality-adjusted life-year; QFT, QuantiFERON-TB; QFT-G, QuantiFERON-TB Gold; QFT-GIT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis; TST, tuberculin skin test.

* Three questions not relevant for CMA; therefore, the quality score is out of 7.

effectiveness measures in CEAs, whereas three studies calculated the number needed to treat [40,41,43].

Conclusions Drawn from the Analyses

The vast majority of the studies concluded that testing for LTBI with IGRAs, either alone or sequentially after a positive TST result, was more cost-effective than a single TST (Table 4). De Perio et al. [17] and Kowada [27] reached the conclusion that IGRAs are more cost-effective than TSTs, both in BCG-vaccinated and in non–BCG-vaccinated populations. In contrast, Marra [38] concluded that the most economically attractive strategy was to administer QFT-G in BCG-vaccinated contacts and TST in non–BCG-vaccinated contacts. Most of the studies that examined the cost-effectiveness of sequential screening of a TST followed by IGRAs in TST-positive individuals concluded that this strategy is more cost-effective than single use of an IGRA, whereas two studies [19,26] found that QFT is more cost-effective than the sequential use of both types of tests. The TST was found to be a better option in only three studies [36,38,43]; in one study [36], the results were very sensitive to changes in the model, and in another [38], this result was relevant to individuals vaccinated with BCG. Oxlade et al. [39] found that screening for LTBI, with either TST or QFT, is cost-effective only if the risk of disease is high and in those cases the most cost-effective use of QFT is to test TST-positive persons. One study found that a no-screening strategy was found to be the most cost-effective option [37].

Discussion

The aim of this review was to identify and systematically review articles of economic evaluations that focus on testing for LTBI using TSTs versus IGRAs. Twenty-eight economic evaluations assessing the cost-effectiveness of TSTs compared with that of IGRAs for the diagnosis of LTBI were included in this review, their quality was assessed, and the study characteristics were synthesized. Most of the studies found IGRAs to be more cost-effective than TSTs; however, the conclusions from the studies varied significantly.

We have shown that in the field of latent TB screening a wide variety of methodological approaches have been used to assess the cost-effectiveness of the two available classes of tests. The observed differences between studies include the type of economic evaluation, time horizon, use of discounting, cost categories included in the analyses, outcome measures, and type of model used. In addition, there are significant differences in the demographic profile of the populations studied. The lack of consistent methods across studies has, in turn, resulted in a lack of clarity regarding the most cost-effective option between TSTs and IGRAs.

The patient populations in the observational and model-based studies included most of the groups usually screened for LTBI. A population of HIV-infected individuals was considered in only one study, even though there is strong evidence connecting the spread of HIV with the increase in the number of cases diagnosed with TB because HIV-positive individuals have a higher risk of contracting TB [1].

Overall, most of the studies were of high quality according to the Drummond checklist [15]; however, a recurring omission was the lack of separate unit prices and resource use for the calculation of costs.

Intervention and comparators varied across studies, and no trend toward the use of either a single test or sequential testing of both TSTs and IGRAs was identified. It is interesting to note that only five studies specified different cutoff points for TSTs [21,22,24,32,40], and, therefore, in most of the studies, the effect of accuracy (or otherwise) of TSTs on the costs and effects/benefits were not estimated.

A wide variety of methods were used in the model-based economic evaluations. Time horizons varied greatly, ranging from 1 year to a lifetime horizon, although in four studies the time horizon was not clearly specified. The use of discounting was omitted in many studies, particularly those with a time horizon of 2 years even though the general recommendation is to use discounting for time horizons longer than 1 year [11]. CEA and CUA were conducted in an equal number of studies (13 studies each), and a similar number of studies used the societal and health care perspectives (13 vs. 12 studies, respectively).

Almost all the studies used modeling techniques. Most used static models, and the vast majority of model-based economic evaluations used a combination of decision trees and static Markov models. It is possible that a static modeling approach was used because of the latent nature of TB because in this state the disease is not infectious. The one-off decision of whether to test was modeled by a decision tree, and the long-term outcomes of the natural history of the disease were modeled by Markov cycles. Only four studies included the probability of the secondary spread of the disease from infected to healthy individuals; however, their choice of a combination of two static models is not appropriate for the modeling of an infectious disease. This is because a static model has a constant rate of infection, and so the impact of the intervention on the transmission of disease cannot be captured using this type of model. Instead a dynamic model should be used because this can better capture this transmission of disease between individuals who are susceptible to disease and those infected. A handful of studies used the number of new active TB cases prevented as the effectiveness measure; however, they did not specify whether this refers to LTBI cases turning into active TB cases, or whether the number of new active TB cases included individuals infected by those people who developed active TB from LTBI.

Overall, it seems that the studies were mostly focused on creating a simple model without accounting for the consequences of latent TB becoming active. If the infectious nature of the TB is modeled, a dynamic model type should be used to model the interactions between individuals that may lead to infection. Independently of whether the infectious nature of the disease is captured in the model, a decision tree is an appropriate way to model a screening pathway; however, this approach cannot account for the long-term outcomes of the disease. Therefore, using Markov cycles as part of an infectious dynamic model at the end of the decision tree branches may be a reasonable approach to capturing the long-terms effects of this disease.

The types of costs and measures of effectiveness varied significantly across the included studies and contributed to the difficulty in identifying common trends across the studies. Almost all the analyses conducted after 2010 used quality-adjusted life-years as the effectiveness measure. It was not always possible to judge whether all the relevant costs associated with both classes of tests were included in the analysis. It seems that the costs associated with adverse events due to LTBI treatment and the costs associated with inaccuracies of the tests were not considered to be of importance in most of the studies and were therefore not included in the analyses. Different sensitivity and specificity estimates were used for groups of people with and without prior BCG vaccination in about one-third of the studies. Because the correlation between prior BCG vaccination and a false-positive TST result is one of the most significant disadvantages of TSTs, the results from the other studies may have unreasonably favored TSTs. A positive finding of this review is that estimates for sensitivity and specificity of tests in most of the studies were derived from published meta-analyses, thus increasing the reliability of the results.

Table 4 – Characteristics of included studies.

Methodology	n	References
Populations*		
Routine screening	17	
Populations with coexisting medical conditions	6	[27,30,31,34,35,44]
Health care workers	3	[17,18,32]
Immigrants	4	[24,35,39,40]
Other populations at high risk of contacting TB	4	[28,29,35,36]
Close contacts	13	[19–23,26,33,35,37–39,41,43]
People with a positive TST result and suspected LTBI	2	[25,42]
Economic evaluation type†		
CMA	1	[20]
CBA	2	[23,25]
CEA	13	[18,19,21,22,24,36,37,39–44]
CUA	13	[17,26–35,38,42]
Study perspective‡		
Health care perspective	12	[19,20,31–33,37,38,40–44]
Societal perspective	13	[17,21–23,26–30,34,36,37,39]
Not reported/not clear	4	[18,24,25,35]
Study design§		
Model-based	26	
Markov state-transition decision-analytic model	18	[17,19,21,22,26–39]
Decision tree	8	[18,20,23,40–44]
Observational study	4	[18,24,25,40]
Sensitivity analysis		
Conducted	27	
Univariate	26	[17–24,26–41,43,44]
Multivariate	13	[20,22,23,27–30,35,36,38,40,42,43]
Probabilistic	12	[17,23,26–34,42]
Scenario analysis	2	[38,42]
Threshold analysis	2	[21,23]
Not conducted	1	[25]
Study conclusion‖		
IGRA favorable	17	[17,19,22–33,35,38,44]
TST favorable	3	[36,38,43]
IGRA after positive TST result favorable	7	[18,20–22,39,41,42]
Inconclusive	3	[34,37,40]

BCG, Bacillus Calmette-Guerin; CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis; IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; QFT-G, QuantiFERON-TB Gold; TB, tuberculosis; TST, tuberculin skin test.

* One study examined both close contacts of people with TB and people routinely screened for TB (immigrants) [39], and one study examined four groups (close contacts of people with TB, people with medical comorbidities, immigrants, and vulnerable populations) [35].

† One study performed both CUA and CEA [42].

‡ One study used both societal and health care perspective for the analysis [37].

§ Two studies were economic evaluations alongside observational studies (both used decision trees) [18,40].

‖ In one study, QFT-G was more cost-effective in BCG-vaccinated contacts and TST was more cost-effective in non–BCG-vaccinated contacts [38], and one study concluded that using T-SPOT.TB alone or in combination with TST for screening of close contacts is highly cost-effective [22].

The methodological differences across the studies resulted in an inconsistency in the conclusions drawn from the studies, making it unclear whether TSTs, IGRAs, or a combination of both tests is the most cost-effective strategy for LTBI screening. The inclusion of costs and outcomes associated with the secondary transmission of disease and test inaccuracies could have affected the results of the analyses; however, there is such variability in the rest of the methods that it is impossible to draw conclusions about the magnitude of this impact. Each methodological aspect contributed to the cost-effectiveness estimates, and it is not possible to isolate the impact size in studies that are not comparable. Although interestingly, all three studies that found TSTs to be more cost-effective compared with IGRAs did not include costs and outcomes incurred because of test inaccuracies. This observation, however, does not mean that cost-effectiveness ratios were affected only by this parameter, and the difference could be attributed to many other methodological variations including the definition of the patient cohorts and differences in setting (i.e., country) within each individual study.

Strengths and Limitations

A particular strength of this review is its methodological rigor. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used to guide the systematic methods, and a comprehensive search of six electronic databases was conducted. Bibliographies of systematic reviews were also

searched manually although gray literature sources were not considered.

One potential limitation of the review is that the quality of the economic evaluations was assessed using Drummond's and Jefferson's 10-item checklist [15]. Other checklists exist, some of which are perhaps more detailed and comprehensive than the Drummond checklist, for example, Philips et al. [49]. The Drummond checklist, however, is accepted as a standard document for the assessment of quality and indeed forms the basis for the checklist for the submission of economic evaluations to the *British Medical Journal*.

Conclusions

This review has shown a wide variability in the approaches used in the economic evaluation of LTBI screening. The lack of consistent methods across studies has resulted in a lack of clarity regarding the most cost-effective option between TSTs and IGRAs; the results of studies cannot be compared and an overall conclusion cannot be drawn because of differences in almost all aspects of the economic evaluations. There is a need to harmonize the methods and improve the quality of economic evaluation studies in the field of LTBI screening. This can include correct reporting of resource use and costs, consideration of the impact of test inaccuracies, and the utilization of a dynamic model if the intervention may have an impact on the onward transmission of disease. The application of a quality checklist can ensure that many of the key issues in an economic evaluation are incorporated and described in the analysis.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2015.11.006 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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