

# Cost-effectiveness of the NICE guidelines for screening for latent tuberculosis infection: the QuantiFERON-TB Gold IGRA alone is more cost-effective for immigrants from high burden countries

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## ABSTRACT

NICE (National Institute for Health and Clinical Excellence) guidelines for new entrant tuberculosis (TB) screening recommend chest x ray (CXR) for immigrants from countries with TB incidence  $>40/10^5$ , and tuberculin skin test (TST) for people with normal CXR from very high TB prevalence countries. A revised screening policy using first-line QuantiFERON-TB Gold (QFT) in high risk immigrants was piloted in 2007. Initially, TST was offered to immigrants from countries with TB incidence  $200-339/10^5$ , and QFT to those from countries with incidence  $>340/10^5$ . When increased resources became available, all immigrants from countries with TB incidence  $>200/10^5$  had QFT. Those with positive QFT were invited for CXR. 1336 immigrants were invited for screening, with a 32% attendance rate. 280 patients had QFT, of which 38% were positive, with  $<2\%$  being indeterminate. Using the NICE approach, the cost of screening these 280 immigrants would be £13 346.75 (£47.67 per immigrant) and would identify 83 cases of latent TB infection (LTBI). Using first-line QFT followed by CXR the cost was £9781.82 (£34.94 per immigrant) and identified 105 cases of LTBI. The cost to identify one case of LTBI following NICE guidelines would be £160.81 and using the present protocol was £93.16. For immigrants from high risk countries QFT blood testing followed by CXR is feasible for TB screening, cheaper than screening using the NICE guideline and identifies more cases of LTBI.

## INTRODUCTION

Notifications of new cases of tuberculosis (TB) have increased over the last 10 years in the UK. This is due to an increase in TB in foreign-born individuals.<sup>1</sup> Effective control of TB requires identification of active and latent TB in populations arriving from high risk countries. Traditionally, screening has been based on chest x ray (CXR) and tuberculin skin testing (TST). QuantiFERON-TB Gold (QFT) is a newer test for TB, based on the quantification of interferon  $\gamma$  released from lymphocytes in whole blood sensitised to specific TB antigens ESAT-6 and CFP-10. Advantages over TST include higher specificity and sensitivity and the need for only one contact with a healthcare professional.

There is a moderate agreement between TST and QFT.<sup>2-3</sup> A study of Dutch army recruits who had been deployed in high risk countries showed an 82% concordance between TST and QFT, with a high discordance between TST-positive QFT-negative

individuals.<sup>4</sup> This suggests that latent TB infection may be overdiagnosed if there is an over-reliance on TST. This is because TST can be positive in people with prior BCG vaccination and environmental mycobacteria. QFT has been shown to reduce screening costs in TB contacts.<sup>5</sup> Another commercially available interferon  $\gamma$  assay, T-SPOT.TB, which shows good agreement with QFT,<sup>6</sup> has been shown to be cost-effective in screening TB contacts.<sup>7</sup> Studies have suggested that a TST followed by a T-SPOT.TB protocol is cost-effective for contact screening for latent TB infection.<sup>8</sup> There are no published data regarding the use of either interferon  $\gamma$  release assay (IGRA) for immigrant screening.

In the UK, National Institute for Health and Clinical Excellence (NICE) guidelines for new entrant TB screening currently recommend CXR for immigrants from countries with TB incidence  $>40/10^5$ , and TST for people with normal CXR from very high TB incidence countries.<sup>9</sup> An IGRA is currently recommended for those with positive TST and normal CXR to confirm the diagnosis of latent TB infection (LTBI). The purpose of this study was to assess the cost-effectiveness of first-line QFT for screening immigrants from high risk countries, a strategy which has not been appraised in the current NICE guidelines due to a lack of information regarding cost-effectiveness in the patient group.

## METHODS

The Leeds TB Screening Service serves a population of 750 000. Due to cost and personnel issues, we are unable to screen all new immigrants from countries with TB incidence  $>40/10^5$ . Previous audit in the department has demonstrated that the majority of cases of TB in this region are found if a threshold of  $200/10^5$  is used. Therefore, since 2005 our policy has been to offer screening to immigrants from countries with TB incidence  $>200/10^5$ . A revised screening policy was introduced on 1 January 2007. Initially, TST was offered to immigrants from countries with TB incidence  $200-339/10^5$ , and QFT to those from countries with incidence  $>340/10^5$ . When increased resources became available, all immigrants from countries with TB incidence  $>200/10^5$  had QFT. Those with positive QFT were invited for CXR.

TFT was carried out using 2 tuberculin units (TU) of purified protein derivative on the volar aspect of the forearm, according to the Mantoux

method. Cut-off for a positive result was 6 mm in those without prior BCG and 15 mm in those with prior BCG. QFT was performed according to the manufacturer's instructions using 1 ml aliquots of whole blood incubated overnight with an antigen-free negative control, a phytohaemagglutinin-positive control and antigens to ESAT-6 and CFP-10.

LTBI was defined as immigrants with normal CXR and positive QFT in the absence of signs or symptoms of active TB infection, following review by a doctor in clinic. Costs were estimated for our protocol and for the NICE protocol based on NICE estimates for the cost of a CXR £23.24, TST £13.69 and QFT £25.67.<sup>9</sup> Data analysis was carried out in Microsoft Office Excel 2003.

## RESULTS

In the catchment area of the Leeds TB screening service, in 2007 there were 2902 new immigrants from countries with TB incidence  $>200/10^5$  who registered with local with general practitioners. A total of 1336 were invited for screening (TST or QFT as described above), with a 32% attendance rate. Self-reported rates of HIV infection were very low (1%). A total of 280 QFT were performed, 139 in men with an average age of 30.8 years; of these 170 (60.7%) QFT were negative and 104 (37.1%) were positive. There were 5 (1.8%) indeterminate results and 1 (0.3%) laboratory processing error. Of the five indeterminate results, four individuals were negative on repeat testing and one had a second indeterminate result. This individual was seen in clinic and clinically diagnosed with LTBI following a normal CXR. The individual whose sample was incorrectly processed had a negative result on second test.

Those individuals with positive QFT were invited for review in clinic. Ninety-four (90.3%) individuals attended; of these 71 individuals had received prior BCG vaccination; 1 individual had been treated for TB in the past and had completed a 6 month course of antibiotics in Somalia; and 10 individuals had known TB contact. None reported infection with HIV. Following CXR, all individuals were diagnosed with LTBI and there were no cases of active TB identified. Sixty-four received chemoprophylaxis and 30 have been invited to attend CXR follow-up for 12 months. Of those with a positive QFT, 24 had been tested with TST, with 13 (54%) being positive.

Overall, 221 individuals reported receiving prior BCG. The previous BCG rate was the same (79%) in the QFT-negative and QFT-positive groups, suggesting that prior BCG is not interacting with QFT. Forty-two individuals received TST and QFT. The correlation between TST and QFT in this group was poor, with agreement in 21 (50%) cases. Eleven individuals with a negative TST had a positive QFT, and 10 with a positive TST had a negative QFT.

Costs for screening using the Leeds protocol (QFT first) were calculated and are shown in table 1. The total cost to screen 280 immigrants was £9781.82 (£34.94 per immigrant) and identified 105 cases of LTBI (£93.16).

Costs which would have been incurred had we followed the NICE protocol in this group of immigrants were estimated. Based on the 42 cases who had both TST and QFT, we assumed that of those with a positive TST, 56% would have positive QFT. The numbers having both tests were too small to enable reliable estimates of the proportion of TST having positive QFT for different subgroups stratified by TB incidence in country of origin. The calculations are shown in table 2. The NICE protocol would have cost an estimated total of £13 346.75 (£47.67 per immigrant) and would have identified 83 cases of LTBI (£160.81

**Table 1** Costing for screening using the Leeds protocol

Leeds protocol (QFT first), 280 immigrants		
Step 1: QFT		
	Unit cost	Total cost
280 QFT	£25.67	£7187.60
6 patients had second QFT	£25.67	£154.02
Step 2: CXR if QFT positive (37%) + 1 patient with 2 indeterminate QFT		
105 CXR	£23.24	£2440.20
<b>Total cost for screening</b>		<b>£9781.82</b>
LTBI cases		105
Cost per case LTBI identified		£93.16

CXR, chest x ray; LTBI, latent tuberculosis infection; QFT, QuantiFERON-TB Gold.

per case identified). This estimate assumes that there were no "false-negative" TST. In fact, of those having both tests, 11 of 24 with positive QFT had negative TST. Allowing for this, the number of QFT done under the NICE protocol would be reduced to 83, cutting the overall cost estimate to £11 549.65 (£41.25 per immigrant) but would only identify 45 cases of LTBI (£256.66 per case identified).

## DISCUSSION

TB services are under considerable pressure to perform immigrant screening on limited resources. This is on a background of increasing incidence of TB, largely related to cases in immigrant populations. Our service is able to screen ~1200 individuals effectively per annum. There is a need to streamline the screening process for immigrants, firstly to allow our services to operate more efficiently and effectively, and secondly to encourage participation in the screening process amongst immigrants. In our region, the aim is to screen 60% of eligible individuals, but in 2007 the attendance rate was only 32%. The potential benefits of QFT over traditional TST are well recognised, but in our view the fact that only one contact with healthcare services is required is a major benefit. We have demonstrated that it is feasible to screen high risk immigrant populations using first-line QFT, although as yet we have no longitudinal data to see if this will increase attendance rates for screening.

Resources were not available to perform QFT and TST in all individuals. The cost of the NICE protocol is therefore based on an estimate of the TST-positive and QFT-positive rates in the subgroup who had both tests. This subgroup includes individuals from countries with TB incidence  $200-339/10^5$  who were initially tested with TST, and those in families with very young children in whom it was not considered practical to test different

**Table 2** Costing for screening using the NICE protocol

NICE protocol (CXR first), 280 immigrants		
Step 1: CXR if age >11 and not pregnant		
	Unit cost	Total cost
275 CXR	£23.24	£6393.75
Step 2: TST if pregnant or age <16 (12 individuals) or age 16-35 from sub-Saharan Africa or from country with TB incidence $>500/10^5$ (209 individuals)		
221 TST	£13.69	£3025.49
Step 3: QFT if positive TST (estimated TST-positive rate 69%)		
153 QFT	£25.67	£3927.51
<b>Total cost for screening</b>		<b>£13 346.75</b>
LTBI cases (estimated QFT-positive rate 54%)		83
Cost per case LTBI identified		£160.81

CXR, chest x ray; LTBI, latent tuberculosis infection; NICE, National Institute for Health and Clinical Excellence; QFT, QuantiFERON-TB Gold; TST, tuberculin skin test.

family members with different tests. QFT was performed in individuals who requested QFT following the TST. This subgroup may not be representative of the entire cohort and there is, therefore, a potential for bias in the estimation of the TST-positive rate. The estimated TST-positive rate of 69% compares with a historical positive TST rate of 32% in sub-Saharan Africans attending our clinic for screening in 2006.<sup>10</sup> The difference may be explained by the high proportion of those in our cohort who had both tests, with a negative TST and a positive QFT. If this proportion were consistent across the whole cohort, the estimated TST positivity rate would be 36%, similar to the historical result. Applying this lower rate of TST positivity to the calculation of cost, the NICE protocol would still cost more than using the QFT test as first line and identify significantly fewer cases of LTBI.

Previous studies have demonstrated a good concordance between TST and QFT when TST is negative; however, these studies are in patients with suspected active TB or in those who are undergoing contact screening. One possible explanation is that the cut-off used in the NICE protocol for a positive TST is 15 mm in those who have had a prior BCG. In our group, >75% of immigrants had received BCG. Our data suggest that cases of LTBI are potentially being missed due to the high cut-off for a positive TST. The 15 mm cut-off is arbitrary, and other groups have suggested a lower cut-off of 10 mm may be more appropriate.<sup>8</sup> We would be interested in the experiences of other groups to see if this observation is repeated in other immigrant populations.

The low incidence of indeterminate QFT results in our study population of 1.8% compares favourably with that seen in other groups.<sup>6</sup> The reduced rate of intermediate results could be due to increasing laboratory familiarity with the use of QFT or to differences in the study populations between different groups.

There is some limitation in our conclusions due to the change in inclusion criteria that occurred during the introduction of the new protocol. Initially we did not have the resources to offer first-line QFT to the immigrants from countries with TB incidence 200–339/10<sup>5</sup>. The QFT-positive rate was 34% in immigrants from countries with TB incidence 200–339/10<sup>5</sup>, and 43% in those from countries with TB incidence >340/10<sup>5</sup>. We believe this difference would not affect our overall results and conclusions. It is interesting that our protocol identified more cases of LTBI. The increase in cases of LTBI is due to those patients who had a positive QFT but a negative TST and would therefore have been missed by the NICE protocol, and by immigrants from countries with a TB incidence of >200/10<sup>5</sup> outside sub-Saharan.

The case for selecting immigrants for screening by geography rather than by TB incidence in the country of origin seems weak, and our approach has enabled us to extend screening for LTBI to high risk countries outside Africa while still reducing the overall cost and increasing the detection of LTBI compared with the NICE protocol.

We have demonstrated that a QFT-first protocol can be carried out more cheaply than a CXR-first protocol, with a cost saving of ~35%. This saving is due to the reduced number of CXRs required. There would be an increase in clinic costs due to monitoring patients having chemoprophylaxis and CXR follow-up; however, these costs would be expected to be recouped due to the prevention of cases of active TB in those patients who receive chemoprophylaxis.

We are in the process of collecting longitudinal data to confirm that there is not an unexpectedly high incidence of active TB in those patients who had a negative QFT. Overall, we believe that using QFT blood testing followed by CXR is more effective and more cost-effective than NICE guideline for screening new entrants from high risk countries, and will continue to use this approach for immigrant screening.

**Competing interests** None.

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