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Title Page

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 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. We piloted a revised screening policy using first-line QuantiFERON-TB Gold (QFT) in high risk immigrants 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 immigrant 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 £9,781.82 (£34.94 per immigrant) and identified 105 LTBI. The cost to identify one case of LTBI following NICE guidelines would be £160.81 and using our protocol was £93.16. For immigrants from high risk countries QuantiFERON-TB Gold 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 ten years in the UK. This is due to an increase in TB in foreign born individuals[1]. 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 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 sensitized 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 health care professional.

There is a moderate agreement between TST and QFT[2,3]. A study of Dutch army recruits who had been deployed in high risk countries showed an 82% concordance between TFT and QFT, with a high discordance between TST-positive QFT-negative individuals[4]. This suggests that latent TB infection may be over diagnosed if there is an overreliance on TST. This is because TST can be positive in people with prior BCG vaccination and environmental mycobacteria. QuantiFERON-TB Gold, has been shown to reduce screening costs in TB contacts[5]. Another commercially available interferon gamma assay, T-SPOT.TB, which shows good agreement with QFT[6], has been shown to be cost effective in screening TB contacts[7]. Studies have suggested that a TST followed by T-SPOT.TB protocol is cost effective for contact screening for latent TB infection[8]. There is no published data regarding the use of either interferon gamma release assay for immigrant screening.

In the UK, NICE guidelines for new entrant tuberculosis (TB) screening currently 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 incidence countries[9]. Interferon gamma release assay is currently recommended for those with positive TST and normal CXR to confirm the diagnosis of latent TB infection. 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 1st 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.

Tuberculin skin testing was carried out using 2-TU of purified protein derivative on the volar aspect of the forearm, according to the Mantoux method. Cut off for a positive result was 6mm in those without prior BCG and 15mm in those with prior BCG. QuantiFERON-TB Gold was performed according to manufacturers instructions using 1ml aliquots of whole blood incubated overnight with an antigen free negative control, a phytohaemagglutinin positive control and antigens to ESAT-6 and CFP-10.

Latent TB infection 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 cost of CXR £23.24, TST £13.69 and QFT £25.67[9]. 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. 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%). 280 QFT were performed, 139 in men with an average age of 30.8 years. 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, 4 individuals were negative on repeat testing and 1 had a second indeterminate result. This individual was seen in clinic and clinically diagnosed with latent TB infection 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. 94 (90.3%) individuals attended. 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. 10 individuals had known TB contact. None reported infection with HIV. Following CXR, all individuals were diagnosed with latent TB infection and there were no cases of active TB identified. 64 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. 42 individuals received TST and QFT. The correlation between TST and QFT in this group was poor, with agreement in 21 (50%) cases. 11 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 £9,781.82 (£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 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).

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	£7,187.60
	6 patients had 2nd QFT	£25.67	£154.02
Step 2: CXR if QFT positive (37%) + 1 patient with 2 indeterminate QFT			
	105 CXR	£23.24	£2,440.20
TOTAL COST FOR SCREENING			**£9,781.82**
LTBI cases			105
Cost per case LTBI identified			£93.16

Table 2: Costing for screening using the NICE protocol

NICE protocol (CXR first), 280 immigrants			
Immigrants from countries with TB incidence 200-339/10^5 (N=180)			
Step1: CXR if age>11 and not pregnant			
		Unit cost	Total cost
	275 CXR	£23.24	£6,393.75
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 (109 individuals)			
	221 TST	£13.69	£3,025.49
Step 3: QFT if positive TST (estimated TST positive rate 69%)			
	153 QFT	£25.67	£3,927.51
TOTAL COST FOR SCREENING			**£13,346.75**
LTBI cases (estimated QFT positive rate 54%)			83
Cost per case LTBI identified			£160.81

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 effectively screen approximately 1,200 individuals 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 QuantiFERON-TB Gold over traditional tuberculin skin testing are well recognized, 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 sub-group who had both tests. This sub-group 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 family members with different tests. QFT was performed in individuals who requested QFT following the TST. This sub-group may not be representative of the entire cohort and there is therefore a potential for bias in the estimation of TST positive rate. The estimated TST positive rate of 69% compares to a historical positive TST rate of 32% in sub-Saharan Africans attending our clinic for screening in 2006[10]. The difference may be explained by the high proportion of those in our cohort who had both tests with negative TST and a positive OFT. 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 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. Once possible explanation is the cut-off used in the NICE protocol for a positive TST is 15mm in those who have had a prior BCG. In our group over 75% of immigrants had received BCG. Our data suggests that cases of LTBI are potentially being missed due to the high cut-off for a positive TST. The 15mm cut off is arbitrary and other groups have suggested a lower cut-off of 10mm may be more appropriate[8]. 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 favorably to that seen in other groups[6]. 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 200-339/10^5. The QFT positive rate was 34% in immigrants from countries with TB incidence 200-339/10^5, and 43% in those from countries with TB incidence 200-339/10^5. 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 NICE protocol, and by immigrants form countries with a TB incidence of more than 200/10^5 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 to 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 approximately 35%. This saving is due to the reduced number of CXR 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 QuantiFERON-TB Gold 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.

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