Tuberculosis Clinical Guideline commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence: Additional analyses for tuberculosis guideline development group meeting – 20/07/2015

Title of project

Accurate diagnosis of latent Tuberculosis in children, in people who are immunocompromised or at risk from immunosuppression, and recent arrivals from countries with a high incidence of Tuberculosis: systematic review and economic evaluation

Name of External Assessment Group (EAG) and project lead

Produced by: Warwick Evidence

Lead author: Peter Auguste[1]

Co-authors: Alexander Tsertsvadze[2]
Joshua Pink[1]
Rachel Court[1]
Farah Seedat[1]
Tara Gurung[1]
Karoline Freeman[1]
Sian Taylor-Phillips[1]
Clare Walker[1]
Jason Madan[3]
Ngianga-Bakwin Kandala[1]
Aileen Clarke[1]
Paul Sutcliffe[1]

[1] Warwick Evidence, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

[2] Evidence in Communicable Disease Epidemiology and Control, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK

[3] Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK

Correspondence to: Dr Paul Sutcliffe
Deputy Director for Warwick Evidence
Populations, Evidence and Technologies
Division of Health Sciences
Warwick Medical School
University of Warwick
Coventry CV4 7AL
Tel: 02476 150189
Email: p.a.sutcliffe@warwick.ac.uk
Date completed: 31 July 2015

Source of funding:
This report was commissioned by the NIHR HTA Programme as project number 13/178/01.

Ngianga-Bakwin Kandala and Aileen Clarke are also supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care West Midlands at University Hospitals Birmingham NHS Foundation Trust

Declared competing interests of authors:
Aileen Clarke is Professor of Public Health & Health Services Research, Warwick Medical School, University of Warwick, UK and is a member of the NIHR HTA and EME Editorial board.

Rider on responsibility for report:
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
TBC

1. Risks associated with hepatotoxicity

Since the use of a high sensitivity, low specificity strategy for diagnosing LTBI (as suggested by the economic models presented to the GDG) will inevitably lead to an increased proportion of people being over-treated (i.e. treated for LTBI infection when none is present), this has the potential to generate increased risks of mortality for people who do not stand to benefit from treatment. Warwick was asked to perform additional analyses, looking specifically at the trade-off in mortality risks between active TB and LTBI-treatment induced hepatotoxicity when moving from a high sensitivity/low specificity strategy to a low sensitivity/high specificity one.

Since, based on information provided by our clinical advisors, children were assumed not be at risk of developing LTBI-treatment induced hepatotoxicity, these analyses were restricted to the immunocompromised and recent arrival populations. The mortality risks of the following strategies were compared in each case:

Recent arrivals

Strategy 1: TST (5mm) alone – High sensitivity and low specificity

Strategy 2: TST (5mm) and IGRA with treatment if both tests are positive – Low sensitivity and high specificity

Immunocompromised

Strategy 1: TST (5mm) and IGRA with treatment if either test is positive – High sensitivity and low specificity

Strategy 2: TST (5mm) and IGRA with treatment if both tests are positive – Low sensitivity and high specificity

Results

On average, for each 1 death from hepatitis prevented by moving from a high sensitivity/low specificity strategy to a high specificity/low sensitivity one, an additional 6.3 deaths from active TB occur in the initial population (secondary TB cases were not considered in this analysis).

There are four important caveats that must be borne in mind when interpreting these results. Specifically:

1) The numbers generated are dependent on the underlying prevalence of LTBI in the population. In a population with a lower prevalence than those considered in these analyses, a higher specificity strategy will become more important.
2) These analyses only consider the mortality impacts of active TB and hepatitis. The morbidity and cost implications are not considered here, although they are included in the results from the main model considered by the GDG.

3) These analyses all use the assumption that the treatment for LTBI would be 6 months of isoniazid. The use of a different treatment strategy (specifically one with higher toxicity), would lead to different results.
4) The ratio of 6.3/1 is only the ratio from moving between different test strategies, once a decision to treat those who test positive has been made. It does not represent the mortality ratio from choosing to treat people for LTBI as opposed to not treat, which could be very different (in either direction).

2. Additional sensitivity analyses requested

In the comments received during the consultation process, two particular parameters in the cost-effectiveness model were mentioned by a number of stakeholders. The first was that proportion of people returning to have their TST read could be unrealistically high. The number used in the model is similar to those which have been used in previous analyses (including that in CG117), and no stakeholder was able to provide an alternative robust data source to estimate a different parameter value (references were made to ongoing trials, but no data are yet available). Nevertheless, an additional set of sensitivity analyses were undertaken, looking at the impact of lowering the proportions of people who have their TST read.

The second parameter commented on was the cost of the diagnostic tests, with people concerned IGRAs could have been costed too high, and TSTs too low. Some of the numbers suggested during the consultation for the cost of IGRAs only appeared to include the cost of the test itself, and so were unsurprisingly lower than the cost included in the model, which also included other elements such as staff time to administer the test an deliver results. Once again, an additional set of sensitivity analyses were undertaken, looking at the impact on cost-effectiveness of using a lower cost for IGRAs and a higher cost for TSTs.

Results: immunocompromised population

The following changes were made to the base-case model:

- Lowering the TST return rate to 75%
- Reducing the cost of IGRAs to £29
- Increasing the cost of TSTs to £29

After these modifications, the IGRA followed by TST strategy remains the most cost-effective option, followed by an IGRA alone. These are identical results to those produced by the base case model. Whilst reducing the TST return rate means this strategy is less effective than in the base case, the use of both tests to obtain the maximum possible sensitivity remains the most cost-effective option.

Results: child population

The following changes were made to the base-case model:

- Reducing the cost of IGRAs to £29
- Increasing the cost of TSTs to £29

After these modifications, the TST followed by IGRA strategy remains the most cost-effective option, followed by an IGRA alone. In the original model the TST alone was the second most cost-effective strategy, but the decrease in test costs of IGRAs means this is no longer the case.

A range of different probabilities of having the TST read were tested. From these results, it was found that if the probability of having the TST read drops below 88%, it becomes more cost-effective to have an IGRA test first, followed by the TST, as the effective sensitivity of the IGRA (Combining test sensitivity and probability of getting results) is now higher. Nevertheless, the strategy of using both tests remains the most cost-effective in both scenarios.

Results: recent arrivals

The following changes were made to the base-case model:

- Reducing the cost of IGRAs to £29
- Increasing the cost of TSTs to £29

After these modifications, the TST (5mm) alone strategy remains the most cost-effective option in line with the original model. If the probability of having a TST read drops below 76%, an IGRA alone becomes the most cost-effective strategy instead.