VALUE IN HEALTH ▮ (2016) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

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

Maria Koufopoulou, MSc, Andrew John Sutton, PhD, Katie Breheny, MSc, Lavanya Diwakar, FRCPath (Imm)*

Health Economics Unit, University of Birmingham, Birmingham, United Kingdom

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

* *Address correspondence to:* Leeds Institute of Health Sciences, Charles Thackrah Building, University of Leeds, 101 Clarendon Rd, LEEDS LS2 9LJ.

E-mail: a.j.sutton@leeds.ac.uk.

1098-3015$36.00 – see front matter © 2016 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

http://dx.doi.org/10.1016/j.jval.2015.11.006

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.