Two interferon gamma release assays for predicting active tuberculosis: the UK PREDICT TB prognostic test study

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Scientific summary

Interferon gamma release assays for predicting active tuberculosis

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Background

Although there has been a decline in the incidence of tuberculosis (TB) in the UK over the past few years, rates remain higher than in most Western European countries. This study has investigated the predictive values and cost-effectiveness of different combinations of the tuberculin skin test (TST) and two interferon gamma release assays (IGRAs) in contacts (of people with TB) and new entrants to the UK.

Objectives

1. To assess the prognostic value of the two current IGRAs compared with the standard Mantoux test for predicting active TB among untreated individuals at increased risk of latent TB infection (LTBI), among contacts of active TB cases and among new entrants to the UK from high-TB-burden countries.
2. To assess the cost-effectiveness of various screening strategies [including the two-step approach recommended by the National Institute for Health and Care Excellence (NICE)] using IGRAs and/or TST in defined patient groups (contacts and new entrants to the UK stratified by age and risk).

Methods

A prospective cohort design was used to investigate the predictive value of the two commercial IGRAs and the tuberculin Mantoux skin test. Participants were recruited in TB clinics, general practices and community settings. Contacts of active TB cases, migrants who were born in high-TB-burden countries but had arrived in the UK within the previous 5 years or those who had travelled frequently in the previous 5 years were eligible to take part if they were aged $\geq$ 16 years. Outcomes include incidence rate ratios comparing the incidence of active TB in those with a positive test result compared with those with a negative result for each assay and combination of assays, positive and negative predictive values and cost per quality-adjusted life-year (QALY) for each screening strategy.

Results

The study recruited 10,045 participants between May 2010 and July 2015. A total of 175 participants had active TB at baseline (diagnosed or treated < 21 days after being recruited) and another 260 were treated for LTBI, leaving 9610 evaluable participants, of whom 97 (1.0%) developed active TB. For the primary analyses, data for the 6386 participants with all test data (including 77 participants who developed active TB) were used.

A positive result for TST^{a} (a skin induration of $\geq$ 5 mm) was a significantly poorer predictor of progression to active TB than positive results for all other tests. Compared with TST^{b} alone [positive if (1) there is a skin induration of $\geq$ 6 mm following the standard TST and the participant was not known to have had a bacillus Calmette–Guérin (BCG) vaccination or (2) there is a skin induration of $\geq$ 15 mm for those known to have had a BCG vaccination], T-SPOT®.TB (Oxford Immunotec Ltd, Oxford, UK), TST^{a} + T-SPOT.TB, TST^{a} + IGRA and the three combination strategies including TST^{b} were significantly superior predictors of progression. Compared with the T-SPOT.TB test alone, TST^{a} + T-SPOT.TB, TST^{b} + QuantiFERON® TB Gold In-Tube (QFT-GIT; Cellestis International Pty Ltd, Chadstone, VIC, Australia) and TST^{b} + IGRA were significantly superior predictors of progression and, compared with QFT-GIT alone, T-SPOT.TB, TST^{a} + T-SPOT.TB, TST^{a} + QFT-GIT, TST^{a} + IGRA, TST^{b} + T-SPOT.TB, TST^{b} + QFT-GIT and TST^{b} + IGRA were significantly superior predictors of progression.

When evaluating the negative predictive performance of tests and strategies, negative results for TST[a] + QFT-GIT were significantly poorer predictors of non-progression than negative results for TST[a], T-SPOT.TB and TST[a] + IGRA. Negative results for TST[b] + QFT-GIT were significantly poorer predictors of non-progression than negative results for TST[a], TST[b], T-SPOT.TB, TST[a] + T-SPOT.TB, TST[a] + IGRA, TST[b] + T-SPOT.TB and TST[b] + IGRA, which all performed better.

The most cost-effective LTBI testing strategy is TST[b] + QFT-GIT. However, the estimated cost and QALY differences between the LTBI testing strategies were small, in particular QFT-GIT, TST[b] + T-SPOT.TB and TST[b] + QFT-GIT gave very similar incremental net benefit estimates.

Conclusion

This study investigated the optimal screening strategy for LTBI, based on existing technologies. It did not find evidence that any particular test or combination of tests was superior to other approaches in identifying individuals who would go on to develop active TB. However, a two-step approach that combined TST[b] with an IGRA was the most cost-effective testing option.

Implications for health care

The current recommendation by NICE for contacts is to offer the Mantoux test using a 5-mm threshold (the more cost-effective option), and consider IGRAs if TST is not available. Our results demonstrate that a two-step process using the more nuanced TST[b] strategy, which stratified the TST by prior BCG vaccination, followed by an IGRA, was the most cost-effective approach.

Implications for future research

Further research to develop new markers with better predictive ability utilising transcriptomics, new antigens and cytokines, metabolomics and proteomics is ongoing. Ongoing work with the Prognostic Evaluation of Diagnostic IGRAs ConsorTium (PREDICT) biobank is likely to result in better biomarkers for progression and the development of new assays. The cost-effectiveness of these new assays, using progression data from this study, should be assessed.

The limited ability of current tests to predict who will progress to active TB limits the utility of latent TB detection and treatment. The widespread treatment of groups who may have a positive IGRA or TST result is unlikely to be cost-effective; the most cost-effective delivery of treatment is likely to be focused on the highest-risk groups. Further research should investigate the implications of these results on the NHS England/ Public Health England national TB screening programme for migrants from high-TB-burden countries.

Study registration

This study is registered as NCT01162265.

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