

# Accurate diagnosis of latent tuberculosis in children, 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

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## Scientific summary

### **Accurate diagnosis of latent tuberculosis in three population groups**

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# Scientific summary

## Background

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The timely identification and prophylactic treatment of people with latent tuberculosis infection (LTBI) is of public health and clinical importance. Unfortunately, there is no diagnostic gold standard for identification of LTBI. Instead, the available screening tests provide indirect and imperfect information. There are two types of tests in use in the UK: (1) the tuberculin skin test (TST), read at two levels (5 mm and 10 mm) and (2) the interferon gamma release assays (IGRAs).

In this review we updated a previous clinical guideline (CG) [National Collaborating Centre for Chronic Conditions, Centre for Clinical Practice at the National Institute for Health and Care Excellence. *Tuberculosis: Clinical Diagnosis and Management of Tuberculosis, and Measures for its Prevention and Control*. CG117. London: NICE; 2011. URL: [www.ncbi.nlm.nih.gov/books/NBK97852/](http://www.ncbi.nlm.nih.gov/books/NBK97852/) (accessed 27 February 2014)] and investigated the clinical effectiveness and cost-effectiveness of screening tests (IGRAs and TST) in LTBI diagnosis in three population groups: children, immunocompromised people and those who have recently arrived in the UK from high-incidence countries. All of these groups are at higher risk of progression from LTBI to active TB.

This review addressed the following questions:

1. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in children?
2. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in people who are immunocompromised?
3. Which diagnostic strategy is most clinically effective and cost-effective in accurately identifying latent TB in people who are recent arrivals from countries with a high incidence of TB?

## Methods

### *Clinical effectiveness*

#### Search strategy

Search strategies included the following main elements: (1) search of electronic bibliographic databases (including MEDLINE, EMBASE, The Cochrane Library, the Science Citation Index and Conference Proceedings Citation Index, Health Economic Evaluations Database) (updated on 2 December 2014); (2) contact with experts in the field; (3) scrutiny of references of included studies and systematic reviews; and (4) screening of manufacturers' and other relevant websites.

#### Study eligibility criteria

English-language studies evaluating and comparing the effectiveness of commercially available tests used for identifying people with LTBI were eligible for inclusion in the review.

### Populations

- Children (both sexes, aged < 18 years, immunocompetent).
- Those who are immunocompromised or at risk of immunosuppression [both sexes, any age, transplant recipients, human immunodeficiency virus (HIV) infection, renal disease, haematological disease, autoimmune disease, recipients of antitumour necrosis factor alpha treatment, steroids or ciclosporins].
- People recently arrived from regions with a high incidence/prevalence of TB (both sexes, any age, immunocompetent, areas with an estimated incidence of  $\geq 40$  per 100,000).

### Interventions

Two IGRAs:

- QuantiFERON®-TB Gold-in-Tube (QFT-GIT) [old version QuantiFERON®-TB Gold (QFT-G)] (Cellestis/Qiagen, Carnegie, VA, Australia)
- T-SPOT.TB (Oxford Immunotec, Abingdon, UK).

### Comparator

- TST 5 mm or 10 mm (Mantoux test) alone or plus IGRA (one- or two-step testing).

### Outcomes

Associations between test results and validity constructs for LTBI:

- progression to active TB
- previous exposure to *Mycobacterium tuberculosis* [(Zopf 1883) Lehmann and Neumann 1896] (MTB; defined by proximity, duration, geographical location or dose–response gradient)
- people at low risk of MTB infection or healthy populations.

### Studies

- Randomised controlled trials and retrospective or prospective cohort studies.
- Cross-sectional or case–control studies.

### Economics

- Decision-analytic models investigating cost-effectiveness.
- Cost studies.

### Exclusions

- Studies using test results as proxies for LTBI.
- Non-commercial/in-house IGRAs, first-generation QFT or tests unavailable in the UK.
- Studies reporting only between-test agreement.

### Study selection, data extraction and quality assessment

Two independent reviewers screened all identified records. Disagreements were resolved by discussion and recourse to a third reviewer.

Similarly, relevant data were extracted independently and disagreements were resolved by recourse to a third reviewer. For each test, summary parameters (e.g. sensitivity, specificity, diagnostic odds ratios, cumulative incidence ratios, per cent concordance, kappa statistic) with corresponding measures of variability [95% confidence intervals (CIs), *p*-value] were extracted or calculated (e.g. using construct validity categories of exposure levels or progression to active TB, when data permitted).

Risk of bias and methodological quality were also assessed independently using the Quality in Prognosis Studies tool and a modified tool by Dinnes *et al.* [Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al.* A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess* 2007;**11**(3)] for incidence and exposure studies and the Consolidated Health Economic Evaluation Reporting Standards and Philips *et al.*'s checklists for economics studies [Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36)].

### Data synthesis and analysis

Predictive values for IGRAs and TST for progression to active TB (incidence studies), the degree of association of IGRA and TST results with previous exposure to MTB (defined by proximity, duration or dose–response gradient) and the specificity of IGRAs and TST in healthy populations were assessed. We measured concordance/discordance between IGRAs and TST.

Summary effectiveness measures were pooled using a random-effects model. Heterogeneity was determined visually and by the  $I^2$  statistic and chi-squared test (two tailed,  $p \leq 0.10$ ). Subgroup analyses (by TST threshold, IGRA type, setting, TB burden and clinical condition) were undertaken to explore heterogeneity. Calculations were performed with Meta-DiSc version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) and Stata version 14 (StataCorp LP, College Station, TX, USA).

### Cost-effectiveness

A de novo model structured in two stages (decision tree for LTBI diagnosis and infectious disease model) was developed in R (version 3.1.1; The R Foundation for Statistical Computing, Vienna, Austria) to compare the cost-effectiveness of diagnostic strategies. The first stage included pathways following testing for 1 year before entering the second stage – an infectious disease model. Four diagnostic strategies were examined for each population:

- TST alone
- IGRA alone
- combinations of sequential TST and IGRA
- simultaneous testing.

For the infectious disease stage the following states were modelled:

- active TB
- LTBI – treated for LTBI
- LTBI – untreated
- no TB/LTBI – treated for LTBI
- no TB/LTBI – untreated.

Information required to parameterise the model included prevalence, sensitivity and specificity, adverse events, resource use, and costs and utilities. We used clinical information from the review. We used Bayesian Markov chain Monte Carlo methods to estimate study prevalence and test performance, accounting for the underlying prevalence in each of the studies in the evidence base. We then made a further assumption about the relationship between prevalence in the studies and that in the decision population. In the models, we used QFT-GIT results as the base-case values for the analysis.

Resource use and costs were obtained from the cost-effectiveness review, NHS reference costs 2012/13, the NHS drug tariffs and clinical experts. Costs were adjusted to 2012/13 prices. The simulation was run for 100 years with a 3.5% discount rate and from a NHS and Personal Social Services perspective. A utility decrement of 0.15 was applied to Health Survey for England values for people who received treatment for active TB.

Outcomes were expressed as incremental cost-effectiveness ratios (ICERs) for cost per quality-adjusted life-year (QALY) and cost per diagnostic error avoided. Univariate and probabilistic sensitivity analyses were undertaken.

## Results

### *Clinical effectiveness*

We identified 6687 records. After removing duplicates, 3757 records were screened, of which 54 (53 unique studies) were included. We included 37 additional studies from CG117.

The majority of included studies compared the strength of association between QFT-GIT/G IGRA and TST (5 mm or 10 mm) in relation to the incidence of active TB or previous TB exposure (e.g. proximity to, relationship with an active case or weighted contact score). Seven of the 15 incidence group studies had a high risk of bias, six had a moderate risk of bias and two had a low risk of bias. Twenty-nine of the 38 exposure studies were of lower quality.

### Children

The results of the 27 studies were:

- Incidence studies:
  - TST 5 mm: there was no difference between TST 5 mm and QFT-GIT [two studies; pooled ratio of cumulative incidence ratios (R-CIR) 1.12, 95% CI 0.72 to 1.75].
  - TST 10 mm: QFT-GIT was better than TST 10 mm (three studies; pooled R-CIR 4.33, 95% CI 1.32 to 14.23).
- Sensitivity and specificity:
  - TST 5 mm: IGRA (QFT-GIT/G) had similar sensitivity (48–100% vs. 57–100%) to and slightly better specificity (49–90% vs. 45–65%) than TST 5 mm.
  - TST 10 mm: IGRA had a higher sensitivity (48–100% vs. 30–56%) and a slightly lower specificity (49–90% vs. 63–93%) than TST 10 mm.
- Exposure studies: IGRA performed better than TST 5 mm/10 mm in 14 studies [pooled ratio of diagnostic odds ratios (R-DOR) 1.98, 95% CI 1.19 to 3.28;  $I^2 = 89\%$ ].
- Subgroup analyses (stratified by TB burden setting):
  - In low TB burden settings IGRAs were superior to TST 5 mm/10 mm (six studies; pooled R-DOR 4.74, 95% CI 2.15 to 10.44).
  - In high TB burden settings there was no difference between the tests (eight studies; pooled R-DOR 1.13, 95% CI 0.78 to 1.65).

### Immunocompromised people

The 48 studies were stratified into those including participants with HIV infection, solid organ transplantation, post-kidney transplantation, haemodialysis (end-stage renal disease), immune-mediated inflammatory diseases before antitumour necrosis factor alpha (TNF- $\alpha$ ) therapy, hepatitis C and lupus erythematosus. The results of the studies were as follows:

- Incidence studies: in the two studies reporting data, R-CIR estimates were non-significant with wide 95% CIs.
- Exposure studies:
  - IGRAs performed better than TST 5 mm/10 mm in people with:
    - haemodialysis (four studies; pooled R-DOR 2.53, 95% CI 1.48 to 4.34)
    - hepatitis C (one study; R-DOR 8.45, 95% CI 3.71 to 19.24).
  - TST 10 mm performed significantly better than QFT-GIT for people with HIV/acquired immunodeficiency syndrome (AIDS) (two studies; pooled R-DOR 0.35, 95% CI 0.15 to 0.83).
- Subgroup analysis (stratified by condition): R-DOR estimates were non-significant/inconclusive with wide 95% CIs in:
  - people with lupus erythematosus
  - people with immune-mediated inflammatory diseases before antiTNF- $\alpha$  therapy
  - solid organ transplantation candidates
  - kidney transplant recipients.

### Recent arrivals from countries with a high incidence of tuberculosis

The results of the 15 studies were:

- Incidence studies:
  - There was no significant difference between TST 5 mm/10 mm and QFT-GIT (two studies; pooled R-CIR 1.57, 95% CI 0.52 to 4.76).
  - There was no significant difference between TST 10 mm and T.SPOT.TB (one study; R-CIR 0.37, 95% CI 0.10 to 1.41).
- Exposure studies: there was no significant difference between TST 10 mm and QFT-GIT (three studies; pooled R-DOR 0.96, 95% CI 0.69 to 1.33).

### Cost-effectiveness

Ten relevant studies were identified and all performed well against frameworks for best practice for reporting economic evaluations.

Bayesian meta-analysis of relevant studies gave the following values with 95% credible intervals for use in the models:

- in children:
  - TST ( $\geq 5$  mm): sensitivity 72.80% (60.59% to 72.94%); specificity 49.03% (47.96% to 50.08%)
  - TST ( $\geq 10$  mm): sensitivity 53.51% (38.21% to 67.69%); specificity 74.81% (34.34% to 76.18%)
  - QFT-GIT: sensitivity 68.84% (58.56% to 78.20%); specificity 61.03% (60.30% to 61.76%)
  - T-SPOT.TB: sensitivity 50.00% (2.45% to 97.64%); specificity 77.58% (67.38% to 86.40%).

- In immunocompromised people:
  - TST ( $\geq 5$  mm): sensitivity 32.42% (11.19% to 58.48%); specificity 74.22% (72.88% to 75.57%)
  - TST ( $\geq 10$  mm): sensitivity 16.82% (2.52% to 38.99%); specificity 83.97% (78.99% to 88.31%)
  - QFT-GIT: sensitivity 55.48% (24.73% to 83.73%); specificity 82.27% (80.52% to 83.96%)
  - T-SPOT.*TB*: sensitivity 66.65% (35.17% to 91.44%); specificity 68.46% (63.46% to 73.37%).
- In recently arrived populations:
  - TST ( $\geq 5$  mm): sensitivity 93.56% (77.86% to 99.77%); specificity 50.11% (47.90% to 52.29%)
  - QFT-GIT: sensitivity 59.15% (35.84% to 81.42%); specificity 79.29% (77.80% to 80.73%)
  - T-SPOT.*TB*: sensitivity 70.01% (39.78% to 92.42%); specificity 39.92% (34.39% to 45.54%).

### Model outputs: incremental cost-effectiveness ratios – cost per quality-adjusted life-year and cost per diagnostic error avoided

- In children:
  - TST ( $\geq 5$  mm) negative followed by QFT-GIT was the most cost-effective strategy with an ICER of £18,900 per QALY gained.
  - T-SPOT.*TB* was the most cost-effective strategy with an ICER of approximately £2700 per diagnostic error avoided compared with TST ( $\geq 10$  mm).
- In immunocompromised people:
  - QFT-GIT negative followed by TST ( $\geq 5$  mm) was the most cost-effective strategy with an ICER of approximately £18,700 per QALY gained.
  - QFT-GIT positive followed by TST ( $\geq 5$  mm) was the most cost-effective strategy with an ICER of approximately £300 per diagnostic error avoided compared with TST ( $\geq 10$  mm).
- In the recently arrived population:
  - TST ( $\geq 5$  mm) alone was the most cost-effective strategy with an ICER of approximately £1500 per QALY gained compared with QFT-GIT.
  - TST ( $\geq 5$  mm) positive followed by QFT-GIT was the most cost-effective strategy with an ICER of approximately £700 per diagnostic error avoided compared with QFT-GIT alone.

## Discussion

### Summary of results

In children the limited evidence suggested that TST 5 mm was the best test for predicting LTBI. TST ( $\geq 5$  mm) negative followed by QFT-GIT was the most cost-effective strategy.

Interferon gamma release assays appeared to outperform TST in low TB burden settings but not high TB burden settings, a finding that is consistent with a growing body of evidence showing reduced sensitivity and specificity of IGRAs in high TB burden settings. This type of effect modification could be explained by higher frequency of exposure to MTB, different transmission dynamics, malnutrition, comorbidity, coinfection with HIV or helminthic infection.

For immunocompromised people most of the evidence was insufficient and inconsistent. There was large variation in the performance of IGRAs compared with TST across different clinical subgroups. QFT-GIT and T-SPOT.TB performed better than TST 5 mm/10 mm in those undergoing haemodialysis and those with hepatitis C. In contrast, QFT-GIT performed significantly worse than TST 10 mm in people with HIV/AIDS. This observation could potentially be explained by T-lymphocyte depletion. For other clinical subgroups of immunocompromised people the evidence was inconclusive because of the high level of uncertainty around the statistically non-significant effect estimates. The QFT-GIT negative followed by TST ( $\geq 5$  mm) strategy was the most cost-effective in this group with an ICER of approximately £18,700 per QALY.

Among recently arrived people from countries with a high TB burden, there was no significant difference between the performance of IGRAs and the performance of TST in identifying LTBI. The TST ( $\geq 5$  mm) alone strategy was the most cost-effective with an ICER of approximately £1500 per QALY.

### Strengths and limitations

The findings of this review warrant a cautious interpretation. The evidence was inconclusive, in large part because of unexplained heterogeneity, poor reporting, missing data and great uncertainty around the effect estimates for the association between test results and the constructs of validity for LTBI. With no 'gold standard' and an inadequate definition of construct validity for LTBI (e.g. definitions of previous exposure may not represent the true presence of LTBI), exposure misclassification was probably an important issue.

Other factors that may have contributed to this variability are study setting, type of population, type of test, previous bacillus Calmette–Guérin (BCG) vaccination and the limitations of screening tests (inter-/intra-rater variability in the interpretation of test results, boosting, conversion, reversion, different cut-offs for test positivity, assay manufacturing, pre-analytical processing and/or incubation delay). Apart from these issues, various sources of methodological bias may have independently distorted the review findings. For example, the study findings may have been biased because of a lack of blinding, selection bias, partial verification bias because of incomplete outcome data assessment and incorporation bias.

The strengths of the cost-effectiveness assessment include the building of a de novo two-stage model and the use of the review findings (coupled with Bayesian meta-analysis) to derive summary estimates of diagnostic accuracy, although we did not adjust for BCG status because of a lack of data. A number of assumptions were made, including that the TST was costed similarly for those that were read and those that were not read. Resource use was estimated with input from our clinical advisors.

### Implications

The findings should be viewed by clinicians and policy makers cautiously because of the limited evidence, the lack of a gold standard diagnostic test and the assumptions made. Clinicians should be mindful of the variation in performance of the different testing strategies among different populations.

### Research priorities

- The inconsistent performance of IGRAs in high- and low-TB settings should be investigated to see whether or not it is replicable.
- Prospective studies are needed for people at high risk of TB to assess progression to active TB.
- The relative benefits of two-step testing with different combinations of IGRAs and TST compared with single-step testing should be investigated.
- For retrospective or cross-sectional studies a standard set of component exposures to aid classification into high and low risk for LTBI is needed, alongside identification of more accurate markers of LTBI.

## Study registration

This study is registered as PROSPERO CRD42014009033.

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